1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

LAVEM, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LAVEM tablet contains:

Lamivudine 300 mg

Tenofovir disoproxil fumarate 300 mg

Dolutegravir sodium equivalent to dolutegravir 50 mg.

Excipient(s) with known effect:

Sugar content: Contains sugar (lactose monohydrate 153 mg and mannitol 184,38 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).
LAVEM IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION. SAFETY AND EFFICACY OF LAVEM 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 DISCONTINUE LAVEM AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

3. PHARMACEUTICAL FORM

Tablets

White to off white, capsule shaped, film-coated tablets, debossed with “HP553” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LAVEM 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.

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

The concentration of isoniazid is increased by concomitant administration of LAVEM.

Adults:

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

For treatment-naive and treatment experienced patients the recommended dose is one tablet daily.

Renal Impairment

Dose adjustment for renal impairment: Significantly increased exposure occurred when tenofovir, as in LAVEM, was administered to patients with moderate to severe renal impairment (see section 4.3).

The pharmacokinetics of tenofovir, as in LAVEM, have not been evaluated in non-haemodialysis patients with creatinine clearance< 80 ml/min); therefore, no dosing recommendations is available for these patients.

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

Paediatric population

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

Method of administration

LAVEM is taken orally, once daily, without regard to food.

4.3 Contraindications

- LAVEM tablets are contra-indicated in patients with known hypersensitivity to lamivudine, tenofovir or dolutegravir or to any of the components of the tablets;
- Impairment of renal function;
- Pregnancy and lactation (see section 4.6);
- Women of child-bearing age not using highly effective contraception;
- Concomitant use with adefovir dipivoxil;

- 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 LAVEM have been established in clinical studies for the treatment of HIV patients. However, safety and efficacy of the fixed-drug combination as in LAVEM for the treatment of HIV have not been established in clinical studies.

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

Metabolic abnormalities:

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

Lipodystrophy:

Combination antiretroviral therapy, including LAVEM, 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.

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 LAVEM. 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 LAVEM 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 LAVEM, have 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 LAVEM. Early symptoms

(symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure.

Lactic acidosis generally 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 2-5 mmol/L: monitor regularly, and be alert for clinical signs.
- Lactate 5-10 mmol/L without symptoms: monitor closely.
- Lactate 5-10 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).

The above lactate values may not be applicable to paediatric patients.

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

Treatment with LAVEM 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 LAVEM 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 up closely. There are no study results demonstrating the effect of LAVEM on clinical progression of HIV-1.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues as contained in LAVEM 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 (hyperlactataemia, hyperlipidaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, 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 LAVEM. 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 LAVEM until diagnosis of pancreatitis is excluded.

Patients with renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of LAVEM is increased due to decreased clearance (see section 4.3).

Liver disease:

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

The safety and efficacy of LAVEM 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 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:

LAVEM is a combination medicine and the dose of the individual components cannot be altered. Tenofovir and lamivudine are principally eliminated by the kidney.

LAVEM is not recommended for patients with creatinine clearance < 80 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 LAVEM.

Renal function:

Since LAVEM is primarily eliminated by the kidneys, co-administration of LAVEM with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of LAVEM 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 unavoidable, renal function should be monitored weekly.

LAVEM 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:

LAVEM 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 LAVEM.

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.
LAVEM 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 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:
LAVEM is not indicated for the treatment of chronic HBV infection. The safety and efficacy of LAVEM 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.

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.

Immune reactivation syndrome/ Immune reconstitution inflammatory syndrome (IRIS):

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (cART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. 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.

Hypersensitivity reactions:

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir and were characterized by rash, constitutional findings and sometimes, organ dysfunction, including liver injury.

Discontinue LAVEM 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 aminotransferase should be monitored and appropriate therapy initiated. Delay in stopping treatment with LAVEM or other suspect medicines after the onset of hypersensitivity may result in a life- threatening reaction.

Paediatric use:

Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established.

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.

Important information about some of the ingredients of LAVEM:

Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take LAVEM.

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interactions with other medicines and other forms of interaction

The likelihood of interactions is low due to the limited metabolism as 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 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 LAVEM. As LAVEM contains tenofovir disoproxil fumarate and lamivudine, any interactions that have been identified with

these individual medicines may occur with LAVEM. Important medicine interaction information for LAVEM is summarised in Tables 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.

