PROFESSIONAL INFORMATION FOR AEDATRI

SCHEDULING STATUS

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1 NAME OF THE MEDICINE

AEDATRI (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Lamivudine 300 mg.

Tenofovir disoproxil fumarate 300 mg.

Dolutegravir 50 mg (as dolutegravir sodium).

Contains sugar: mannitol 145 mg.

For full list of excipients, see **section 6.1**.

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE SECTION 4.4). AEDATRI IS NOT INDICATED FOR TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. THE SAFETY AND EFFICACY OF AEDATRI HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED

WITH HBV AND HIV AND HAVE DISCONTINUED THE COMBINATION TABLET. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE CO-INFECTED WITH HIV AND HBV AND WHO DISCONTINUED THE COMBINATION TABLET. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

3 PHARMACEUTICAL FORM

Blue coloured, capsule shaped, biconvex film-coated tablet, debossed with ‘C’ on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AEDATRI is indicated for the treatment of HIV-1 infection in adults aged 18 years and older.

4.2 Posology and method of administration

Posology

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Adults

The dose of AEDATRI is one tablet taken orally, once daily, without regard to food.

Paediatrics

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AEDATRI is not recommended for use in patients younger than 18 years of age.

Dose adjustment for renal impairment

Significantly increased exposure occurred when tenofovir, as in AEDATRI, was administered to patients with moderate to severe renal impairment (see **section 4.3**).

The pharmacokinetics of tenofovir, as in AEDATRI, have not been evaluated in non-haemodialysis patients with creatinine clearance < 50 mL/min; therefore, no dosing recommendations are available for these patients.

AEDATRI is not suitable for use in patients with renal impairment with creatinine clearance less than 50 mL/min.

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking AEDATRI.

Method of administration

AEDATRI tablets are to be taken orally, once daily, without regard to food.

4.3 Contraindications

- AEDATRI is contraindicated in patients with known hypersensitivity to dolutegravir, lamivudine, tenofovir disoproxil fumarate or any of the components of AEDATRI.
- Uncontrolled renal failure (see **section 4.4**).
- Pregnancy and lactation (see **section 4.6**).
- Women of child-bearing age not using highly effective contraception.
- Concomitant use with adefovir dipivoxil.

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- Co-administration with dofetilide and pilsicainide.
- Co-administration with didanosine.
- Co-administration with metformin.
- Patients younger than 18 years of age.
- Moderate and severe hepatic impairment.

4.4 Special warnings and precautions for use

Safety and efficacy of the individual active ingredients in various antiretroviral combination regimens with similar dosages as contained in AEDATRI have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed-drug combination as in AEDATRI for the treatment of HIV have not been established in clinical studies.

The complete patient information leaflets of the other medicines used in combination should be consulted before initiation of therapy.

Metabolic abnormalities

Combination antiretroviral therapy, including AEDATRI has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Lipodystrophy

Combination antiretroviral therapy, including AEDATRI, has also been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting and breast enlargement in HIV patients.

A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Fasting serum lipids and blood glucose levels should be monitored. Lipid disorders should be managed as clinically appropriate. Patients with evidence of lipodystrophy should also have a thorough cardiovascular risk assessment.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination anti-retroviral therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, atypical mycobacterial infections, cytomegalovirus retinitis, *pneumocystis jirovecii*, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued, and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease, Guillain-Barre syndrome, polymyositis) have also been reported as IRIS

reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART), including components of AEDATRI. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving AEDATRI may continue to develop opportunistic infections and other complications of HIV infection and therefore should remain under close clinical observation by doctors experienced in the treatment of patients with HIV associated diseases.

The risk of HIV transmission to others

Patients must be advised that treatment with AEDATRI has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis, usually associated with hepatic steatosis, including fatal cases, has been reported with the use of nucleoside analogues, such as in AEDATRI. Early

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symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure.

Lactic acidosis generally occurs after a few or several months of treatment. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.
In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and respond as follows:

- Lactate 2 to 5 mmol/L: monitor regularly and be alert for clinical signs.
- Lactate 5 to 10 mmol/L without symptoms: monitor closely.
- Lactate 5 to 10 mmol/L with symptoms: STOP all therapy. Exclude other causes (e.g., sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality in case studies).

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with a raised lactate level.

Lactic acidosis and sever hepatomegaly with steatosis, including fatal cases, have been reported with the use of AEDATRI alone or in combination, in the treatment of HIV infection. Most cases were women.
Caution should be exercised when administering AEDATRI to patients with known risk factors for liver disease.

Treatment with AEDATRI should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity. Caution should be exercised when administering nucleoside analogues as contained in AEDATRI to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicines and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk. Patients at increased risk should be followed closely. However, cases have also been reported in patients with no known risk factors.

Patients at increased risk should be followed closely.
There are no study results demonstrating the effect of AEDATRI on clinical progression of HIV-1.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues as contained in AEDATRI have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders

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(hyperlactataemia, hyperlipidaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsions, abnormal behaviour). Whether the neurological disorders are transient or permanent is unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

Pancreatitis

Pancreatitis has been observed in some patients receiving lamivudine, as in AEDATRI. It is unclear whether this is due to lamivudine or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of AEDATRI until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of AEDATRI is increased due to decreased clearance. The dose of AEDATRI should therefore be adjusted (see **section 4.2**).

Liver disease

Use of AEDATRI can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis).

