PROFESSIONAL INFORMATION FOR

LOMIDA (FILM-COATED TABLETS)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LOMIDA (50/300 mg film-coated tablets).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains dolutegravir sodium equivalent to dolutegravir 50 mg and lamivudine 300 mg.

Contains sugar: mannitol 145,00 mg.

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

3. PHARMACEUTICAL FORM

Film-coated tablets.

LOMIDA are grey coloured, capsule shaped, biconvex, film-coated tablets debossed with “C” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOMIDA is indicated for the treatment of human immunodeficiency virus (HIV type-1) infection in treatment naïve adults aged 18 years and older, who have no known or suspected resistance to either antiretroviral component.

4.2 Posology and method of administration

Posology

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

LOMIDA is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments, such as those with creatinine clearance less than 50 mL/min.

A separate preparation of dolutegravir is available where a dose adjustment is required due to interactions (see **section 4.5**).

For patients with integrase inhibitor resistance, LOMIDA is not recommended.

In this case, the doctor should refer to the dolutegravir tablet product information.

The recommended adult dose of LOMIDA in treatment naïve, treatment experienced, and integrase inhibitor naïve patients is one tablet (50/300 mg) once daily.

Special populations

Renal impairment

Whilst no dosage adjustment of dolutegravir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to decreased clearance. LOMIDA is not recommended for use in patients with a creatinine clearance less than 50 mL/min (see **section 5.2**).

Hepatic impairment

No dosage adjustment is necessary in patients with mild to moderate liver disease (Child-Pugh grade A or B) unless accompanied by renal impairment.

There is no data on the use of LOMIDA in patients with severe hepatic impairment, therefore caution should be exercised.

Elderly

There are limited data on the use of LOMIDA in patients aged 65 years and older. However, there is no evidence that elderly patients require a different dose than younger adult patients (see **section 5.2**). When treating elderly patients, consideration needs to be given to greater frequency of decreased hepatic and renal function, haematological abnormalities and concomitant medicines or disease.

Method of administration

LOMIDA is for oral administration and should be swallowed whole.

LOMIDA can be taken with or without food.

4.3 Contraindications

LOMIDA is contraindicated:

- in patients with known hypersensitivity to dolutegravir, lamivudine, or any of its excipients (listed in **section 6.1**)
- in combination with dofetilide and pilsicainide
- in patients with severe hepatic impairment
- in patients with severe renal impairment (with a creatinine clearance of < 50 mL/min due to the lamivudine component (see **section 5.1** – Renal impairment).

4.4 Special warnings and precautions for use

Clinical studies were not conducted with the fixed dose combination (FDC) of dolutegravir (DTG) and lamivudine (3TC).

Only the mono-components were used in the clinical studies.

Hypersensitivity reactions

Hypersensitivity reactions such as rash, constitutional findings, and sometimes organ dysfunction, including liver injury may occur with LOMIDA administration.

Discontinuation of LOMIDA may be considered should serious hypersensitivity reactions occur (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 LOMIDA or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Lactic acidosis/hyperlactataemia

Lamivudine, which is an active constituent of LOMIDA, can cause potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features include nausea, abdominal pain, dyspnoea, fatigue, and weight loss.

The venous lactate level (normal 2 mmol/L) and the serum bicarbonate level in patients with suspicious symptoms and biochemistry should be measured and handled as follows:

- Lactate 2 - 5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5 - 10 mmol/L with symptoms and/or reduced standard bicarbonate: Change NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Other possible causes such as sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, and hyperthyroidism should be excluded.
- Lactate > 10 mmol/L: Stop all therapy (80 % mortality).

Caution should be exercised when treating patients with known risk factors for liver disease. Treatment with LOMIDA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with body fat redistribution including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Hepatic impairment

The unbound fraction of dolutegravir, an active constituent of LOMIDA, is doubled in blood in patients with moderate hepatic impairment.

LOMIDA is contraindicated in patients with severe hepatic impairment.

Lamivudine, which is also an active constituent of LOMIDA, may cause hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of medicines containing lamivudine has not been established in patients with significant underlying liver disorders.

Co-infection with hepatitis B or C

Patients with chronic hepatitis B or C and treated with antiviral therapy are at an increased risk of developing severe and potentially fatal hepatic adverse reactions.

Doctors should refer to the current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

LOMIDA contains lamivudine which is active against hepatitis B. Dolutegravir however lacks such activity. Lamivudine monotherapy is generally not considered an adequate treatment for hepatitis B since the risk for hepatitis B resistance development is high. An additional antiviral medicine is therefore needed if LOMIDA is used in HBV co-infected patients.

