NEW ZEALAND DATA SHEET

LAMIVUDINE VIATRIS

1. Product Name

LAMIVUDINE VIATRIS, 150 mg dose film-coated tablets.

2. Qualitative and Quantitative Composition

Each LAMIVUDINE VIATRIS 150 mg film-coated tablet contains 150 mg of lamivudine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

LAMIVUDINE VIATRIS 150 mg: A white to off-white film coated, capsule shaped biconvex tablet debossed with “M105” on one side of the tablet and a functional score on the other side.

4. Clinical Particulars

4.1 Therapeutic indications

Lamivudine in combination with other anti-retroviral agents is indicated for the treatment of HIV infected adults and children.

4.2 Dose and method of administration

LAMIVUDINE VIATRIS therapy should be initiated by a physician experienced in the management of HIV infection.

Dose

Adults, adolescents and children weighing at least 25 kg

The recommended dose of lamivudine is 300 mg daily. This may be administered as either 150 mg twice daily or 300 mg once daily.

Children weighing ≥ 20 kg to < 25 kg

The recommended total daily dose of lamivudine is 225 mg daily. This may be administered as, either 75 mg (one half of 150 mg tablet) in the morning and one whole 150 mg tablet in the evening, or 225 mg (one and a half 150 mg tablets) once daily.

Children weighing 14 kg to < 20 kg

The recommended total daily dose of lamivudine is 150 mg daily. This may be administered as, either 75 mg (one half of 150 mg tablet) twice daily, or one whole 150 mg tablet once daily.

For children weighing less than 14 kg requiring lower doses, the use of the oral solution is recommended.

Special populations

Elderly

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.

Renal impairment

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance (see section 5.2). The dosage should therefore be reduced for patients with a creatinine clearance of <50 mL/minute as shown in the table below.

There are no data available on the use of lamivudine in children with renal impairment.

The same percentage reduction in the adult dose is recommended for paediatric patients with renal impairment.

Dosing recommendations – adults, adolescents and children weighing at least 25 kg

Creatinine clearance (mL/min)	**First dose**	**Maintenance dose**
30 to <50	150 mg	150 mg once daily
<30	As doses below 150 mg are needed, the use of the oral solution is recommended	

Hepatic impairment

No dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment (see section 5.2).

Method of administration

LAMIVUDINE VIATRIS can be taken with or without food.

4.3 Contraindications

The use of LAMIVUDINE VIATRIS is contraindicated in patients with known hypersensitivity to lamivudine or to any ingredients listed in section 6.1.

4.4 Special warnings and precautions for use

LAMIVUDINE VIATRIS is not recommended for use as monotherapy.

Opportunistic infections

Patients receiving lamivudine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Renal impairment

Lamivudine plasma concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance. The dose should therefore be adjusted (see section 4.2).

Pancreatitis

Pancreatitis has been observed in some patients receiving lamivudine. However, it is unclear whether this was due to treatment with the medicinal product or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of lamivudine until diagnosis of pancreatitis is excluded.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including lamivudine. A majority of these cases have been in women. Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea). Caution should be exercised when administering lamivudine particularly to those with known risk factors for liver disease. Treatment with LAMIVUDINE VIATRIS should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Serum lipids and blood glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune reconstitution syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* (*P. carinii*) pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre 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 and sometimes can be an atypical presentation.

Patients co-infected with hepatitis B virus

Clinical trial and marketed use of lamivudine, have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If LAMIVUDINE VIATRIS is discontinued in a patient with HIV and HBV co-infection, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Special populations

Paediatric

Children who at any time received lamivudine oral solution concomitantly with other antiretroviral oral solutions in clinical trials experienced lower rates of virological suppression, had lower plasma lamivudine exposure and developed viral resistance more frequently than children receiving tablets.

An all-tablet antiretroviral regimen should be used when possible. Lamivudine oral solution given concomitantly with sorbitol-containing medicines should be used only when an all-tablet regimen cannot be used and the benefits of treatment outweigh possible risks including lower virological

suppression. Consider more frequent monitoring of HIV-1 viral load when lamivudine is used with chronically-administered, sorbitol containing medicines (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

The likelihood of interactions is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system for example trimethoprim. Other active substances (for example ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

Active substances shown to be predominantly excreted either via the active organic anionic pathway, or by glomerular filtration are unlikely to yield clinically significant interactions with lamivudine.

Effect of other agents on the pharmacokinetics of lamivudine

Lamivudine is a substrate of multidrug and toxin extrusion protein 1 (MATE1), MATE2-K and organic cation transporter 2 (OCT2) *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations, however this interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Lamivudine is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP), however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore, co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

Effect of lamivudine on the pharmacokinetics of other agents

In vitro, lamivudine demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, BCRP or Pgp, MATE1, MATE2-K or OCT3. Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 *in vitro* with IC_{50} values of 17 and 33 uM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg).

Interactions relevant to lamivudine

Co-administration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32% and 36% in lamivudine exposure (AUC_∞) and 28%, 52% and 55% in the C_{max} of lamivudine in adults. When possible, avoid use of lamivudine with sorbitol-containing medicines or consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided (see section 4.4).

