# WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

*This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities (term to be revised).*
*The medicine may be authorised for additional or different uses by national medicines regulatory authorities.*

# 1. NAME OF THE MEDICINAL PRODUCT

[HA521 trade name]*

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients see 6.1.

# 3. PHARMACEUTICAL FORM

White, film-coated, capsule shaped tablets debossed with 'H' and score line on one side and '2' on other side.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

[HA521 trade name] is indicated in combination with another antiretroviral agent for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing over 25 kg.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

For use of antiretroviral agents for post-exposure prophylaxis consult the most recent official guidelines, e.g. those of the WHO.

## 4.2 Posology and method of administration

Oral use.

Therapy should be initiated by a health care provider experienced in the management of HIV infection.

*Adults, adolescents and children (weighing at least 25 kg):*

The recommended dose of [HA521 trade name] is one tablet twice a day, approximately every 12 hours (see section 4.4).

*Children weighing less than 25 kg*

This product is not suitable for children weighing less than 25 kg because it cannot be given at the correct dose. For these patients, other formulations should be used, e.g. a tablet which contains a smaller amount of lamivudine and zidovudine.

[HA521 trade name] 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.

*Note*. Where discontinuation of one of the active substances of [HA521 trade name] is necessary, or the dose needs to be adjusted, lamivudine and zidovudine preparations can be given separately. They are available as tablets and oral solutions.

*Elderly*

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

*Renal impairment*

Since dose adjustment may be necessary in patients with renal impairment (creatinine clearance $\leq$ 50 ml/minute), it is recommended that separate preparations of lamivudine and zidovudine are used (see section 4.4).

* Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

*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 zidovudine doses may need to be adjusted, it is recommended that separate preparations of lamivudine and zidovudine are used in patients with severe hepatic impairment.

*Haematological adverse reactions*

Adjustment of zidovudine dosage may be necessary if the haemoglobin level falls below 9 g/dl or 5.59 mmol/litre or the neutrophil count falls below $1 \times 10^9$ /litre (see sections 4.3 and 4.4). As the dosage of [HA521 trade name] cannot be adjusted, separate preparations of zidovudine and lamivudine should be used.

*Missed dose*

If a dose is missed it should be taken as soon as it is noted. If the next dose is due in less than 6 hours, the forgotten dose should be skipped and the next regular dose taken when it is due. The patient should not take a double dose to make up for a missed dose.

## 4.3 Contraindications

[HA521 trade name] is contraindicated in patients with:

- Hypersensitivity to lamivudine, zidovudine or to any excipient in the formulation
- Abnormally low neutrophil count ($< 0.75 \times 10^9$/litre) (see section 4.4),
- Abnormally low haemoglobin (< 7.5 g/dl or 4.65 mmol/litre) (see section 4.4).

## 4.4 Special warnings and precautions for use

Concomitant use of stavudine with zidovudine should be avoided (see section 4.5).

*Dose adjustment*

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

*Opportunistic infections*

Patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by health care providers experienced in the treatment of HIV infection.

*Transmission of HIV*

Patients should be advised that antiretroviral therapy has not been proven to prevent the transmission of HIV through sexual contact or through contaminated blood. Precautions should continue to be taken to prevent transmission.

*Haematological adverse reactions*

Anaemia, neutropenia and leucopenia can occur in patients receiving zidovudine, especially in patients with advanced HIV disease (poor bone-marrow reserve) or with vitamin $B_{12}$ deficiency, and usually after at least 4–6 weeks of therapy.

Therefore, monitoring of haematological parameters is recommended in patients receiving [HA521 trade name], 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: e.g. 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 to clinically significant levels, separate preparations of lamivudine and (if appropriate) zidovudine should be used.

*Pancreatitis*

Treatment with [HA521 trade name] 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 a 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 medicinal products 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*

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 transitory. 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*

In HIV-infected patients with severe immune deficiency, typically in the first few weeks or months of initiating combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, *Pneumocystis jirovecii* pneumonia) may cause serious clinical conditions or aggravate symptoms. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

*Liver disease*

Caution should be exercised when administering [HA521 trade name] to 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 [HA521 trade name] 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.

The combination of lamivudine with cladribine is not recommended (see section 4.5).

## 4.5 Interaction with other medicinal products and other forms of interaction

As [HA521 trade name] contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur.

Whereas lamivudine undergoes limited metabolism and is almost completely eliminated via the kidneys, zidovudine is primarily eliminated by hepatic conjugation, to form an inactive glucuronide metabolite.

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 medicinal products metabolised by major P450 enzymes.