Patients co-infected with HIV and HBV who discontinue LOMIDA should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post treatment exacerbation of hepatitis may lead to hepatic decompensation.
AST and ALT abnormalities as well as liver chemistry elevations consistent with immune reconstitution syndrome may be increased in patients co-infected with hepatitis B and/or C that are treated with LOMIDA. If there is worsening liver disease in these patients, temporary or permanent discontinuation of treatment must be considered.

Immune reconstitution inflammatory syndrome (IRIS)

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, cytomegalovirus retinitis, *pneumocystis jiroveci* pneumonia, mycobacterium avium infection, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued, and ART continued. 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) 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). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness, or difficulty in movement.

Co-administration with other medicines

Caution should be exercised when co-administering LOMIDA with medicines which may alter the exposure to LOMIDA, or those which are exposed may be altered by LOMIDA (see **section 4.5**).

Co-administration of LOMIDA with polyvalent cation-containing antacids is not recommended. These medicines should be administered 2 hours after or 6 hours before LOMIDA.

When taken with food, LOMIDA and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. However, when taken on an empty stomach, these supplements or vitamins should be taken 2 hours after or 6 hours before LOMIDA.

Metformin concentrations may be increased by co-administration with LOMIDA. A dose adjustment of metformin should be considered when starting and stopping co-administration of LOMIDA with metformin, to maintain glycaemic control (see **section 4.5**).

The combination of LOMIDA and cladribine is not recommended.

LOMIDA should not be taken with any other medicine which contains lamivudine or dolutegravir, except where a dose adjustment of dolutegravir is indicated due to medicine-medicine interactions (see **section 4.5**).

Opportunistic infections

Patients receiving LOMIDA should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including LOMIDA, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues such as lamivudine, which is an active constituent in LOMIDA, may cause variable degrees of mitochondrial damage. Mitochondrial dysfunction may even occur in HIV negative infants which are exposed to LOMIDA *in utero* and/or postnatally.

Apart from lactic acidosis, other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy.

Some neurological disorders such as hypertonia, convulsions, and abnormal behaviour may occur. It is unknown whether these disorders are transient or permanent.

Any infant which has been exposed *in utero* to nucleoside and nucleotide analogues, regardless of their HIV status, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs and symptoms.

Renal impairment

The terminal half-life of lamivudine, an active constituent of LOMIDA, is increased in patients with moderate to severe renal impairment. LOMIDA is therefore not recommended for use in patients with a creatinine clearance less than 50 mL/min (see **section 4.2**).

Pancreatitis

Pancreatitis has been reported in patients receiving lamivudine which is an active constituent of LOMIDA. It is uncertain whether this was due to treatment or underlying HIV disease. Pancreatitis should be considered if clinical symptoms like nausea, vomiting, and/or abdominal pain, or elevated biochemical markers indicative of pancreatitis occur. Therapy should be discontinued until pancreatitis is excluded.

Weight and metabolic parameters

The use of antiretroviral therapy may result in an increase in weight and blood lipid and glucose levels. Patients being treated with LOMIDA should be advised to lead a healthy lifestyle and their lipid and glucose levels should be monitored.

LOMIDA contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Effect of LOMIDA on other medicines

Dolutegravir, which is in LOMIDA, has no direct, or weak inhibition of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or transporters Pgp, BCRP, OATP1B3, OCT1 or MRP2. It also does not induce CYP1A2, CYP2B6 or CYP3A4. Dolutegravir is therefore not expected to have an impact on the pharmacokinetics of medicines that are substrates of these enzymes or transporters, such as reverse transcriptase and protease inhibitors, opioid analgesics, antidepressants, statins, azole antifungals, proton pump inhibitors and medicines used to treat erectile dysfunction.

Dolutegravir does not have a clinically relevant effect on the following medicines: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, telaprevir and oral contraceptives containing norgestimate and ethinyl estradiol.

Dolutegravir inhibits the renal organic cation transporter 2 (OCT2) as well as MATE-1 and therefore may increase plasma concentrations of medicines in which excretion is dependent upon OCT2, such as dofetilide, pilsicainide or metformin.

Effect of other medicines on LOMIDA

Dolutegravir, an active constituent of LOMIDA, is mainly metabolised by UGT1A1. It is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP. Medicines that induce these enzymes may decrease plasma concentrations of dolutegravir, thereby reducing the therapeutic effect of LOMIDA.

Co-administration of LOMIDA with medicines that inhibit UGT1A3, UGT1A9, CYP3A4 and/or Pgp may decrease dolutegravir plasma concentrations.

Efavirenz, nevirapine, rifampicin and tipranavir when combined with LOMIDA reduce plasma concentrations of dolutegravir.

