

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AVOCOMB*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg lamivudine and 300 mg zidovudine. For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet White to off-white, capsule-shaped film-coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'RX923' debossed (stamped into) one side and are plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVOCOMB is indicated as part of antiretroviral combination therapy for the treatment of HIV-1 infection in adults, adolescents and children weighing at least 25 kg. Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Oral use. Antiretroviral therapy should be prescribed by a health care provider experienced in the management of HIV infection. Posology

Adults, adolescents and children weighing at least 25 kg:

The recommended dose of AVOCOMB is one tablet twice a day, approximately every 12 hours. Children weighing less than 25 kg AVOCOMB is not suitable for children weighing less than 25 kg. Formulation containing lower amounts of lamivudine and zidovudine are more suitable. Elderly Special care is advised in the elderly because of age-associated changes such as decreased renal function and alteration of haematological parameters. Renal impairment Since dose adjustment may be necessary in patients with severe renal impairment (creatinine clearance less than 30 mL/minute), it is recommended that other formulations of lamivudine and zidovudine are used (see section 4.4). Hepatic impairment Data from patients with

moderate to severe hepatic impairment show that hepatic dysfunction does not affect lamivudine pharmacokinetics significantly. However, limited data in patients with cirrhosis suggest that zidovudine may accumulate in patients with hepatic impairment because of decreased glucuronidation. As †Formerly Ranbaxy Laboratories Ltd * Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility. Lamivudine/Zidovudine 150mg/300mg tablets WHOPAR Part 4 November 2023 (Sun Pharmaceutical Industries Ltd†), HA286 zidovudine doses may need to be adjusted, it is recommended that separate preparations or other formulations of lamivudine and zidovudine are used in patients with severe hepatic impairment. Haematological adverse reactions Since substitution or dose reduction of zidovudine should be considered in patients whose haemoglobin concentrations or neutrophil counts fall in a clinically significant way, it is recommended that separate preparations of lamivudine and (if appropriate) zidovudine be administered (see section 4.4). Missed dose If a dose is missed and this is noticed within 6 hours (for twice-daily dosing), the patient should take the missed dose as soon as possible. The patient should then take the next regular dose at the usual time. If it is longer since the missed dose, the patient should take the normal dose when it is next due. No double dose should be given to make up for a forgotten dose. Method of administration AVOCOMB may be taken with food or between meals. To ensure that the patient takes the entire dose, the tablet should be swallowed whole. For patients who cannot swallow tablets, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

AVOCOMB must not be used in patients with:

- abnormally low neutrophil count (less than $0.75 \times 10^9/L$) (see section 4.4),
- abnormally low haemoglobin (less than 75 g/L or 4.65 mmol/L) (see section 4.4).

4.4 Special warnings and precautions for use

Dose adjustment It is recommended that separate preparations or other formulations of lamivudine and zidovudine are used for any dosage adjustment (see section 4.2).

Opportunistic infections Health care providers should tell patients with impaired immunity that opportunistic infections or other complications of HIV infection may still develop while receiving antiretroviral medicines. This risk reduces as the immune system recovers.

Haematological adverse reactions Anaemia, neutropenia and leucopenia can occur in patients receiving zidovudine, especially in patients with advanced HIV disease or poor bone-marrow reserve or with vitamin B12 deficiency, and usually after at least 4–6 weeks of therapy. Therefore, haematological parameters should be monitored in patients receiving AVOCOMB, e.g. as follows:

- In advanced HIV disease, at least every 2 weeks during the first 3 months of therapy, and monthly thereafter.
- In early (non-symptomatic) HIV disease, every 1–3 months according to the patient's overall condition.

Since substitution, dose reduction or interruption of zidovudine therapy may be necessary in patients whose haemoglobin concentration or neutrophil count fall in a clinically significant way, separate preparations or other formulations of lamivudine and (if appropriate) zidovudine should be used.