The safety and efficacy of AEDATRI has not been established in patients with significant underlying liver disorders. Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function

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abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal impairment

AEDATRI is a combination medicine and the dose of the individual components cannot be altered. Tenofovir and lamivudine are principally eliminated by the kidney. AEDATRI is not recommended for patients with creatinine clearance < 50 mL/min or patients who require haemodialysis. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) has been reported with the use of tenofovir disoproxil fumarate in clinical practice. Careful monitoring of renal function (serum creatinine and serum phosphate) is therefore recommended before taking AEDATRI.

Renal function

Since AEDATRI is primarily eliminated by the kidneys, co-administration of AEDATRI with medicines that reduce renal function or compete for active tubular secretion, may increase serum concentrations of AEDATRI and/or increase the concentrations of other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, aciclovir, valaciclovir, ganciclovir and valganciclovir.

Renal safety with tenofovir has only been studied to a very limited degree in adult patients with impaired renal function (creatinine clearance < 80 mL/min).

Renal monitoring

It is recommended that renal function (creatinine clearance and serum phosphate) is assessed in all patients prior to initiating therapy with tenofovir disoproxil fumarate and that it is also monitored every four weeks during the first year of tenofovir disoproxil fumarate therapy, and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

Co-administration and risk of renal toxicity

Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicine (e.g., aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic medicines is unavoidable, renal function should be monitored weekly.

Tenofovir disoproxil fumarate has not been clinically evaluated in patients receiving medicines which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g., cidofovir, a known nephrotoxic medicine). These renal transport proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir. Consequently, the pharmacokinetics of these medicines, which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4, might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicines which are secreted by the same renal pathway is not recommended, but if such use is

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unavoidable, renal function should be monitored weekly.

AEDATRI should be avoided with concurrent or recent use of a nephrotoxic medicine. Patients at risk of, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic substances should be carefully monitored for changes in serum creatinine and phosphorus.

K65R mutation

AEDATRI should be avoided in antiretroviral experienced patients with HIV-1 harbouring the K65R mutation.

Bone mineral density

Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate as contained in AEDATRI. Decreases in bone mineral density of the hip are significantly greater. Clinically relevant bone fractures are reported. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia.

AEDATRI may cause a reduction in bone mineral density. The effects of tenofovir disoproxil fumarate-associated changes in bone mineral density on long-term bone health and future fracture risk are currently unknown.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation

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may be beneficial for all patients. If bone abnormalities are suspected, then appropriate consultation should be obtained. Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

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

AEDATRI is not indicated for the treatment of chronic HBV infection. The safety and efficacy of AEDATRI has not been established for the treatment of patients co-infected with HBV and HIV.

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines.

Patients with chronic hepatitis B or C treated with AEDATRI are at an increased risk for severe and potentially fatal hepatic adverse reactions. Doctors should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

Exacerbations of hepatitis

Flares on treatment:

Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy,

serum ALT may increase in some patients. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation:

Acute exacerbations of hepatitis have been reported in patients after the discontinuation of hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Hypersensitivity reactions

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir and were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Discontinue AEDATRI and other suspect medicines immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial

oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with AEDATRI or other suspect medicines after the onset of hypersensitivity may result in a life-threatening reaction.

Important identified risks

Depression (including suicidal ideation and behaviours, particularly in patients with pre-existing history of depression or psychiatric illness).

Use in elderly

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Excipients

AEDATRI contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicines and other forms of interaction

The likelihood of interactions is low due to the limited metabolism and plasma protein binding and almost complete renal clearance. Zidovudine plasma levels are not significantly altered when co-administered with lamivudine. Zidovudine has no effect on the pharmacokinetics of lamivudine. Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine. Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in

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lamivudine plasma levels. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole. The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route is renal.

No medicine interaction studies have been conducted using AEDATRI. As AEDATRI contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with these individual medicines may occur with AEDATRI. Important medicine interaction information for AEDATRI is summarised in Table 1, 2 and 3. The medicine interactions described are based on studies conducted with tenofovir disoproxil fumarate or lamivudine as individual medicines or are potential medicine interactions. While the tables include potentially significant interactions, they are not all inclusive. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450-mediated interactions involving tenofovir with other medicines is low.

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed.

Tenofovir

Renally eliminated medicines

Tenofovir, as in AEDATRI, is primarily excreted by the kidneys by a combination of

glomerular filtration and active tubular secretion. Co-administration of AEDATRI with medicines that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered medicines due to competition for this elimination pathway. Medicines that decrease renal function may also increase serum concentrations of tenofovir, as in AEDATRI.

Tenofovir has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives and ribavirin. Tables 1 and 2 summarise pharmacokinetic effects of co-administered medicine on tenofovir pharmacokinetics and effects of tenofovir on the pharmacokinetics of co-administered medicine.

When administered with multiple doses of tenofovir, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown.

When didanosine 250 mg enteric-coated capsules were administered with tenofovir, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 1 Medicine interactions: changes in pharmacokinetic parameters for tenofovir[1] in the presence of co-administered medicines

Co-administered medicine	Dose of co-administered medicine (mg)	N	% Change of tenofovir pharmacokinetic parameters[2] (90 % CI)

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			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↔	↔	NC
Adefovir dipivoxil	10 once	22	↔	↔	↔
Atazanavir	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	↔	↔	↔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	↔	↔	↔
Efavirenz	600 once daily x 14 days	29	↔	↔	↔
Emtricitabine	200 once daily x 7 days	17	↔	↔	↔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑33)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↔	↔	↔
Lopinavir/ ritonavir	400/100 twice daily x 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)

1. Patients received tenofovir disoproxil fumarate 300 mg once daily.
2. Increase = ↑; Decrease = ↓; No effect = ↔; NC = Not calculated.