Etravirine also reduces plasma concentrations of dolutegravir, but this effect is mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir, therefore there is no need for an increase in dolutegravir intake with LOMIDA. Fosamprenavir in combination with ritonavir also reduces dolutegravir plasma concentrations but no additional dose is required. Caution is warranted when these combinations are given to integrase inhibitor (INI) resistant patients.

UGT1A1 inhibitor atazanavir does not result in clinically significant increases in plasma dolutegravir concentrations.

Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole have no or minimal effect on the pharmacokinetics of dolutegravir.

Lamivudine elimination is predominantly mediated by organic cationic transporter 2 (OCT2) and multidrug and toxin extrusion transporters (MATE1 and MATE2-K) secretion and therefore may interact with other medicines which are concurrently administered, particularly those whose main route of elimination is active renal secretion via the organic

transporter. Trimethoprim which is an inhibitor of these transporters may increase plasma concentrations of lamivudine. This increase, however, is not clinically significant.

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

Although lamivudine is a substrate of BCRP and P-gp, given its high absolute bioavailability (see **section 5.2**), inhibitors of the efflux transporters are unlikely to result in a clinically relevant impact on lamivudine concentrations.

List of medicines that interact with LOMIDA

Anti-retroviral medicines:

Nucleoside reverse transcriptase inhibitors:

Zalcitabine

Lamivudine, which is an active component of LOMIDA, may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. The combination of these medicines is therefore not recommended.

Emtricitabine

Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two are administered concurrently. In addition, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these medicines in combination therapy may be limited. The combination of medicines containing lamivudine, such as LOMIDA, with emtricitabine is therefore not recommended.

Non-Nucleoside reverse transcriptase inhibitors (NRTI's):

Etravirine

Co-administration of etravirine with LOMIDA could result in reduced plasma concentrations of dolutegravir, an active substance of the medicine. This may lead to a loss in virologic response and possible resistance to dolutegravir.

Efavirenz

Co-administration of LOMIDA and efavirenz decreases dolutegravir exposure. Alternative combinations that do not include efavirenz should be used in possible INI-resistant patients.

Nevirapine

Co-administration of LOMIDA with nevirapine has the potential to decrease plasma levels of dolutegravir due to enzyme induction and has not been studied. The effect of nevirapine on dolutegravir exposure is likely to be similar to or less than that of efavirenz. The recommended dose of dolutegravir is 50 mg twice daily for patients taking nevirapine. As LOMIDA is a fixed-dose tablet, an additional dose of 50 mg dolutegravir should be administered, approximately 12 hours after LOMIDA. In this case, the doctor should refer to the individual professional information for dolutegravir.

Protease inhibitors:

Atazanavir

When it is co-administered with LOMIDA, atazanavir increases plasma concentrations of dolutegravir.

Atazanavir/ritonavir

When it is co-administered with LOMIDA, atazanavir/ritonavir increases plasma concentrations of dolutegravir. No dose adjustment is necessary.

Tipranavir/ritonavir

Tipranavir/ritonavir decreases plasma concentrations of dolutegravir when co-administered with LOMIDA. The recommended dose of dolutegravir is 50 mg twice daily for patients taking tipranavir/ritonavir. As LOMIDA is a fixed-dose tablet, an additional dose of 50 mg dolutegravir should be administered, approximately 12 hours after LOMIDA. In this case, the doctor should refer to the individual professional information for dolutegravir.

Fosamprenavir/ritonavir

Concomitant use of fosamprenavir/ritonavir with LOMIDA may lead to decreased exposure to dolutegravir but based on limited data not resulting in reduced efficacy in Phase III studies, no dose adjustment is necessary in INI-naïve patients.

Nelfinavir

The interaction has not been studied, although an inhibitor of CYP3A3, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.

Lopinavir/ritonavir

Lopinavir/ritonavir did not alter dolutegravir plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.

Darunavir /ritonavir

Darunavir/ritonavir did not alter dolutegravir plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.

Other medicines

Dofetilide and pilsicainide

Concomitant use of dofetilide or pilsicainide with LOMIDA has the potential to increase plasma concentrations of dofetilide and pilsicainide due to inhibition of the OCT2 transporter. Co-administration is contraindicated due to potentially life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see **section 4.3**).

Phenytoin, phenobarbital, carbamazepine, and St. John's wort

Co-administration of LOMIDA with these medicines may decrease plasma concentrations of dolutegravir. The recommended dose of dolutegravir is 50 mg twice daily for patients taking these medicines. As LOMIDA is a fixed-dose tablet, an additional dose of 50 mg dolutegravir should be administered, approximately 12 hours after LOMIDA. In this case, the doctor should refer to the individual professional information for dolutegravir.