A modest increase in C_{max} (28%) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine had no effect on the pharmacokinetics of lamivudine (see section 5.2).

Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2).

Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole for the treatment of *Pneumocystis jiroveci (P. carinii)* pneumonia and toxoplasmosis has not been studied.

Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed dose combinations.

4.6 Fertility, pregnancy and lactation

Pregnancy

Lamivudine has been evaluated in the Antiretroviral Pregnancy Registry in over 11,000 women during pregnancy and postpartum. The registry consists of over 4,200 exposures during the first trimester, over 6,900 exposures during the second/third trimester and includes 135 and 198 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.6, 3.7%) and in the second/third trimester, 2.8% (2.4, 3.2%). Among pregnant women in the reference population, the background rate of birth defects was 2.7%. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for lamivudine compared to the background rate. However, there are no adequate and well-controlled trials in pregnant women and the safe use of lamivudine in human pregnancy has not been established.

Studies in humans have confirmed that lamivudine crosses the placenta. Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies (see section 5.3) are not always predictive of human response, the findings in the rabbit suggest a potential risk of early embryonic loss.

There have been reports of mild, 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). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Breast-feeding

Health experts recommend that where possible women infected with HIV do not breast feed their infants in order to avoid the transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

In a study following repeat oral dose of either 150 mg lamivudine twice daily (given in combination with 300 mg zidovudine twice daily) or 300 mg lamivudine twice daily, lamivudine was excreted in human breast milk (0.5 to 8.2 micrograms/ml) at similar concentrations to those found in serum. In other studies following repeat oral dose of 150 mg lamivudine twice daily (given either in combination with 300 mg zidovudine or as zidovudine-containing fixed dose combinations) the maternal breast milk:plasma ratio ranged between 0.6 and 3.3. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/mL and were not detectable in one of the studies (assay sensitivity 7 ng/mL). Intracellular lamivudine triphosphate (active metabolite of lamivudine) levels in the breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compound measured is unknown.

Fertility

Studies in animals showed that lamivudine had no effect on fertility (section 5.3).

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of lamivudine on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of lamivudine. Nevertheless, the clinical status of the patient and the adverse event profile of lamivudine should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The following events have been reported during therapy for HIV disease with lamivudine alone and in combination with other anti-retroviral agents. With many it is unclear whether they are related to medicinal products or are as a result of the underlying disease process.

The following convention has been utilised for the classification of undesirable effects:

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000) very rare (<1/10,000).

Blood and lymphatic systems disorders

Uncommon: neutropenia, anaemia, thrombocytopenia.
Very rare: pure red cell aplasia.

Metabolism and nutrition disorders

Common: hyperlactataemia.
Rare: lactic acidosis (see section 4.4).

Nervous system disorders

Common: headache.
Very rare: paraesthesia. Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain.

Gastrointestinal disorders

Common: nausea, vomiting, upper abdominal pain, diarrhoea.
Rare: pancreatitis, although a causal relationship to treatment is uncertain. Rises in serum amylase.

Hepatobiliary disorders

Uncommon: transient rises in liver enzymes (AST, ALT).

Skin and subcutaneous tissue disorders

Common: rash, alopecia.

Musculoskeletal and connective tissue disorders

Common: arthralgia, muscle disorders.
Rare: rhabdomyolysis.

General disorders and administration site conditions

Common: fatigue, malaise, fever.

Paediatric population

The safety database to support lamivudine once daily dosing in paediatric patients comes from the ARROW Trial (COL105677) in which 669 HIV-1 infected paediatric subjects received abacavir and lamivudine either once or twice daily (see section 5.1). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

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 professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

No specific signs or symptoms have been identified following acute overdose with lamivudine, apart from those listed as undesirable effects.

If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside analogue, ATC code: J05AF05.

Mechanism of action

Lamivudine is a potent, selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. It is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine is metabolised intracellularly to the 5'-triphosphate, the active moiety, which has an intra-cellular half-life of 16-19 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependant activities of HIV reverse transcriptase, its main mode of action is as a chain terminator of HIV reverse transcription. No antagonistic effects *in vitro* were seen with lamivudine and other anti retrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine). Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*. Lamivudine therefore has, *in vitro*, a high therapeutic index.

Resistance

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine and zalcitabine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

Clinical efficacy and safety

In clinical trials, lamivudine in combination with zidovudine has been shown to reduce HIV-1 viral load and to increase CD_4 cell count. Clinical end-point data indicate that lamivudine in combination with zidovudine alone or in combination with zidovudine containing treatment regimens results in a significant reduction in the risk of disease progression and mortality.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy. Evidence from clinical studies show that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior anti-retroviral therapy.

Lamivudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (nucleoside reverse transcriptase inhibitors) or different classes (protease inhibitors, non-nucleoside reverse transcriptase inhibitors).

Multiple medicine antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naive patients as well as in patients presenting with viruses containing the M184V mutations.