Following multiple dosing to HIV-negative subjects receiving either chronic methadone

maintenance therapy, oral contraceptives, or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a lack of clinically significant medicine interactions between these medicines and tenofovir disoproxil fumarate.

Table 2 Medicine interactions: changes in pharmacokinetic parameters for co-administered medicines in the presence of tenofovir

Co-administered medicine	Dose of co-administered medicine (mg)	N	% Change of co-administered medicine pharmacokinetic parameters[1]		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 122 (↑ 1 to ↑ 26)	↔	NA
Adefovir dipivoxil	10 once	22	↔	↔	NA
Efavirenz	600 once daily x 14 days	30	↔	↔	↔
Emtricitabine	200 once daily x 7 days	17	↔	↔	↔
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 to ↑12)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓12)	↔	↔
Lopinavir/ ritonavir	400/100 twice daily x 14 days	21	↔	↔	↔

Methadone[2]	40 to 110 once daily x 14 days[3]	13	↔	↔	↔
Oral contraceptives[4]	Ethinyl oestradiol/ norgestimate Once daily x 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NA
Ritonavir	Lopinavir/ritonavir 400/100 twice daily x 14 days	24	↔	↔	↔
Atazanavir[5]	400 once daily x 14 days	29	↓ 21 (↓27 to ↓ 14)	↓ 25 (↓30 to ↓19)	↓ 40 (↓48 to ↓32)
Atazanavir[5]	Atazanavir/ritonavir 300/100 once daily x 42 days	10	↑ 28 (↑ 50 to ↑ 5)	↑ 25 (↑ 42 to ↑ 3)	↑ 23[6] (↑ 46 to ↑ 10)

1. Increase = ↑; Decrease = ↓; No effect = ↔; NA = Not applicable.
2. R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir as tenofovir disoproxil fumarate 300 mg.
3. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
4. Ethinyl oestradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir as tenofovir disoproxil fumarate 300 mg.
5. Reyataz US Prescribing Information (Bristol-Meyers Squibb).

6. In HIV-infected patients, addition of tenofovir disoproxil fumarate to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2,3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

Lamivudine

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

Zidovudine plasma levels are not significantly altered when co-administered with AEDATRI. Zidovudine has no effect on the pharmacokinetics of AEDATRI.

Table 3 Medicine interaction: changes in pharmacokinetic parameters for co-administered medicines in the presence of lamivudine

Co-administered medicine	**Dose of co-administered medicine (mg)**	**% Change of co-administered medicine pharmacokinetic parameters[1]**		
		C_{max}	**AUC**	**C_{min}**
Trimethoprim/ sulphametoxazole	160/800 mg	NS	↑ 40	NS
Zidovudine	150/300 twice daily	↑ 28	↑ 13	NS

1. Increase = ↑; NS = Not studied.

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and

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a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

AEDATRI may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. AEDATRI is therefore not recommended to be used in combination with zalcitabine.

Administration of trimethoprim, a constituent of co-trimoxazole causes an increase in AEDATRI plasma levels. Unless the patient has renal impairment, no dosage adjustment of AEDATRI is necessary. AEDATRI has no effect on the pharmacokinetics of co-trimoxazole.

The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route is renal.

The co-administration of AEDATRI with etravirine (ETR) is not recommended unless the patient is also receiving concomitant atazanavir + ritonavir (ATV + RTV), lopinavir + ritonavir (LPV + RTV) or darunavir + ritonavir (DRV + RTV).

Dolutegravir

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given with AEDATRI.

There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in AEDATRI.

Effects of AEDATRI on the pharmacokinetics of other medicines

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In vitro, dolutegravir demonstrated no direct, or weak inhibition of the enzymes cytochrome P450, uridine diphosphate glucuronosyl transferase or the transporters Pgp.

In vitro, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Therefore, dolutegravir in AEDATRI is not expected to affect the pharmacokinetics of medicines that are substrates of the these enzymes or transporters [i.e. reverse transcriptase and protease inhibitors, opioid analgesics, antidepressants, statins, azole antifungals (such as fluconazole, itraconazole, clotrimazole), proton pump inhibitors (such as esomeprazole, lansoprazole, omeprazole), anti-erectile dysfunction medicines (such as sildenafil, tadalafil, vardenafil), acyclovir, valaciclovir, sitagliptin, adefovir].

Dolutegravir as in AEDATRI does not have any clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro, dolutegravir inhibits the renal organic cation transporters 2 (OCT2). Based on this, AEDATRI may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin).

Effects of other medicines on the pharmacokinetics of dolutegravir as in AEDATRI

Dolutegravir as in AEDATRI is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp and BCRP; therefore, medicines that induce those enzymes may theoretically decrease

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dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir in AEDATRI.

Co-administration of AEDATRI and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration.

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduces the plasma concentrations of dolutegravir significantly and requires dolutegravir dose adjustment of 50 mg twice daily. Etravirine also reduces plasma concentrations, but the effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir. Therefore, no dose adjustment is necessary when co-administered with etravirine. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment. Caution is warranted, and clinical monitoring is recommended when these combinations are given in INI-resistant patients. A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no dose adjustment of dolutegravir is required when co-administered with these medicines.