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Pancreatitis Treatment with AVOCOMB should be stopped immediately if signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Lactic acidosis Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of zidovudine. It generally occurred after a few months of treatment. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has high mortality and may be associated with pancreatitis, liver failure, or renal failure. Treatment with zidovudine should be discontinued if there is symptomatic hyperlactataemia and metabolic or lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels. Zidovudine should be given with caution

to any patient (particularly obese women) with hepatomegaly, hepatitis or other risk factors for liver disease and hepatic steatosis (including certain medicines and alcohol). Patients co-infected with hepatitis C and treated with interferon alfa and ribavirin may constitute a special risk. Patients at increased risk should be followed closely. Mitochondrial dysfunction following exposure in utero Nucleoside and nucleotide analogues can cause mitochondrial damage. Mitochondrial dysfunction has been reported in HIV-negative infants exposed to nucleoside analogues in utero or postnatally. The main adverse reactions are haematological disorders (anaemia and neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These reactions are often transient. Some late-onset neurological disorders have been reported (hypertonia, convulsion and abnormal behaviour). It is not known if the neurological disorders are transient or permanent. These findings should be considered for any child exposed in utero to nucleoside and nucleotide analogues who has severe features of unknown aetiology, particularly neurological effects. Lipoatrophy Treatment with zidovudine is associated with loss of subcutaneous fat, which has been linked to mitochondrial toxicity. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the face, limbs and buttocks, may not be reversible when switching to a zidovudine-free regimen. Patients should be regularly assessed for lipoatrophy during therapy with zidovudine-containing products. Therapy should be switched to an alternative regimen if lipoatrophy is suspected.

Weight and metabolic parameters:

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is some evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. HIV treatment guidelines should be used for recommendations on monitoring blood lipids and glucose. Lipid disorders should be managed as clinically appropriate. Immune reactivation syndrome Immune reactivation syndrome has been reported in patients treated with combination antiretroviral therapy. During early stages of treatment, patients whose immune system responds to antiretroviral therapy may develop an inflammatory response to slow-developing or residual opportunistic

infections (such as *Mycobacterium avium* infection, cytomegalovirus retinitis, *Pneumocystis jirovecii* pneumonia, or tuberculosis). These reactions may require further evaluation and treatment. Lamivudine/Zidovudine 150mg/300mg tablets
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Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, polymyositis, and Guillain-Barré

syndrome) have also been reported in the setting of immune reactivation; however, the reported time to onset

is more variable and these events can occur many months after starting antiretroviral treatment. Liver disease AVOCOMB should be used with caution in any patient with chronic hepatitis B infection. Lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication and discontinuation of lamivudine or virological failure after development of resistance to lamivudine by HBV may cause hepatic deterioration and a hepatitis flare. If AVOCOMB is discontinued in a patient with HBV infection, the patient should be periodically monitored, both clinically and by assessment of liver function tests (ALT and bilirubin levels) and markers of HBV replication, for at least 4 months, and then as clinically indicated. Patients with chronic hepatitis B or C who are treated with combination antiretroviral therapy, have an increased risk of severe and potentially fatal hepatic adverse events.

Patients with liver dysfunction have an increased risk of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If liver disease worsens in such patients, interruption or discontinuation of therapy should be considered. Osteonecrosis Cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease or long-term exposure to combination antiretroviral therapy. Additional risk factors for this condition include corticosteroid use, alcohol consumption, severe immunosuppression and higher body mass index. Patients should be advised to seek medical advice if they develop joint aches and pain, joint stiffness or difficulty in movement. Renal impairment Patients with creatinine clearance between 30 and 49 mL/minute receiving AVOCOMB may have 1.6- to 3.3-fold higher lamivudine exposure (AUC) than patients with creatinine clearance more than 50 mL/minute. Patients with creatinine clearance between 30 and 49 mL/minute should be

monitored for lamivudine-related adverse events, notably haematologic toxicity. If neutropenia or anaemia worsen, lamivudine dose should be reduced.