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

Paediatric population

A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. The results are summarised in the table below:

Virological response based on plasma HIV-1 RNA less than 80 copies/mL at Week 48 and Week 96 in the once daily versus twice daily abacavir + lamivudine randomisation of ARROW (observed analysis)

	Twice Daily n/N (%)	Once Daily n/N (%)
Week 0 (After ≥ 36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/mL	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/mL	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/mL	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

The abacavir/lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200 c/mL, <400 c/mL, <1000 c/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex,

age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

At the time of randomisation to once daily vs twice daily dosing (Week 0), those patients who had received tablet formulations had a higher rate of viral load suppression than those who had received any solution formulations at any time. These differences were observed in each different age group studied. This difference in suppression rates between tablets and solutions remained through Week 96 with once daily dosing.

Proportions of subjects in the once daily versus twice daily abacavir + lamivudine randomisation of ARROW with plasma HIV-1 RNA <80 copies/mL: subgroup analysis by formulation

	Twice Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)	Once Daily Plasma HIV-1 RNA <80 c/mL: n/N (%)
Week 0 (after 36 weeks on Treatment)		
Any solution regimen at any time	14/26 (54)	15/30 (50)
All tablet based regimen throughout	236/305 (77)	222/305 (73)
Week 96		
Any solution regimen at any time	13/26 (50)	17/30 (57)
All tablet based regimen throughout	221/300 (74)	213/301 (71)

Genotypic resistance analyses were conducted on samples with plasma HIV-1 RNA >1000 copies/mL. More cases of resistance were detected among patients who had received lamivudine solution, in combination with other antiretroviral solutions, compared with those who received similar doses of tablet formulation. This is consistent with the lower rates of antiviral suppression observed in these patients.

Post-exposure prophylaxis (PEP)

Lamivudine can be used for PEP. Refer to internationally recognised guidelines such as the World Health Organisation *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* for the latest recommendations for PEP.

5.2 Pharmacokinetic properties

Absorption

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. At therapeutic dose levels i.e. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1-1.9 mcg/mL. Co-administration of lamivudine with food resulted in a delay of t_{max} and a lower C_{max} (decreased by up to 47%). However, the extent (based on the AUC) of lamivudine absorbed was not influenced. No dose adjustment is needed when co-administered with food.

Absorption differences have been observed between adult and paediatric populations.

Distribution

From intravenous studies, the mean volume of distribution is 1.3 L/kg. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding to albumin. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebro-spinal fluid (CSF). The mean lamivudine CSF/serum concentration ratio 2-4 hours after oral

administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Biotransformation

The plasma lamivudine half-life after oral dosing is (18 to 19 hours) and the active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours). In 60 healthy adult volunteers, lamivudine 300 mg once daily has been demonstrated to be pharmacokinetically equivalent at steady-state to lamivudine 150 mg twice daily with respect to intracellular AUC_{24} and C_{max}. The likelihood of adverse interactions between lamivudine and other medicinal products is low due to limited metabolism and plasma protein binding and almost complete renal elimination of unchanged lamivudine.

Elimination

Lamivudine mean systemic clearance is approximately 0.32 L/h/kg, with predominantly renal clearance (>70%) via the organic cationic transport system, and little (<10%) hepatic metabolism.

Special populations

Renal impairment

Lamivudine plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. The dosage should therefore be reduced for patients with a creatinine clearance of <50 mL/minute (see section 4.2).

Hepatic impairment

Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

Paediatric

The absolute bioavailability (approximately 58-66%) was reduced and more variable in paediatric patients below 12 years of age. In children, administration of tablets delivered higher plasma lamivudine AUC_{∞} and C_{max} than oral solution. Paediatric pharmacokinetic studies have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose.

Elderly

No pharmacokinetic data are available in patients over 65 years of age.

Pregnancy

The pharmacokinetics of lamivudine are similar to that of non-pregnant adults. In humans, consistent with passive transmission of lamivudine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

5.3 Preclinical safety data

Animal toxicology

Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. Reductions of erythrocyte and neutrophil counts were identified as the effects most likely to be of clinical relevance.

Mutagenicity

Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be

confirmed in *in vivo* tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

Carcinogenicity

The results of long term oral carcinogenicity studies with lamivudine in rats and mice did not show any carcinogenic potential.

Reproductive toxicology

Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. Lamivudine produced small increases in early embryonic loss when administered to pregnant rabbits, at exposure levels comparable to those achieved in man. However, there was no evidence of embryonic loss in rats at exposure levels of approximately 35 times the clinical exposure (based on C_{max}).

6. Pharmaceutical Particulars

6.1 List of excipients

LAMIVUDINE VIATRIS 150 mg film-coated tablets also contain:

- microcrystalline cellulose
- sodium starch glycollate
- magnesium stearate
- hypromellose
- titanium dioxide
- propylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

LAMIVUDINE VIATRIS 150 mg:
HDPE bottle with a child-resistant closure, pack-size of 60 film-coated tablets.
Blister pack, pack-size of 60 film-coated tablets.

Not all pack types may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
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AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

19 May 2011

10. Date of Revision of the Text

3 August 2023

Summary table of changes

Section	Summary of new information
4.9	Update to overdose signs and symptoms.
5.2	Update to lamivudine elimination half-life.