Table 4 Dolutegravir medicine interactions

Concomitant medicine class: medicine name	**Effect on concentration of dolutegravir or concomitant medicine**			
	Dolutegravir/	**AUC**	**C_{max}**	**C_T**

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	concomitant medicine			
HIV-1 Antiviral medicines				
Non-nucleoside reverse transcriptase inhibitor: etravirine (ETR)	Dolutegravir ↑ ETR ↔	↓ 71 %	↓ 52 %	↓ 75 %
Non-nucleoside reverse transcriptase inhibitor: efavirenz (EFV)	Dolutegravir ↓ EFV ↔	↓ 57 %	↓ 39 %	↓ 75 %
Non-nucleoside reverse transcriptase inhibitor: nevirapine	Dolutegravir ↓	NS	NS	NS
Protease inhibitor: atazanavir (ATV)	Dolutegravir ↑ ATV ↔	↑ 91 %	↑ 49 %	↑ 180 %
Protease inhibitor: atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ ATV ↔ RTV ↔	↑ 62 %	↑ 33 %	↑ 121 %
Protease inhibitor: tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ TPV ↔ RTV ↔	↓ 59 %	↓ 47 %	↓ 76 %
Protease inhibitor: fosamprenavir/ritonavir (FPV + RTV)	Dolutegravir ↓ FPV ↔ RTV ↔	↓ 35 %	↓ 24 %	↓ 49 %
Protease inhibitor: nelfinavir	Dolutegravir ↔	NS	NS	NS
Protease inhibitor: lopinavir/ritonavir	Dolutegravir ↔ LPV ↔	↔	↔	↔

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(LPV + RTV)	RTV ↔			
Protease inhibitor: darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ DRV ↔ RTV ↔	↓ 32 %	↓ 11 %	↓ 38 %
Nucleoside reverse transcriptase inhibitor: tenofovir (TDV)	Dolutegravir ↔ TDV ↔	NA	NA	NA
Protease inhibitor: lopinavir/ritonavir + etravirine (LPV/RTV + ETR)	Dolutegravir ↔ LPV ↔ RTV ↔ ETR ↔	↑ 10 %	↑ 7 %	↑ 28 %
Other medicines				
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	NS	NS	NS
Oxcarbazepine Phenytoin Phenobarbitone Carbamazepine St. John's Wort	Dolutegravir ↓	NS	NS	NS
Antacids containing polyvalent cations (e.g., Mg, Al, or Ca)	Dolutegravir ↓	↓ 74 %	↓ 72 %	↓ 74 %
Calcium supplements	Dolutegravir ↓	↓ 39 %	↓ 37 %	↓ 39 %
Iron supplements	Dolutegravir ↓	↓ 54 %	↓ 57 %	↓ 56 %
Metformin	Metformin ↑	N/A	N/A	N/A
Rifampicin	Dolutegravir ↓	↓ 54 %	↓ 43 %	↓ 72 %
Oral contraceptives (ethinyl	EE ↔	↑ 3 %	↓ 1%	↑ 2%

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estradiol (EE) and norgestromin (NGMN))	NGMN ↔	↓ 2%	↓ 11 %	↓ 7 %
Methadone	Methadone ↔	↓ 2 %	↔ 0 %	↓ 1 %

Abbreviations: ↑ = Increase; ↓ = Decrease; ↔ = No significant change; NA = Not applicable; NS = Not studied.

Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter. Dofetilide or pilsicainide co-administration with AEDATRI is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentrations (see **section 4.3**).

Co-administration of antacids containing polyvalent cations (e.g., Mg, Al, Fe or Ca) decreases dolutegravir plasma concentration.

AEDATRI should not be co-administered with polyvalent cation-containing antacids. AEDATRI is recommended to be administered 2 hours before or 6 hours after these medicines (see **section 4.5**).

Metformin concentrations may be increased by AEDATRI. Metformin is contraindicated in patients taking AEDATRI (see **section 4.3**).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (see below), including consideration of using effective contraceptive measures.

Perform pregnancy testing before initiation of AEDATRI in women of childbearing potential to exclude inadvertent (unintentional) use of AEDATRI during the first trimester of pregnancy.

If a woman plans pregnancy, the benefits and risks of starting or continuing treatment with dolutegravir versus using another antiretroviral regimen should be discussed with her.

Pregnancy

AEDATRI is contraindicated in pregnancy (see **section 4.3**).

Use of dolutegravir during pregnancy was associated with a small increase in the prevalence of neural tube defects (0,19 %) compared to non-dolutegravir regimens (0,11 %). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period).

Dolutegravir was shown to cross the placenta in humans, leading to significant exposure to the foetus, but the implications of such exposure are not yet known.

Tenofovir, dolutegravir and lamivudine were shown to cross the placenta in reproductive toxicity studies in animals. Late onset neurological disorders, including seizures, have been observed in children who have been exposed to nucleoside analogues such as tenofovir and lamivudine (see **section 4.4**).

AEDATRI should not be prescribed in women who plan to become pregnant. Women

of child-bearing age should not use AEDATRI unless they are reliably using highly effective contraception. Treatment with AEDATRI should not be initiated without a medically supervised negative pregnancy test. This test should be repeated at frequent intervals during treatment with AEDATRI; and especially in the event that pregnancy is suspected.