4.5 Interaction with other medicinal products and other forms of interaction

Lamivudine undergoes limited metabolism and is almost completely eliminated via the kidneys. Active renal secretion of lamivudine is mediated by organic cation transporters (OCT). Co-administration of lamivudine with OCT inhibitors or nephrotoxic drugs may increase lamivudine exposure. Zidovudine is primarily eliminated by hepatic conjugation by UGT enzymes, to form an inactive glucuronide metabolite. Therefore co-administration of inducers or inhibitors of UGT enzymes could alter zidovudine

exposure. Lamivudine and zidovudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) and do not inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicines metabolised by major P450 enzymes. Lamivudine/Zidovudine 150mg/300mg tablets WHOPAR Part 4 November 2023 (Sun Pharmaceutical Industries Ltd†), HA286 The following list of interactions is not exhaustive but is representative of the classes of medicines where caution should be exercised. AVOCOMB interactions Drugs (grouped by therapeutic Recommendation on co- Interaction

area) administration

HIV antiretrovirals Emtricitabine with Potential competition for metabolism.

Emtricitabine should not be colamivudine administered with AVOCOMB. Stavudine with zidovudine In vitro antagonism of anti-HIV Stavudine should not be coactivity between stavudine and administered with AVOCOMB. zidovudine could result in decreased efficacy of both drugs. Other antivirals Ribavirin with zidovudine Exacerbation of anaemia has been Ribavirin and zidovudine should not be reported in patients receiving ribavirin co-administered, particularly in patients and zidovudine. with zidovudine-administered anaemia. Anti-infectives Albendazole with zidovudine Potential haematological toxicity Haematological parameters should be monitored Clarithromycin with Zidovudine AUC ↓12% Administration of AVOCOMB and zidovudine (500 mg twice clarithromycin should be separated by daily/100 mg

every 4 hours) at least 2 hours. Dapsone with zidovudine Potential renal and haematological Renal function and haematological toxicity parameters should be monitored and dose reduction should be considered. Trimethoprim + Lamivudine: AUC ↑40% No dosage adjustment of AVOCOMB sulfamethoxazole with Trimethoprim: AUC ↔ is necessary, unless patient has renal lamivudine (160 mg/800 mg Sulfamethoxazole: AUC ↔ impairment. When concomitant once daily for 5 days/300 mg administration with trimethoprim + (Organic cation transporter inhibition) single dose) sulfamethoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim + sulfamethoxazole for treating *Pneumocystis jirovecii* pneumonia and toxoplasmosis have not been studied and should be avoided. Trimethoprim + Potential renal and haematological Renal function and haematological sulfamethoxazole with toxicity parameters should be monitored and zidovudine dose reduction should be considered. Sulfadiazine with lamivudine Sulfadiazine is associated with renal Renal function should be monitored. toxicity and in some cases renal failure. Potential for renal toxicity as lamivudine is mainly excreted by active renal transport. Sulfadiazine with zidovudine Potential haematological toxicity Haematological parameters should be monitored Vancomycine and zidovudine Potential haematological toxicity Haematological parameters should be monitored Lamivudine/Zidovudine 150mg/300mg tablets WHOPAR Part 4 November 2023 (Sun Pharmaceutical Industries Ltd†), HA286 Drugs (grouped by therapeutic Recommendation on co- Interaction area) administration

Antifungal Amphotericin B and Potential renal and haematological Renal function and haematological zidovudine toxicity parameters should be monitored and dose reduction should be considered. Fluconazole with zidovudine Zidovudine AUC ↑74% Co-administration may increase (400 mg once daily/200 mg zidovudine exposure. Routine dose (UGT inhibition) three times daily) modification is not warranted, however monitor for signs of zidovudine toxicity (section 4.8). Flucytosine with lamivudine Potential for haematological toxicity Haematological parameters should be monitored, and dose reduction should be considered Flucytosine with zidovudine Potential renal and haematological Renal function and haematological toxicity parameters should be monitored and dose reduction should be considered