Renally eliminated medicines:

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

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)		
			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 DF 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 medicines 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 Tenofovir Pharmacokinetic Parameters[2] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑ 122 (↑ 1 to ↑ 26)	↔	NA
Adefovir dipivoxil	10 once	22	↔	↔	NA
Efavirenz	600 mg once daily x 14 days	30	↔	↔	↔
Emtricitabine	200 mg once daily x 7 days	17	↔	↔	↔
Indinavir	800 mg three times daily x 7 days	12	↑ 14 (↓3 to ↑33)	↔	↔
Lamivudine	150 mg twice daily x 7 days	15	↔	↔	↔
Lopinavir/ Ritonavir	400/100 mg twice daily x 14 days	21	↔	↔	↔
Methadone[2]	40-110 once daily x 14 days[3]	13	↔	↔	↔
Oral Contraceptives[4]	Ethinyl oestradiol/ Norgestimate (Ortho-Tricyclen®) Once daily x 7 days	20	↔	↔	↔
Ribavarin	600 once	22	↔	↔	NA
Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	↔	↔	↔
Atazanavir[5]	400 once daily x 14 days	29	↔	↔	↔

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 DF 300 mg

5. REYATAZ US Prescribing Information (Bristol-Myers 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 LAVEM. Zidovudine has no effect on the pharmacokinetics of LAVEM.

Table 3:

Medicine Interactions: Co-administered medicines in the presence of Lamivudine

Co-administered Medicine	Effect of co-administered medicine	Clinical significance

Zidovudine	13 % increase in zidovudine exposure 28 % increase in peak plasma levels	No dosage adjustment necessary
Zalcitabine	May inhibit intracellular phosphorylation of zalcitabine	Usage not recommended
Trimethoprim	Increase in lamivudine plasma levels No effect on pharmacokinetics of co-trimoxazole	No dosage adjustment necessary. Only if patient as renal impairment, dosage should be adjusted

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.

LAVEM may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently.

LAVEM is therefore not recommended to be used in combination with zalcitabine.

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

Effect of dolutegravir on the pharmacokinetics of other medicines:

Rifampicin decreases the blood levels of dolutegravir. A supplementary dose of dolutegravir should be given to patients taking LAVEM. There is evidence that the concentration of isoniazid is increased by dolutegravir, as contained in LAVEM.

Dolutegravir is not expected to affect the pharmacokinetics of 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 does not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpirivine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol. Dolutegravir may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, metformin) (see Table 4: Medicine Interactions).

Metformin concentrations may be increased by LAVEM. Metformin is contra- indicated in patients taking LAVEM (see section 4.3).

Effect of other medicines on the pharmacokinetics of dolutegravir:

Dolutegravir 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 decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Co-administration of dolutegravir and other medicines inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgb may increase in dolutegravir plasma concentration (see Table 4).

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require dolutegravir dose adjustment to 50 mg twice daily. Etravirine also reduced 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 LAVEM dose adjustment is necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir.

Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of LAVEM. Caution is warranted and clinical monitoring is recommended when these combinations are given in INI- resistant patients (see Table 4: Medicine Interactions – HIV-1 Antiviral Medicines). 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, rilpirivine, bocepravir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no LAVEM dose adjustment is required when co-administered with these medicines.

LAVEM should not be co-administered with polyvalent cation-containing antacids. LAVEM is recommended to be administered 2 hours before or 6 hours after these medicines.

TABLE 4: Medicine interactions

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of LAVEM or Concomitant Medicine**	**Clinical Comment**
HIV-1 Antiviral Medicines		
Non-nucleoside Reverse	Dolutegravir ↓ AUC↓71 % C_{max}↓52 %	Etravirine decreased dolutegravir plasma concentration, which may

Transcriptase Inhibitor: Etravirine (ETR)	Cτ ↓ 88 % ETR ↔	result in loss of virologic response and possible resistance to dolutegravir. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC↓57 % C_{max}↓39 % Cτ ↓ 75 % EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC↑91 % C_{max}↑49 % Cτ ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC↑62 % C_{max}↑33 % Cτ ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC↓59 % C_{max}↓47 % Cτ ↓ 76 % TPV ↔ RTV↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of dolutegravir **is** 50 mg twice daily when co-administered with tipranavir/ritonavir. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.

Protease Inhibitor: Fosamprenavir/ritonavir (FPV + RTV)	Dolutegravir ↓ AUC↓35 % C_{max}↓24 % Cτ ↓ 49 % FPV ↔ RTV↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INI resistant patients.
Protease Inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV + RTV)	DTG ↔ AUC ↔ C_{max} ↔ Cτ↔ LPV↔ RTV↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir (DRV + RTV)	Dolutegravir ↓ AUC↓32 % C_{max}↓11 % Cτ ↓ 38 % DRV ↔ RTV↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDV)0	Dolutegravir ↔ TDV↔	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC↑10 % C_{max}↑7 % Cτ ↑ 28 % LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	Dolutegravir ↔ AUC↓25 % C_{max}↓12 % Cτ ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Medicines		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or