The following list of interactions is not exhaustive, but is representative of the classes of medicinal products where caution should be exercised.

| **Drugs** | **Interaction Geometric mean change (%) (Possible mechanism)** | **Recommendation concerning co-administration** |
|---|---|---|
| **Antiretrovirals** | | |
| Emtricitabine/Lamivudine | Overlapping resistance and lack of additive antiretroviral effects. | Emtricitabine should not be co-administered with [HA521 trade name]. |
| Stavudine/Zidovudine | *In vitro* antagonism of anti-HIV activity between stavudine and zidovudine could result in decreased efficacy of both drugs. | Stavudine should not be co-administered with [HA521 trade name]. |
| **Anti-infectives** | | |
| Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours) | Zidovudine AUC ↓12% | Administration of [HA521 trade name] and clarithromycin should be separated by at least 2 hours. |
| Rifampicin/Zidovudine (600 mg once daily/200 mg three times daily) | Zidovudine AUC ↓48%<br>(UGT induction) | Insufficient data to recommend dosage adjustment. |

| **Drugs** | **Interaction Geometric mean change (%) (Possible mechanism)** | **Recommendation concerning co-administration** |
|---|---|---|
| Trimethoprim + sulfamethoxazole/Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose) | Lamivudine: AUC ↑40%<br>Trimethoprim: AUC ↔<br>Sulfamethoxazole: AUC ↔<br>(Organic cation transporter inhibition) | No dosage adjustment of [HA521 trade name] is necessary, unless patient has renal impairment (section 4.2). When concomitant administration with trimethoprim + sulfamethaxazole is warranted, patients should be monitored clinically. High doses of trimethoprim + sulfamethoxazole for treating *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia and toxoplasmosis have not been studied and should be avoided. |
| **Antifungal** | | |
| Fluconazole/Zidovudine (400 mg once daily/200 mg three times daily) | Zidovudine AUC ↑74%<br>(UGT inhibition) | The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8). |
| **Antimalarial** | | |
| Atovaquone/Zidovudine (750 mg twice daily with food/200 mg three times daily) | Zidovudine AUC ↑33%<br>Atovaquone AUC ↔ | The clinical significance is not known. |
| **Anticonvulsants** | | |
| Phenobarbital/Zidovudine | Interaction not studied. Potential to slightly decrease zidovudine plasma concentrations through UGT induction. | Insufficient data to recommend dosage adjustment. |
| Phenytoin/Zidovudine | Phenytoin AUC ↑↓ | Monitor phenytoin concentration. |
| Valproic acid/Zidovudine (250 mg or 500 mg three times daily/100 mg three times daily) | Zidovudine AUC ↑80%<br>(UGT inhibition) | The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8). |
| **Cytotoxics** | | |
| Cladribine/Lamivudine | Interaction not studied<br>*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 (see section 4.4) |

| Drugs | Interaction<br>Geometric mean change (%)<br>(Possible mechanism) | Recommendation concerning co-administration |
|---|---|---|
| **Opioids** | | |
| Methadone/Zidovudine (30–90 mg once daily/200 mg every 4 hours) | Zidovudine AUC ↑43%<br>Methadone AUC ↔ | The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8). Methadone dosage adjustment may be required only occasionally. |
| **Uricosuric** | | |
| Probenecid/Zidovudine(500 mg four times daily/2 mg/kg three times daily) | Zidovudine AUC ↑106%<br>(UGT inhibition) | The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8). |
| **Miscellaneous** | | |
| Sorbitol solution (3.2g, 10.2g, 13.4g) /Lamivudine | Single dose lamivudine oral solution 300mg<br>Lamivudine:<br><br>AUC ↓ 14%; 32%; 36%<br>$C_{max}$ ↓ 28%; 52%: 55% | When possible, avoid chronic coadministration of [HA521 trade name] with medicinal products containing sorbitol or other osmotic acting poly-alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided |
| ↑ = Increase<br>↔ = no significant change<br>↓ = decrease | AUC = area under the concentration versus time curve<br>$C_{max}$ = maximum observed concentration | |

Ribavirin can exacerbate anaemia when zidovudine is also part of the regimen used to treat HIV. Therefore, concomitant use of ribavirin with [HA521 trade name] is not recommended (see section 4.4), particularly in patients with a history of zidovudine-induced anaemia.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, dapsone, pyrimethamine, trimethoprim + sulfamethoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) and zidovudine may increase the risk of adverse reactions. If concomitant therapy with [HA521 trade name] 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 breastfeeding

*Pregnancy*

No increased risk of birth defects has been reported for lamivudine or for zidovudine (www.apregistry.com), However, risks to the fetus cannot be ruled out.

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.