Antimalarial Amodiaquine and zidovudine Potential haematological toxicity
Haematological parameters should be monitored Primaquine and zidovudine
Potential haematological toxicity Haematological parameters should be monitored
Antimycobacterial Rifampicin and zidovudine Zidovudine AUC ↓48% Insufficient data
to recommend dosage (600 mg daily/200 mg three adjustment times daily)
Antipsychotics Fluphenazine with zidovudine Potential haematological toxicity.
Haematological parameters should be Quetiapine with zidovudine monitored
Antiepileptics Phenobarbital with Interaction not studied. Potential to Response to
antiretroviral therapy zidovudine slightly decrease zidovudine plasma should be
monitored. Insufficient data concentrations through UGT induction. to recommend
dosage adjustment. Phenytoin with zidovudine Phenytoin AUC ↑↓ Phenytoin
concentration should be

monitored. Need for dosage adjustment

unlikely Valproic acid with zidovudine Zidovudine AUC ↑80% Patient should be
monitored for signs of (250 mg or 500 mg three zidovudine toxicity (section 4.8).
(UGT inhibition) times daily/100 mg three times daily) Cytotoxics Carboplatin with
zidovudine Potential renal and haematological Renal function and haematological
toxicity parameters should be monitored and dose reduction should be considered.
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area) administration

Cladribine with lamivudine Interaction not studied Concomitant use of lamivudine
with In vitro lamivudine inhibits the cladribine is not recommended. intracellular
phosphorylation of cladribine leading to a potential loss of cladribine efficacy. Some
clinical findings also support a possible interaction between lamivudine and
cladribine Cisplatin with lamivudine Potential renal toxicity Renal function should
be monitore Chlorambucil with Potential haematological toxicity Haematological
parameters should be zidovudine monitored Cisplatin with zidovudine
Cyclophosphamide with zidovudine Cytarabine with zidovudine Dacarbazine with
zidovudine Daunorubicin with zidovudine Docetaxel with zidovudine Fluorouracil

with zidovudine Gemcitabine with zidovudine Ifosfamide with zidovudine Imatinib
with zidovudine Mercaptopurine with zidovudine Methotrexate with zidovudine
Oxaliplatin with zidovudine Paclitaxel with zidovudine Doxorubicin with zidovudine
Potential renal and haematological Concomitant use of doxorubicin and

toxicity. zidovudine is not advised. However, if

used, renal function and haematological parameters should be monitored, and dose
reduction considered. Vinblastine with zidovudine Potential renal and

haematological Renal function and haematological toxicity parameters should be
monitored and Vincristine with zidovudine dose reduction should be considered.

Opioids Methadone with zidovudine Zidovudine AUC ↑43% The clinical significance
is not known. (30–90 mg once daily/200 mg Monitor for signs of zidovudine

Methadone AUC ↔ every 4 hours) toxicity. Methadone dosage adjustment may be
required occasionally. Uricosuric Probenecid with zidovudine Zidovudine AUC

↑106% The clinical significance is not known. (500 mg four times The patient should
be monitored for (UGT inhibition) daily/2 mg/kg three times signs of zidovudine

toxicity. daily) Miscellaneous Lamivudine/Zidovudine 150mg/300mg tablets

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Drugs (grouped by therapeutic Recommendation on co- Interaction

area) administration

Methyldopa with zidovudine Potential haematological toxicity. Haematological
parameters should be monitored Sorbitol solution (3.2 g, Lamivudine: When
possible, chronic co-

**10.2 g, 13.4 g) with AUC ↓ 14%; 32%; 36% administration of AVOCOMB should
be**

lamivudine, single dose avoided with medicines containing lamivudine oral solution
C_{max} ↓ 28%; 52%; 55% sorbitol or other osmotic-acting poly- 300 mg alcohols (e.g.
xylitol, mannitol, lactitol, maltitol). More frequent monitoring of HIV-1 viral load
should be considered when chronic co-administration cannot be avoided □