		pilsicainide co-administration with LAVEM is contra-indicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Metformin	Metformin↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contra-indicated in patients taking LAVEM (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort	Dolutegravir↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ↓ AUC↓74 % C_{max}↓72 % C_{24}↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. LAVEM is recommended to be administered 2 hours before or 6 hours after taking antacid medicines containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC↓39 % C_{max}↓37 % C_{24}↓ 39 %	LAVEM is recommended to be administered 2 hours before or 6 hours after taking medicines containing calcium, or alternatively, administer with food.
Iron supplements	Dolutegravir ↓ AUC↓549 % C_{max}↓57 % C_{24}↓ 56 %	LAVEM is recommended to be administered 2 hours before or 6 hours after taking medicines containing iron, or alternatively, administer with food.
Rifampicin	Dolutegravir ↓ AUC↓54 % C_{max}↓43 % $C\tau$↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of LAVEM is 50 mg twice daily when co-administered with rifampicin. Alternatives to rifampicin should be used where possible for INI resistant patients.
Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMN)	Effect of dolutegravir: EE↔ AUC↑ 3 % C_{max}↓1 % $C\tau$ ↑ 2 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral

	Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11% Cτ↓ 7 %	contraceptives is necessary when co-administered with LAVEM.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max}↓ 0 % Cτ ↑ 1 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with LAVEM.
Azole anti-fungals: Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary. Based on data from other CYP3A4 inhibitors, a marked increase is not expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

LAVEM is contraindicated in pregnancy and lactation. Neural tube defects have been noted in an observational study in humans, where dolutegravir-based regimens were used at the time of conception and early pregnancy, (see section 4.3).

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

LAVEM should not be prescribed in women who plan to become pregnant. Women of child-bearing age should not use LAVEM unless they are reliably using highly effective contraception. Treatment with LAVEM should not be initiated without a medically supervised negative pregnancy test.

This test should be repeated at frequent intervals during treatment with LAVEM; and especially in the event that pregnancy is suspected.

Lactation

Mothers breastfeeding their infants should not use LAVEM. Lamivudine is excreted in human milk at similar concentrations to those found in serum; tenofovir is excreted in breast milk and it is not known whether dolutegravir is excreted in human milk.

4.7 Effects on ability to drive and use machines

LAVEM may affect the ability to drive and use machines as it may cause dizziness and drowsiness. Patients should ensure that they do not engage in driving or using machines until they know how LAVEM affects them.

4.8 Undesirable effects

a. Summary of the safety profile

Not Applicable

b. Tabulated summary of adverse reactions

LAVEM can have side effects.

Lamivudine:

The following side-effects have been reported during therapy for HIV disease with LAVEM tablets alone and in combination with other antiretrovirals.

Blood and the 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 (redistribution/accumulation of body fat)

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; vomiting; upper abdominal pain or cramps; diarrhoea

Less frequent: Pancreatitis; elevations in serum amylase

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

Frequent: Rash; alopecia

Musculoskeletal and connective tissue disorders:

Frequent: arthralgia; muscle disorders

Less frequent: rhabdomyolysis; decrease in bone mineral density; osteopenia; fractures

General disorders and administration site conditions:

Frequent: fatigue; malaise; fever

Tenofovir Disoproxil Fumarate:

Immune system disorders:

Less frequent: Allergic reaction

Gastrointestinal disorders:

Frequent: Abdominal pain; anorexia; dyspepsia; flatulence

Less frequent: Increased amylase; pancreatitis

Hepato-biliary disorders:

Less frequent: Increased liver enzymes (ALT, AST, gamma GT);

hepatitis

Metabolism and nutrition disorders:

Frequent: Hypophosphataemia

Less frequent: Lactic acidosis

Renal and urinary disorders

Frequent: Renal insufficiency; acute renal failure; proximal tubulopathy; proteinuria; increases creatinine; acute tubular necrosis; nephrogenic diabetes insipidus; Fanconi syndrome, polyuria; interstitial nephritis.

Respiratory, thoracic, and mediastinal disorders

Frequency not known: Dyspnoea

Nervous system disorders:

Frequent: dizziness

Musculoskeletal, connective tissue and bone disorders:

Less frequent: rhabdomyolysis[1]; muscular weakness[1]; osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 2], myopathy[1]

[1]This side effect may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.

[2]This side effect was identified through post-marketing surveillance.

General disorders and administration site conditions:

Frequent: asthenia

Dolutegravir:

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 not known: Abdominal pain; abdominal discomfort

Hepatobiliary disorders:

Frequency not known: Hepatitis

Skin and subcutaneous tissue disorders:

Frequent: Rash; pruritus

General disorders and administration site conditions:

Frequent: Fatigue

c. Description of selected adverse reactions

Not Applicable

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 "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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.

Lamivudine:

Limited data are available on the consequences of ingestion of acute overdoses in humans. If overdosage occurs the patient should be monitored, and palliative supportive treatment applied as required.

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 LAVEM. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. As LAVEM is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside analogue, ATC Code: J05AF05.