Breastfeeding

AEDATRI is contraindicated in lactation (see **section 4.3**).

HIV infected mothers should not breastfeed their infants in order to avoid transmission of HIV or follow appropriate guidelines.

Mothers breastfeeding their infants should not use AEDATRI. Lamivudine is excreted in human milk at similar concentrations to those found in serum; tenofovir is excreted in breast milk. Dolutegravir is excreted in human breast milk, and there is significant exposure to the neonate/infant due to slow elimination; the half-life of dolutegravir in the newborn was 33 hr compared to 14 hr in adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

Fertility

There are no data on the effects of dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility.

4.7 Effects on ability to drive and use machines

AEDATRI causes dizziness, impaired concentration and/or drowsiness and may affect the ability to drive and use machines.

Patients should ensure that they do not engage in driving or using machines until they know how AEDATRI affects them.

4.8 Undesirable effects

a. Summary of the safety profile

Studies revealed the most severe adverse reactions linked to dolutegravir treatment are hypersensitivity reactions that include rash and severe liver effects. The most common adverse reactions of dolutegravir are nausea (13 %), diarrhoea (18 %) and headache (13 %).

Renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported rarely in patients receiving tenofovir disoproxil. Monitoring of renal function is recommended for patients receiving AEDATRI (see **section 4.4**).

b. Tabulated list of adverse reactions

Table 5 Adverse effects for AEDATRI

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MedDRA system organ class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Neutropenia, anaemia, thrombocytopenia, pure red cell aplasia.
Immune system disorders	Less frequent	Hypersensitivity, immune reactivation syndrome.
Metabolism and nutrition disorders	Frequent	Hypophosphatemia.
	Less frequent	Lactic acidosis.
	Frequency unknown	Hypokalaemia.
Psychiatric disorders	Frequent	Insomnia, abnormal dreams, depression, anxiety.
	Less frequent	Suicidal ideation or suicide attempt.
Nervous system disorders	Frequent	Headache, dizziness.
	Less frequent	Peripheral neuropathy, paraesthesia.
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, nasal symptoms.
	Less frequent	Dyspnoea.
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort.
	Less frequent	Pancreatitis, elevated serum amylases.
Hepato-biliary disorders	Less frequent	Hepatitis.
	Frequency unknown	Hepatic steatosis.
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, hair loss.
Musculoskeletal, connective	Less frequent	Arthralgia, myalgia.

tissue and bone disorders	Frequency unknown	Rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, osteonecrosis.
Renal and urinary disorders	Less frequent	Rare acute renal failure, renal failure, proximal renal tubulopathy (including Fanconi syndrome), increased serum creatinine, acute tubular necrosis.
	Frequency unknown	Nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.
General disorders and administrative site conditions	Frequent	Fatigue, malaise, fever.
	Less frequent	Asthenia.
	Frequency unknown	Immune reconstitution syndrome.
Investigations	Frequent	Raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST), raised creatinine kinase.

Table 6 Adverse effects for dolutegravir

MedDRA system organ class	Frequency	Side effects
Immune system disorders	Less frequent	Hypersensitivity, immune reconstitution syndrome.
Psychiatric disorders	Frequent	Insomnia.
Nervous system disorders	Frequent	Headache, dizziness, abnormal dreams.
Gastrointestinal disorders	Frequent	Nausea, diarrhoea.
	Less frequent	Vomiting, flatulence, upper abdominal pain.
	Frequency unknown	Abdominal pain, abdominal discomfort.
Hepato-biliary disorders	Frequency unknown	Hepatitis.
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus.

Table 7 Adverse effects for lamivudine

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MedDRA system organ class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Neutropenia, anaemia, thrombocytopenia.
	Frequency unknown	Pure red cell aplasia.
Metabolism and nutrition disorders	Frequent	Hyperlactataemia.
	Less frequent	Lactic acidosis, lipodystrophy.
Nervous system disorders	Frequent	Headache, insomnia.
	Less frequent	Peripheral neuropathy (or paraesthesia), late onset neurological disorders in children exposed *in utero.*
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, vomiting, upper abdominal pain or cramps, stomatitis.
	Less frequent	Pancreatitis, elevation in serum amylase.
Hepato-biliary disorders	Less frequent	Transient rises in liver enzymes (AST, ALT).
Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia.
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia, muscle disorders.
	Less frequent	Rhabdomyolysis, decrease in bone mineral density, osteopenia, fractures.
General disorders and administrative site conditions	Frequent	Fatigue, malaise, fever.

Table 8 Adverse effects for tenofovir disoproxil fumarate

MedDRA system organ class	**Frequency**	**Side effects**
Immune system disorders	Less frequent	Allergic reaction.
Metabolism and nutrition disorders	Frequency unknown	Hypophosphataemia, lactic acidosis.
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea.
Gastrointestinal disorders	Frequent	Abdominal pain, anorexia, dyspepsia, flatulence.
	Less frequent	Increased amylase, pancreatitis.
Hepato-biliary disorders	Less frequent	Increased liver enzymes, hepatitis.
Musculoskeletal and connective tissue disorders	Frequency unknown	Decreased bone mineral density (see **section 4.4**)
Renal and urinary disorders	Frequent	Renal insufficiency, renal failure, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus.

c. Description of selected adverse reactions

Changes in serum creatinine

Serum creatinine can increase in the first week of treatment with dolutegravir and then remain stable. A mean change from baseline of 10 µmol/L occurred after 48 weeks of treatment. Creatinine increases were comparable between various background

regimens. These changes are not considered clinically relevant since they do not reflect a change in glomerular filtration rate.