Decreased AUC area under the curve (bioavailability) □ Increased C_{max} maximum
(peak) concentration (in plasma or blood) □ No change C_{min} minimum (trough)

concentration (in plasma or blood) Concomitant treatment, especially acute therapy,

with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, pyrimethamine, ganciclovir, and interferon) and zidovudine may increase the risk of adverse reactions. If concomitant therapy with AVOCOMB and any of these medicines is necessary then extra care should be taken to monitor renal function and haematological parameters and, if required, the dose of one or more agents should be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy No increased risk of birth defects has been reported for lamivudine or for zidovudine (www.apregistry.com). A large amount of cumulative information on pregnant women taking lamivudine or zidovudine indicate that malformation is unlikely. The use in pregnant women of zidovudine alone, with subsequent treatment of the newborn infants, can reduce the rate of maternal-fetal transmission of HIV-infection. No such data are available for lamivudine. Consideration should be given to possibility of recurrence of hepatitis on discontinuation of lamivudine in patients who are co-infected with hepatitis and were treated with lamivudine containing medicines such as AVOCOMB and who subsequently become pregnant. A variable degree of mitochondrial damage may occur with the use of nucleoside and nucleoside analogues. There are reports of mitochondrial dysfunction in HIV-negative infants exposed in utero or postnatally to nucleoside analogues. **Breast-feeding** Both lamivudine and zidovudine are present in breast milk at concentrations similar to those in the serum. Current recommendations on HIV and breast-feeding (e.g. those from the WHO) should be consulted to advise patients on this matter. Preferred options may vary depending on the local circumstances. **Fertility** Neither zidovudine nor lamivudine have impaired fertility in studies in male and female rats. There are no data on their effect on human female fertility. In men, zidovudine has not been shown to affect sperm count, morphology or motility.

4.7 Effects on ability to drive and use machines

AVOCOMB is not expected to affect the patient's ability to drive or use machines. However, the patient's clinical status and individual experience of adverse effects (e.g. fatigue) should be borne in mind to determine if the patient can safely perform

skilled tasks. Lamivudine/Zidovudine 150mg/300mg tablets WHOPAR Part 4
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4.8 Undesirable effects

AVOCOMB contains lamivudine and zidovudine and adverse reactions associated with each of the active substances may be expected. There is no evidence of added toxicity with concurrent administration of the two active substances. The most frequently reported adverse reactions are headache and nausea. The most common serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia (see section 4.4). The undesirable effects of AVOCOMB are listed below. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from the available data).

Blood and lymphatic systems disorders
Common anaemia, neutropenia, leucopenia
Uncommon thrombocytopenia, pancytopenia
Rare pure red cell aplasia
Very rare aplastic anaemia

Metabolic and nutrition disorders
Rare lactic acidosis, anorexia
Frequency not known lipoatrophy, weight increase, hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia,

Psychiatric disorders
Rare anxiety, depression

Nervous system disorders
Very common headache
Common dizziness, insomnia
Rare paraesthesia, somnolence, loss of mental acuity, convulsions

Cardiac disorders
Rare cardiomyopathy

Respiratory, thoracic and mediastinal disorders
Common cough, nasal symptoms
Uncommon dyspnoea

Gastrointestinal disorders
Very common nausea
Common vomiting, abdominal pain or cramps, diarrhoea
Uncommon flatulence
Rare pancreatitis, raised serum amylase, oral mucosa pigmentation, taste perversion, dyspepsia

Hepatobiliary disorders
Common elevated liver enzymes and bilirubin
Rare hepatitis, severe hepatomegaly with steatosis

Skin and subcutaneous tissue disorders
Common rash, hair loss
Uncommon pruritus

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Rare nail and skin pigmentation, urticaria, sweating, angioedema

Musculoskeletal and connective tissue disorders
Common arthralgia, myalgia
Uncommon myopathy
Rare rhabdomyolysis
Frequency not known

osteonecrosis Renal and urinary disorders Rare urinary frequency Reproductive system and breast disorders Rare gynaecomastia

General disorders and administration site disorders:

Common malaise, fatigue, fever Uncommon asthenia, generalised pain Rare chest pain, influenza-like syndrome, chills Frequency not known immune reactivation syndrome See also sections 4.4 and 4.5. Reporting of suspected adverse reactions Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