*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 before advising 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

No studies are available on the effects of [HA521 trade name] on the ability to drive and use machines. Nevertheless, the clinical status of the patient and the adverse reaction profile of [HA521 trade name] should be borne in mind when considering the patient's ability to drive or operate machinery.

### 4.8 Undesirable effects

As [HA521 trade name] 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 with concurrent administration of the two compounds.

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).

Adverse events considered to be at least possibly related to treatment with zidovudine and lamivudine, are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (1/100–1/10), uncommon (1/1000–1/100), rare (1/10 000–1/1000) or very rare (≤ 1/10 000). In addition, adverse events identified during post-approval use of lamivudine, zidovudine, and lamivudine/zidovudine as a fixed-dose combination are listed but their frequency cannot be estimated (frequency category: 'unknown').

**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

*Unknown*: Lipoatrophy, weight increase, hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia, (see section 4.4)

**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
*Rare*: Nail and skin pigmentation, urticaria, sweating, angioedema

**Musculoskeletal and connective tissue disorders**
*Common*: Arthralgia, myalgia
*Uncommon*: Myopathy
*Rare*: Rhabdomyolysis
*Unknown*: 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
*Unknown*: Immune reconstitution syndrome (see section 4.4)
See also sections 4.4 and 4.5

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

### 4.9 Overdose

There is limited experience of overdosage with lamivudine/zidovudine. No specific signs and symptoms have been identified following acute overdose with zidovudine or lamivudine 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. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

*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, 68% of subjects achieved plasma HIV RNA < 50 copies/ml 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 (> 300-fold reduced susceptibility). 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). The clinical relevance of these findings is not established. Indeed, available clinical data are very limited and preclude any reliable conclusion in the field. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should be considered only when the activity of the best available NRTI backbone is significantly compromised.

On virological failure, resistance to zidovudine is developed along two separate, though not mutually exclusive, pathways. The first of these include M41L, L210W and T215F/Y. The second includes D67N, K70R and K219E/Q. Collectively these mutations are termed 'thymidine analogue mutations' (TAM). In viruses with M184V, two to three TAMs are generally required for phenotypically detectable and clinically significant zidovudine resistance. M41L, L210W, and T215Y have a greater effect on zidovudine susceptibility and cross-resistance to other NRTIs than the other TAMs. Other important mutations selected for by zidovudine include T69 insertion mutations and the Q151M complex, where this mutation appears in combination with mutations at positions 75, 77, and 116. Both of these patterns confer high-level resistance to zidovudine and all other presently available NRTIs.

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 co-infected with HBV.

## 5.2 Pharmacokinetic properties

*Absorption of [HA521 trade name]*

As [HA521 trade name] met the WHO criteria for a BCS-based biowaiver a bioequivalence study was not conducted. Therefore, no pharmacokinetic data are available for this product.

Comparability between the WHO-accepted comparator product and [HA521 trade name] regarding the qualitative and quantitative composition of the formulations have been sufficiently proven.

Pharmacokinetics of Lamivudine and Zidovudine

| | **Lamivudine** | **Zidovudine** |
|---|---|---|
| **Absorption** | | |
| Oral bioavailability | 80-85% | 60-70% |
| **Distribution** | | |
| Volume of distribution (mean) | 1.3 L/kg | 1.6 L/kg |
| Plasma proteinbindingin vitro | < 36% | 34-38% |
| **Metabolism** | | |
| | Only minor route (< 10%) | Glucuronidation<br>Major metabolite: 5'-zidovudine-glucuronide |

| | **Lamivudine** | **Zidovudine** |
|---|---|---|
| Active metabolite(s) | None | None |
| **Elimination** | | |
| Elimination half life | 5–7 hours<br>22 hours for intracellular lamivudine triphosphate | 1.1 hours [IV]<br>7 hours [intracellular zidovudine triphosphate] |
| Mean systemic clearance (Cl/F) | 0.32 L/hour/kg | 0.34 L/hour/kg |
| % of dose excreted in urine | > 70% (Predominantly cleared unchanged) | > 50–80% |
| % 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

Neither lamivudine nor zidovudine is mutagenic in bacterial tests, but like many nucleoside analogues they show activity in mammalian in vitro 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.

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.

In reproductive toxicity studies lamivudine has demonstrated evidence of increasing early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in man, 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: Colloidal silicone dioxide
Magnesium stearate
Microcrystalline cellulose
Sodium starch glycolate

Film-coating: Hypromellose
Macrogol (polyethylene glycol)
Polysorbate 80
Titanium dioxide

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Do not store above 30°C. Tablets should be kept in a tightly closed container, protected from light.