Immune reactivation syndrome

In HIV patients with severe immune deficiency at the start of combination antiretroviral therapy (cART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the time to onset is more variable and these events can occur many months after starting treatment (see **section 4.4**).

Renal impairment

As lamivudine and tenofovir disoproxil may cause renal damage, monitoring of renal function is recommended (see **section 4.4**). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medicines) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see **section 4.4**).

Renal tubulopathy

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not likely

to be causally associated with tenofovir disoproxil therapy in the absence of proximal renal tubulopathy.

Interaction with didanosine

Co-administration of tenofovir disoproxil and didanosine is not recommended as it results in a 40 to 60 % increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see **section 4.5**). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see **section 4.4**).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to cART. The frequency of this is unknown (see **section 4.4**).

Co-infection with hepatitis B or C

When taking dolutegravir, as contained in AEDATRI, the rates of AST and ALT abnormalities may be higher in patients with hepatitis B or C co-infection. Liver enzyme elevations consistent with immune reactivation syndrome may occur in some subjects with hepatitis B or C co-infection at the start of AEDATRI therapy, particularly in those whose hepatitis B therapy was stopped. The side effect profile in patients also infected with hepatitis B or C or both are similar to that of patients without hepatitis, provided

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that the baseline liver function tests do not exceed 5 times the upper limit of normal.

Limited data on patients co-infected with HIV/HBV or HIV/HCV indicate that the adverse reaction profile of emtricitabine and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection.

However, as would be expected, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis may occur after discontinuation of treatment (see **section 4.4**).

Other special populations

Elderly

Caution should be exercised since elderly patients are more likely to have decreased renal function.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “Med Safety APP” (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Cipla Medpro (Pty) Ltd., by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Dolutegravir

Management should be as clinically indicated or as recommended by the national poisons centre, where available.

There is no specific treatment for an overdose of AEDATRI. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As AEDATRI is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Lamivudine

Limited data are available on the consequences of ingestion of acute overdose in humans.

If overdosage occurs the patient should be monitored, and palliative supportive treatment applied as required.

Tenofovir disoproxil fumarate

If overdose occurs the patient must be monitored for evidence of toxicity and palliative supportive treatment be applied as necessary.

Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 mL/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 20.2.8 – Antiviral medicine.

Pharmacotherapeutic group: Direct acting antivirals, Antivirals for treatment of HIV infections, combinations.

ATC code: J05AR12

Dolutegravir

Dolutegravir inhibits HIV integrase by binding to the integrase active sites and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. *In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex ($t_{1/2}$ 71 hours).

Resistance in vitro

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir have not been observed during HIV-1 passage. During wild type HIV-1 passage in the presence of dolutegravir integrase substitution observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wild type subtype B, C and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

Anti-HIV activity against resistant strains: Reverse transcriptase inhibitor- and protease inhibitor-resistant strains: Dolutegravir demonstrated equivalent potency against 2 non-nucleoside (NN)-RTI-resistant, 3 nucleoside (N)-RTI-resistant and 2 PI-resistant HIV-1 mutant clones (1 triple and 1 sextuple) compared to the wild type strain.

Integrase inhibitor-resistant HIV-1 strains: Dolutegravir showed anti-HIV activity (susceptibility) with FC < 5 against 27 of 28 integrase inhibitor-resistant mutant viruses with single substitutions including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, and N155H.

Integrase inhibitor-resistant HIV-2 strains: Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with raltegravir who showed virologic failure. Overall, the HIV-2 FCs observed were similar to HIV-1 FCs observed for similar pathway mutations.

Resistance in vivo: integrase inhibitor naïve patients: No integrase inhibitor (INI) resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment-naïve studies.

Effects on renal function: The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated. A small decrease of 10 – 14 % in mean serum creatinine clearance (CrCl) was observed with dolutegravir within the first week of treatment. Dolutegravir has no significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). *In vitro* studies suggest that the increases in creatinine observed in clinical studies are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Lamivudine

Lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI), is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro.*

Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an intracellular half-life of 16 – 19 hours.

Lamivudine 5'-triphosphate is a weak inhibitor of the RNA- and DNA-dependent activities of HIV reverse transcriptase, its mode of action is a chain terminator of HIV reverse transcription.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy.

Lamivudine-resistant HIV-1 mutants are cross-resistant to didanosine and zalcitabine. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

Tenofovir

Tenofovir disoproxil fumarate, is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate and is converted *in vivo* to tenofovir. It is a nucleoside reverse transcriptase inhibitor.

Tenofovir is phosphorylated by cellular enzymes to form tenofovir diphosphate.

Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into

DNA, by chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase ɣ.

Medicine resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro* and a K65R mutation in reverse transcriptase have been selected *in vitro* and, in some patients, treated with tenofovir in combination with certain antiretroviral medicines. In treatment-naïve patients treated with tenofovir + lamivudine + efavirenz, viral isolates from 17 % of patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-experienced patients, some of the tenofovir-treated patients with virologic failure through week 96 showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

Cross-resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognised. The K65R mutation can also be selected by abacavir, didanosine, or zalcitabine and results in reduced susceptibility to these medicines plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil fumarate should be avoided in antiretroviral-experienced patients with strains harbouring the K65R mutation. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate.