There is limited experience of overdosage with lamivudine and zidovudine. No specific signs and symptoms have been identified following acute overdose with lamivudine or zidovudine apart from those listed as undesirable effects. No fatalities occurred and the patients recovered. If overdose occurs, patients should be monitored for toxicity (see section 4.8), and standard supportive treatment given as necessary. Since elimination of lamivudine and the glucuronide metabolite of zidovudine are enhanced by haemodialysis, continuous haemodialysis could be used in the treatment of overdosage but this has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC Code J05AR01 Mechanism of action Lamivudine and zidovudine are nucleoside analogues that are active against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both compounds are metabolised intracellularly to their active moieties, lamivudine 5'-triphosphate (TP) and zidovudine 5'-triphosphate, respectively. Their main modes of action are as chain terminators of viral reverse transcription. Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication in vitro; lamivudine is also active against zidovudine-resistant clinical isolates of HIV.

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(Sun Pharmaceutical Industries Ltd†), HA286 Clinical efficacy In clinical trials, lamivudine and zidovudine in combination with a third antiretroviral agent reduce HIV-1 viral load and increases CD4 cell count. In a trial of zidovudine and lamivudine in combination with efavirenz, plasma HIV RNA was < 50 copies/mL in 68% of patients after 48 weeks, by intention-to-treat

analysis. Lamivudine and zidovudine have been widely used as components of antiretroviral combination

therapy with other antiretroviral agents. Resistance In the great majority of cases when combination antiretroviral therapy comprising zidovudine and lamivudine fails virologically, the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine. In vitro data suggest that continuation of lamivudine in antiretroviral regimen despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness).

However, clinical data are very limited and preclude any reliable conclusion.

Therefore, continuing lamivudine therapy despite emergence of M184V mutation should be considered only when other effective nucleoside reverse transcriptase inhibitors (NRTIs) are not available. Resistance to thymidine analogues (of which zidovudine is one) is well characterised and is conferred by the stepwise accumulation of up to six specific mutations in the HIV reverse transcriptase at codons 41, 67, 70, 210, 215 and 219. Viruses acquire phenotypic resistance to thymidine analogues through the combination of mutations at codons 41 and 215 or by the accumulation of at least four of the six mutations. These thymidine analogue mutations alone do not cause high-level cross-resistance to any of the other nucleosides, allowing for the subsequent use of any of the other approved reverse transcriptase inhibitors. Two patterns of multi-drug resistance mutations, the first characterised by mutations in the HIV reverse transcriptase at codons 62, 75, 77, 116 and 151 and the second involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to zidovudine as well as to the other approved

NRTIs. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic

options. The likelihood of a gradual accumulation of mutations conferring resistance to the entire class of NRTI, upon virological failure with combination therapy including zidovudine and lamivudine, underscores the importance of early detection of virological failure. Delayed detection of virological failure may severely limit the options for second-line therapy. The combination of lamivudine and zidovudine has not been specifically investigated in HIV patients coinfecting with HBV.

5.2 Pharmacokinetic properties

Absorption of AVOCOMB The absorption characteristics of AVOCOMB have been determined after administration of a single 150mg/300mg tablet in healthy volunteers in the fasting state as follows: Pharmacokinetic variable Mean value ($\pm$ standard deviation %) Lamivudine Zidovudine Maximum concentration (C_{max})* 1554.6 ng/mL (34.1) 1623.0 (46.6) Area under the curve (AUC_{0- ∞}),* a measure of the extent of absorption (25.3) 5729.3 ng·hour/mL 2034.9 ng·hour/mL (46.9) Time to attain maximum concentration (t_{max}) † 1.226 hours (59.1) 0.868 hours (99.1) * geometric mean † arithmetic mean

Pharmacokinetics of Lamivudine and Zidovudine Lamivudine/Zidovudine 150mg/300mg tablets WHOPAR Part 4 November 2023 (Sun Pharmaceutical Industries Ltd†), HA286