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

Drug 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 % 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 to 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 0 (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.

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 AUC0-∞ of tenofovir were increased. 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.

Dolutegravir

Dolutegravir inhibits HIV integrase by binding to the integrase active site 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 substitutions 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 HJV-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 had 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.

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 received dolutegravir 50 mg once daily.

Table 1: 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 that there was 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 (CL_{cr} < 30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 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 8 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 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 were not associated with differences in the pharmacokinetics of dolutegravir.

Co-infection with Hepatitis B or C:

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

5.2 Pharmacokinetic properties

Lamivudine

Pharmacokinetics in adults: Lamivudine is well absorbed from the gastrointestinal tract and the bioavailability of oral lamivudine in adults is normally between 80 % and 85 %. The mean C_{max} for lamivudine in LAVEM is 2283,8279 ng/ml, the mean time (T_{max}) to maximum serum

concentration (C_{max}) is 2,240 hours and the mean terminal half-life $T_{1/2}$ is 4,2651 hours. The mean systemic clearance of lamivudine is approximately 0,32 l/kg/h, with predominantly renal clearance (> 70 %) via active tubular secretion, but little (< 10 %) hepatic metabolism. 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 reported.

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, whether it is disease- or age-related. A recommended dosage regimen for patients with creatinine clearance below 50 ml/min is shown in the dosage section.

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 drug 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 patient also has renal impairment. Administration of co-trimoxazole with the lamivudine/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 was approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Pharmacokinetics in children: In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability of lamivudine (approximately 58-66 %) 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 age groups. At present, the available data do not suggest that lamivudine is less efficacious in this group. There are limited pharmacokinetic data for patients less than three months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely to be due to immature renal function and variable absorption.

Pharmacokinetics in pregnancy: Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant women.

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 yet no information on the tumorigenic risk in animals, and therefore any potential risk to man must be balanced against the expected benefits of treatment.

Tenofovir

Tenofovir DF has an oral bioavailability of 25 %. A high-fat meal increases the oral bioavailability to 39 %, but the medicine can be taken without food. Tenofovir is not bound significantly to plasma proteins. The mean C_{max} for tenofovir in LAVEM is 354,7628 ng/ml, the mean time (T_{max}) to maximum serum concentration (C_{max}) is 1,317 hours and the mean terminal half-life $T_{1/2}$ is 18,4231 hours.

Tenofovir undergoes both glomerular filtration and active tubular secretion. Between 70 % and 80 % of an intravenous dose is recovered unchanged in the urine.

Dolutegravir

Absorption:

The mean C_{max} for dolutegravir in LAVEM is 3056,8828 ng/ml and the mean time (T_{max}) to maximum serum concentration (C_{max}) is 3,042 hours. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation.

Following oral administration of tablet formulations, dolutegravir exhibits non-linear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however, increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg.

Dolutegravir may be administered with or without food. The absolute bioavailability of dolutegravir has not been established.

Distribution:

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins based on *in vitro* data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12,5 L. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma drug-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, approximately 0,4 to 0,5 % in 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).

Metabolism:

Dolutegravir is primarily metabolised via UGT1A1 with minor CYP3A component (9,7 %) of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (<1 % of the dose). Fifty-three percent of total oral dose is 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 either 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).

Elimination:

The mean terminal half-life $T_1/_2$ for dolutegravir in LAVEM is 17,2772 hours. Dolutegravir has an apparent clearance (CL/F) of 0,56 L/hr.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients are:

Core tablet: Microcrystalline cellulose, croscarmellose sodium, povidone, lactose monohydrate, pregelatinized starch, magnesium stearate, mannitol, sodium starch glycolate and sodium stearyl fumarate.

Film coat: Polyvinyl alcohol partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol and talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life: 36 months

6.4 Special precautions for storage

Store at or below 30 °C. Keep HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

28 or 30 tablets are packed in a 100 cc, white opaque, HDPE container and closed with a 38 mm, white opaque, polypropylene closure. Each HDPE container contains a HDPE canister containing silica gel.

84 or 90 tablets are packed in a 200 cc, white opaque, HDPE container and closed with a 38 mm, white opaque, polypropylene closure. Each HDPE container contains a HDPE canister containing silica gel.

180 tablets are packed in a 400 cc, white opaque, HDPE container and closed with a 53 mm, white opaque, polypropylene closure. Each HDPE container contains a HDPE canister containing silica gel.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Emcure Pharmaceuticals SA (Pty) Ltd.

Arizona House, First floor, South Wing, Aspen Business Park

1 Madison Avenue, Aspen Lakes, Extension 13

Johannesburg South

2190

8. REGISTRATION NUMBER

Registration number: 53/20.2.8/0090

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 10 October 2018

10. DATE OF REVISION OF THE TEXT

Date amended: 06 September 2024