Antiviral activity

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-

1 has been assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50 % inhibitory concentration) values for tenofovir were in the range of 0,04 µM – 8,5 µM. In medicine combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0,5 µM to 2,2 µM). The IC_{50} values of tenofovir against HIV-2 ranged from 1,6 µM to 4,9 µM.

5.2 Pharmacokinetic properties

Dolutegravir

Dolutegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. In Phase 1 studies in healthy subjects, between-subjects CVb % for AUC and C_{max} ranged from ~ 20 to 40 % and C_T from 30 to 56 % across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw %) is lower than between-subject variability.

Absorption

Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours post-dose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and $C_{24\ h}$ ranging from 1,2 to 1,5.

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegravir is a P-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established.

Dolutegravir may be administered with or without food. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate and high fat meals increased dolutegravir AUC $_{(0-\infty)}$ by 33 %, 41 % and 66 %, increased C_{max} by 46 %, 52 % and 67 % and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.

Distribution

Dolutegravir is highly bound (greater than or equal to 98,9 %) to human plasma proteins based on *in vivo* data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50 mg once-daily administration is estimated at 17,4 L based on a population pharmacokinetic analysis. Binding of dolutegravir to plasma proteins is independent of concentration. Total blood and plasma medicine-related radioactivity concentration ratios averaged between 0,441 to 0,535 indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy subjects with moderate hepatic impairment, and 0,8 to 1,0 % in subjects with severe renal impairment and 0,5 % in HIV-1 infected patients. Dolutegravir is present in cerebrospinal fluid (CSF). In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13,2 ng per mL (range: 3,74 ng per mL to 18,3 ng per mL) 2 to 6 hours post-dose after 16 weeks of treatment. The clinical relevance of this finding

has not been established.

Metabolism

Dolutegravir is primarily metabolised via UGT1A1 with some contribution from CYP3A. Dolutegravir is the predominant circulating compound in plasma. After a single oral dose of [^{14}C] dolutegravir, 53 % of the total oral dose was excreted unchanged in faeces. It is unknown if all or part of this is due to unabsorbed medicine or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose). Renal elimination of unchanged drug was low (less than 1 % of the dose).

Elimination

Dolutegravir has a terminal half-life of ~14 hours and an apparent oral clearance (Cl/F) of 1,0 L per hour based on population pharmacokinetic analyses.

Special populations

Adolescents

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to 18 years of age) showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure comparable to that observed in adults who receive dolutegravir 50 mg once daily.

Table 9: Adolescent pharmacokinetic parameters

Age/weight	Dolutegravir dose	Dolutegravir pharmacokinetic parameter estimates geometric mean (CV %)		
		$AUC_{(0-24)}$ µg.hr/mL	C_{max} µg/mL	C_{24} µg/mL
12 to < 18 years ≥ 40 kg[a]	50 mg once daily[a]	46 (43)	3,49 (38)	0,90 (59)

[a]One subject weighing 37 kg received 35 mg once daily.

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed there is no clinically relevant effect of age on dolutegravir exposure. Pharmacokinetic data for dolutegravir in subjects of > 65 years old are limited.

Renal impairment

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CrCl < 30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCl < 30 mL/min) and matching healthy subjects were observed. AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40 %, 23 % and 43 % respectively, compared with those in matched healthy subjects. No dosage adjustment is necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B score 7 to 9) to

8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in metabolising enzymes

There is no evidence that common polymorphisms in metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32 % lower clearance of dolutegravir and 46 % higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41). Polymorphisms in CYP3A4, CYP3A5 and NR1I2 are not associated with differences in the pharmacokinetics of dolutegravir.

Co-infection with hepatitis B or C

Population pharmacokinetic analysis indicate that hepatitis C virus co-infection has no clinically relevant effect on the exposure to dolutegravir. There are limited data on patients with hepatitis B co-infection.

Lamivudine

Absorption

Following oral administration, lamivudine is rapidly absorbed and extensively distributed. Absolute bioavailability in 12 adult subjects was 86 % ± 16 % (mean ± SD) for the 150 mg tablet and 87 % ± 13 % for the oral solution. After oral administration of

2 mg per kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (C_{max}) was 1,5 ± 0,5 µg per mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0,25 to 10 mg per kg. The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1,50 following 15 days of oral administration of 2 mg per kg twice daily.

The mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour.

Effects of food on oral absorption

Lamivudine tablets and oral solution may be administered with or without food. An investigational 25 mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-1-infected subjects on 2 occasions, once in the fasted state and once with food (1099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate).

Absorption of lamivudine was slower in the fed state (T_{max}: 3,2 ± 1,3 hours) compared with the fasted state (T_{max}: 0,9 ± 0,3 hours); C_{max} in the fed state was 40 % ± 23 % (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC_{∞}) in the fed and fasted states.

Distribution

The apparent volume of distribution after IV administration of lamivudine to 20 subjects was 1,3 ± 0,4 L per kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (less than 36 %). *In vitro* studies showed that over the concentration range of 0,1 to 100 µg per mL, the amount of

lamivudine associated with erythrocytes ranged from 53 % to 57 % and was independent of concentration.

Metabolism

Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite (approximately 5 % of an oral dose after 12 hours). Serum concentrations of this metabolite have not been determined. Lamivudine is not significantly metabolised by CYP450 enzymes.