## 6.5 Nature and contents of container

Round white HDPE bottle closed with continuous thread polypropylene cap.
Pack size: 60 tablets.

## 6.6 Instructions for use and handling and disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

# 7. SUPPLIER

Hetero Labs Limited
Unit III, #22-110, I.D.A., Jeedimetla
Qutubullapur Municipality
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## 8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA521

## 9. DATE OF PREQUALIFICATION

14 June 2013

## 10. DATE OF REVISION OF THE TEXT

November 2019

**References**

The main reference source for this text is the European SPC for Combivir, available at: http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000190/WC500032326.pdf (accessed on May 21, 2018)

Further references relevant to sections of the SPC include:

Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach - second edition 2016.
http://www.who.int/hiv/pub/arv/arv-2016/en/

**Section 4.4**
Gulick RM et al., N. Engl. J. Med. 2004; 350: 1850
Arenas-Pinto A et al., Sex Transm. Infect. 2003; 79: 340
Carr A., Clin Infect Dis 2003; 36 (Suppl.2): S96

**Section 4.5**
Squires KE et al., AIDS 2000; 14: 1591
Moore KH et al., Clin. Pharmacol. Ther. 1996; 59: 550
Van Leeuwen R et al. AIDS 1992; 6, 1471
D. D. Richman et al., N. Engl. J. Med. 1987; 317: 192
Hoggard PG et al. Antimicrob. Agents Chemother 1997; 41: 1231-6

**Section 4.6**
Alvarez D et al., J Viral Hepat 2006; 13: 63-9

**Section 4.8**
Shapiro RL. et al., J. Infect. Dis. 2005; 192: 720
Pluda JM et al., J. Infect. Dis. 1995; 171: 1438
J. Fellay J et al., Lancet 2001; 358: 1322
Richman DD et al., N. Engl. J. Med. 1987; 317: 192
Eron JJ Jr. et al., AIDS 2000; 14: 1601
Gallant JE et al., N. Engl. J. Med. 2006; 354: 251
European SPC Retrovir:
http://www.medicines.org.uk/EMC/medicine/10419/SPC/Retrovir+100+mg+10ml%2C+oral+solution/
Huynh TK et al., Scand. J. Infect. Dis. 2003; 35: 62
Imhof A et al., Clin. Infect. Dis. 2005; 41: 721
Mokrzycki MH et al., Clin. Infect. Dis. 2000; 30: 198
Johri S. et al., AIDS 2000; 14: 1286
Coghlan ME et al., Clin. Infect. Dis. 2001; 33: 1914
Fellay J et al., Lancet 2001; 358: 1322
Boubaker K et al., Clin. Infect. Dis. 2001; 33: 1931
Van Leeuwen R et al., J. Infect. Dis. 1995; 171: 1166

Eron JJ et al., N. Engl. J. Med. 1995; 333: 1662
Van Leeuwen R et al., AIDS 2003; 17: 987
European SPC Epivir: https://www.medicines.org.uk/EMC/medicine/744/SPC/Epivir+150+mg+film-coated+tablets/
Fong IW, Lancet 1994; 344: 1702

**Section 5.1**

*Clinical efficacy*

Gallant JE et al., N. Engl. J. Med. 2006; 354: 251
Staszewski S et al., N. Engl. J. Med. 1999; 341: 1865
Squires KE et al., AIDS 2000; 14: 1591
Eron JJ Jr. et al., AIDS 2000; 14: 1601
Staszewski S al., JAMA 2001; 285: 1155
Carr A et al, AIDS 2000; 14: 1171
Podzamczer D et al., Antivir. Ther. 2002; 7: 81
French M et al., HIV. Clin. Trials 2002; 3: 177
Robbins GK et al., N. Engl. J. Med. 2003; 349: 2293
Gathe J Jr. et al., J. Acquir. Immune. Defic. Syndr 2002; 31: 399
Shafer RW et al., N. Engl. J. Med. 2003; 349: 2304
DeJesus E et al., Clin. Infect. Dis. 2004 39: 1038
DeJesus E et al., Clin. Infect. Dis. 2004; 39: 411
Vibhagool A et al., Curr. Med. Res. Opin. 2004; 20: 1103
Squires KE et al., J. Acquir. Immune Defic. Syndr. 2004; 36: 1011
Paediatric European Network for Treatment of AIDS. Lancet 2002; 359:733

*Resistance*

Castagna A et al., AIDS 2006; 20: 795
The Stanford HIV drug resistance database. Available at https://hivdb.stanford.edu/
Sungkanuparph S, Clin Inf Dis. 2007; 44: 447

**Section 5.2**

Anderson PL, AIDS 2003; 17: 2159

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/.