Oxcarbazepine

The interaction has not been studied, although an inhibitor of CYP3A3, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.

Antacids containing polyvalent cations (e.g., Mg, Al, or Ca)

Co-administration of antacids containing polyvalent cations with LOMIDA decreases plasma concentrations of dolutegravir. LOMIDA should be administered 2 hours before or 6 hours after these antacids.

Calcium supplements

It is recommended that LOMIDA should be administered 2 hours before or 6 hours after calcium containing supplements. Alternatively, when taken together, they should be administered with food.

Sorbitol

When possible, chronic administration of lamivudine, as contained in LOMIDA, with medicines containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols such as xylitol, mannitol, lactitol, maltitol should be avoided. HIV-1 viral load should be frequently monitored when co-administration cannot be avoided.

Iron supplements

It is recommended that LOMIDA should be administered 2 hours before or 6 hours after iron containing supplements. Alternatively, when taken together, they should be administered with food.

Metformin

Co-administration of medicines containing dolutegravir, such as LOMIDA, with metformin causes increased concentrations of metformin. A dose adjustment of metformin should be considered when starting and stopping co-administration of LOMIDA with metformin, to maintain glycaemic control (see **section 4.4**).

Rifampicin

Rifampicin decreases the plasma concentrations of dolutegravir, which is an active component of LOMIDA. The recommended dose of dolutegravir is 50 mg twice daily for patients taking rifampicin. As LOMIDA is a fixed-dose tablet, an additional dose of 50 mg

dolutegravir should be administered, approximately 12 hours after LOMIDA. In this case, the doctor should refer to the individual professional information for dolutegravir.

Trimethoprim/sulphamethoxazole

Administration of trimethoprim/sulphamethoxazole 160/800 mg (co-trimoxazole) causes a 40 % increase in lamivudine exposure, which is an active ingredient in LOMIDA. This increase in lamivudine is caused by the trimethoprim component. Lamivudine has no impact on the pharmacokinetics of co-trimoxazole. Unless the patient has renal impairment, no dose adjustment of lamivudine is necessary. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jirovecii* pneumonia and toxoplasmosis has not been studied. LOMIDA is not recommended for use in patients with CrCl < 50 mL/min.

Oral contraceptives (ethinyl estradiol and norelgestromin)

Dolutegravir did not alter ethinyl estradiol and norelgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptive is necessary when co-administered with LOMIDA.

Methadone

Dolutegravir did not alter methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with LOMIDA.

Daclatasvir

Daclatasvir did not alter dolutegravir plasma concentrations to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment of daclatasvir is necessary when co-administered with LOMIDA.

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 LOMIDA in women of childbearing potential to exclude inadvertent (unintentional) use of LOMIDA during the first trimester of pregnancy.

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

Pregnancy

Use of dolutegravir, as contained in LOMIDA, 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).

If a pregnancy is confirmed in the first trimester while on LOMIDA, the benefits and risks of continuing LOMIDA versus switching to another antiretroviral regimen should be discussed with the patient, taking the gestational age and the critical time period of neural tube defect development into account.

LOMIDA may be used during the second and third trimester of pregnancy when the expected benefit outweighs the potential risk to the foetus. 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.

There have been reports of mild and transient elevations in serum lactate levels due to mitochondrial dysfunction in neonates and infants exposed *in utero* or peri-partum to nucleoside reverse transcriptase inhibitors such as lamivudine, which is contained in LOMIDA. There have also been reports of developmental delay, seizures, and other neurological disorders. However, a causal relationship between these events and lamivudine exposure *in utero* and peri-partum has not been established.

Lamivudine was associated with findings in animal reproductive toxicity studies.

Breastfeeding

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

Both dolutegravir and lamivudine, which are active components of LOMIDA, are secreted in human breast milk, and there is significant exposure to the neonate/infants due to slow elimination; the half-life of dolutegravir in the newborn was 33 hours compared to 14 hours in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

Lamivudine is excreted in human milk at similar concentrations to those found in serum.

Fertility

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

4.7 Effects on ability to drive and use machines

LOMIDA has no or negligible impact on the ability to drive and operate machinery. However, it has been reported that LOMIDA causes dizziness, associated with

dolutegravir, therefore the patient should be cautioned against driving and/or operating heavy machinery.

4.8 Undesirable effects

Summary of side effect profile

In a bioequivalence study done with LOMIDA, a total of one (01) adverse event (vomiting) was reported during the entire course of the study. The reported adverse event was mild in severity, possibly related to LOMIDA. No serious or significant adverse events were reported during the entire course of the study.