Elimination

The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300 mg oral dose of lamivudine, renal clearance was 199,7 ± 56,9 mL per min (mean ± SD). In 20 HIV-1-infected subjects given a single IV dose, renal clearance was 280,4 ± 75,2 mL per min (mean ± SD), representing 71 % ± 16 % (mean ± SD) of total clearance of lamivudine.

In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398,5 ± 69,1 mL per min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0,25 to 10 mg per kg.

No dose adjustment is needed when co-administered with food as lamivudine bioavailability is not altered, although a delay in T_{max} and reduction in C_{max} have been observed. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose

range and displays limited binding to the major plasma protein albumin.

Lamivudine elimination will be affected by renal impairment.

Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary. The likelihood of adverse medicine interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patients also have renal impairment. Administration of co-trimoxazole with the 3TC/zidovudine combination in patients with renal impairment should be carefully assessed. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2 – 4 hours after oral administration is approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Special populations

Pharmacokinetics in children

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55 – 65 %) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age approaching adult values around 12 years of age. Recent findings indicate that exposure in children 2 to < 6 years of age may be reduced by about 30 % compared with other pharmacokinetic data for

patients < 3 months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely due to immature renal function and variable absorption.

Pharmacokinetics in pregnancy

Following oral administration, lamivudine pharmacokinetics in late pregnancy were similar to non-pregnant adults. Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia. Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenic assay.

Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 30 – 40 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. There is as yet no information on the tumorigenic risk in animals, and therefore any potential risk to humans must be balanced against the expected benefits of treatment.

Tenofovir disoproxil fumarate

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25 %. Following oral administration of a single 300 mg dose of tenofovir disoproxil fumarate to HIV-1 infected subjects in the fasted state, maximum serum concentrations (C_{max}) were achieved in 1,0 ± 0,4 hrs (mean ± SD), and C_{max} and AUC values are 0,30 ± 0,09 µg/mL and 2,29 ± 0,69 µg•hr/mL, respectively. The pharmacokinetics of tenofovir are dose proportional over a dose range of 75 to 600 mg and are not affected by repeated dosing.

In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 113,4 g apple sauce) in healthy adult volunteers, the mean C_{max} of tenofovir was 26 % lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was similar between the oral powder and tablet formulations.

Effects of food on oral absorption

Administration of tenofovir following a high-fat meal (~700 to 1000 kcal containing 40 % to 50 % fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40 % and an increase in C_{max} of approximately 14 %. However, administration of tenofovir with a light meal does not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the medicine. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 0,33 ± 0,12 µg/mL and 3,32 ± 1,37 µg•hr/mL following multiple doses of tenofovir disoproxil 300 mg once daily in the fed state, when meal content was not controlled.

Distribution

In vitro binding of tenofovir to human plasma proteins is less than 0,7 % and 7,2 %, respectively over the tenofovir concentration range of 0,01 – 25 µg/mL.

The volume of distribution at steady-state is 1,3 ± 0,6 L/kg and 1,2 ± 0,4 L/kg, following intravenous administration of tenofovir 1,0 mg/kg and 3,0 mg/kg.

Metabolism

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes. Following IV administration of tenofovir, approximately 70 – 80 % of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir 300 mg once daily (under fed conditions), 32 ± 10 % of the administered dose is recovered in urine over 24 hours.

Elimination

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special populations

Paediatrics and the elderly

Pharmacokinetic studies have not been performed in children (< 18 years) or in the elderly (> 65 years).

Hepatic impairment

Tenofovir pharmacokinetics after a 300 mg single dose have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. Change in tenofovir dosing is not required in patients with hepatic impairment.

Renal impairment

Tenofovir pharmacokinetics are altered in patients with renal impairment. In patients with creatinine clearance < 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} and $AUC_{0-\infty}$ of tenofovir were increased. It is recommended that the dosing interval for tenofovir be modified in patients with creatinine clearance < 50 mL/min or in patients with ESRD who require dialysis (see **section 4.2**). Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a four-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium

Magnesium stearate

Mannitol

Microcrystalline cellulose

Insta Moist shield Aqua II A22G21202 (containing polyvinyl alcohol, triacetin, talc, sodium lauryl sulfate, titanium dioxide, FD&C Blue no. 2 aluminium lake, FD&C Blue no. 1 aluminium lake)

Povidone

Sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the container tightly closed.

Keep in the original container until required for use.

6.5 Nature and contents of container

Containers of 28’s:	AEDATRI is packed in a 85 cc white HDPE bottle with 38 mm non-child resistant cap containing 28 tablets and two 2 g silica gel bags.
Containers of 30’s:	AEDATRI is packed in a 85 cc white HDPE bottle with 38 mm non-child resistant cap containing 30 tablets and two 2 g silica gel bags.
Containers of 84’s:	AEDATRI is packed in a 200 cc white HDPE bottle with 45 mm screw cap containing 84 tablets and five 2 g silica gel bags.
Containers of 90’s:	AEDATRI is packed in a 200 cc white HDPE bottle with 45

mm screw cap containing 90 tablets and five 2 g silica gel bags.

Not all pack sizes may be marketed.

7 HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO MANUFACTURING (PTY) LTD.

1474 South Coast Road

Mobeni

Durban

4052

Customer Care: 080 222 6662

8 REGISTRATION NUMBER

52/20.2.8/0450

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 August 2018

Renewal: 03 August 2023

10 DATE OF REVISION OF THE TEXT

28 March 2025

S.G