Lamivudine Absorption Oral bioavailability 80–85% 60–70% Distribution Volume of distribution (mean) 1.3 L/kg 1.6 L/kg Plasma protein binding in vitro < 36% 34–38% Tissue distribution CSF/plasma ratio 0.12 CSF/plasma ratio 0.5 Metabolism Only minor route (5–10%) Glucuronidation Major metabolite: 5'-zidovudineglucuronide Active metabolite(s) None None Elimination Elimination half life 18–19 hours 1.1 hours [IV] 16–19 hours for intracellular 7 hours for intracellular zidovudine lamivudine triphosphate triphosphate Mean systemic clearance (Cl/F) 0.32 L/hour/kg 1.6 L/hour/kg % of dose excreted in urine > 70% (predominantly cleared > 50–80% unchanged) % of dose excreted in faeces NA* NA*

Pharmacokinetic linearity Linear pharmacokinetics NA* **Drug interactions** (in vitro) Transporters OCT (organic cationic transporters) Metabolising enzymes UGT-Uridine 5'-diphospho- – glucuronosyltransferase NA* = Information not available

Pharmacokinetics in pregnancy The pharmacokinetics of lamivudine and zidovudine during pregnancy were similar to that of non- pregnant women. Pharmacokinetics in children In children over the age of 5–6 months, the pharmacokinetic profile of

zidovudine is similar to that in adults. In general, lamivudine pharmacokinetics in paediatric patients are similar to adults

5.3 Preclinical safety data

General toxicity The clinically relevant effects of lamivudine and zidovudine in combination are anaemia, neutropenia and leucopenia. **Mutagenicity and carcinogenicity** Lamivudine and zidovudine were not mutagenic in bacterial tests but, like many nucleoside analogues, they inhibit cellular DNA replication in in vitro mammalian tests such as the mouse lymphoma assay. Lamivudine has not shown any genotoxic activity in in vivo studies at doses that produced plasma concentrations up to 40–50 times higher than clinical plasma levels. Zidovudine showed clastogenic effects in an oral repeated dose micronucleus test in mice. A transplacental genotoxicity study in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at exposures equivalent to those in humans. That study demonstrated that fetuses exposed in utero to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple fetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine

alone. The clinical significance of these findings is unknown.

Lamivudine/Zidovudine 150mg/300mg tablets WHOPAR Part 4 November 2023 (Sun Pharmaceutical Industries Ltd†), HA286 The carcinogenic potential of a combination of lamivudine and zidovudine has not been tested. In oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. In oral carcinogenicity studies with zidovudine in mice and rats, late-appearing vaginal epithelial tumours were

observed. The vaginal tumours were the result of long-term local exposure of the rodent vaginal epithelium

to high concentrations of unmetabolised zidovudine in urine. In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study zidovudine an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight) were seen. In a second study, mice were administered zidovudine at

doses up to 40 mg/kg for 24 months. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen. While the clinical relevance of these findings is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit. Reproductive toxicology Lamivudine has demonstrated evidence of increased early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in humans, but not in the rat even at very high systemic

exposure. Zidovudine had a similar effect in both species, but only at very high systemic exposures.

Lamivudine was not teratogenic in animal studies. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of fetal abnormalities was observed at lower doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: microcrystalline cellulose colloidal silicon dioxide sodium starch glycolate magnesium stearate Film-coating: propylene glycol hypromellose titanium dioxide This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30°C. Store in the original package protected from moisture.

6.5 Nature and contents of container

Tablets are available in the following packs:

HDPE bottle White opaque plastic (HDPE) bottle containing 60 tablets. The bottle has a round, opaque white plastic (polypropylene) child-resistant screw cap and an internal seal (liner). Lamivudine/Zidovudine 150mg/300mg tablets WHOPAR Part 4

November 2023 (Sun Pharmaceutical Industries Ltd†), HA286 Blisters Plastic (PA/PVC or PVC/PVdC) on aluminium foil blister cards each containing 6 tablets. Available in packs of 10x6 tablets

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

14479/R1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2026 August 31

10. DATE OF REVISION OF THE TEXT

2026 August 31