The most common adverse events associated with combinations of dolutegravir and lamivudine, such as LOMIDA, include upper abdominal pain, diarrhoea, and vomiting.

Tabulated list of adverse reactions

The following adverse reactions have been classified in the following way: “Frequent, less frequent and frequency not known.” They have been listed according to the active component with which they are associated.

System organ class	Dolutegravir-related side effects	Lamivudine-related side effects
Blood and lymphatic system disorders		**Less frequent:** Neutropenia, anaemia, thrombocytopenia, pure red cell aplasia.
Immune system disorders	**Less frequent:** Hypersensitivity, immune reconstitution syndrome.	
Metabolism and nutrition disorders		**Frequent:** Hyperlactataemia. **Less frequent:** Lactic acidosis, lipodystrophy.

Psychiatric disorders	**Frequent:** Insomnia, depression, anxiety, abnormal dreams. **Less frequent:** Suicide ideation and suicide attempt, particularly in patients with a pre-existing history of depression and psychiatric illness.	**Frequent:** Insomnia, depression, anxiety, abnormal dreams.
Nervous system disorders	**Frequent:** Headache, dizziness, abnormal dreams, somnolence.	**Frequent**: Headache. **Less frequent:** Peripheral neuropathy, paraesthesia.
Gastrointestinal disorders	**Frequent:** Upper abdominal pain, diarrhoea, flatulence, vomiting. **Less frequent:** Abdominal pain, abdominal discomfort.	**Frequent:** Upper abdominal pain, nausea, diarrhoea, vomiting. **Less frequent:** Pancreatitis, increases in serum amylase.
Hepatobiliary disorders	**Less frequent:** Hepatitis, acute hepatic failure.	**Less frequent:** Transient rises in liver enzymes (AST, ALT), acute hepatic failure.
Skin and subcutaneous tissue disorders	**Frequent:** Rash, pruritus.	**Frequent:** Rash, alopecia.
Musculoskeletal and connective tissue disorders	Frequency unknown: Myalgia, arthralgia.	**Frequent:** Arthralgia, muscle disorders (including myalgia). **Less frequent:** Rhabdomyolysis.
General disorders and administration site conditions	**Frequent:** Fatigue.	**Frequent:** Fatigue, malaise, fever.

Investigations	**Frequent:** Creatine phosphokinase (CPK) elevations, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations. **Less frequent:** Amylase elevations, increased weight.	**Frequent:** Creatine phosphokinase (CPK) elevations.

Description of selected adverse reactions

Changes in laboratory biochemistries

Dolutegravir is associated with an increase in serum creatinine occurring in the first week of treatment when administered with other antiretroviral medicines. Serum creatinine increases occur within the first four weeks of treatment with dolutegravir and lamivudine and remains stable through 48 weeks.

Metabolic parameters

Weight and levels of blood glucose and lipids may increase during antiretroviral therapy.

Osteonecrosis

Osteonecrosis may occur particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combined antiretroviral therapy (cART).

Immune response syndrome

In HIV patients with severe immune deficiency at the time of initiation of combined antiretroviral therapy (cART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders such a Graves' disease have

also been reported, however, the time to onset is variable and these events may occur many months after initiation of treatment.

Paediatric population

There are no data on the effects of LOMIDA in paediatric patients.

Other special populations

Patients co-infected with hepatitis B and/or hepatitis C virus

Liver chemistry elevations consistent with immune reconstitution syndrome may occur in patients co-infected with hepatitis B and/or C at the start of dolutegravir containing therapy, such as LOMIDA, particularly in those whose anti-hepatitis B therapy was withdrawn**.**

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 Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd. by e-mail: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

No specific signs and symptoms have been identified for the overdose of LOMIDA. An overdose could result in the increased severity of undesirable effects (see **section 4.8**).

Management of overdosage

There is no specific treatment for an overdose with LOMIDA. If an overdose occurs, the patient should be monitored and treated supportively. Since lamivudine can be removed with dialysis, haemodialysis could be used in the treatment of an overdose. As dolutegravir is highly bound by plasma proteins, it is unlikely that it will be removed by dialysis**.**

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 20.2.8

Pharmacotherapeutic group: antivirals for systemic use.

ATC Code: J05AR25

Mechanism of action

Dolutegravir is a second-generation integrase strand transfer inhibitor (INSTI) which 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 this process, the integrase inhibitor chelates with two Mg^{2+} ions in the integrase catalytic active site and prevents the integrase enzyme from completing the strand transfer. Accumulation of 2-long terminal repeat (2-LTR) circles in treated cells indicate the integrase strand transfer reaction inhibition by a lower DTG concentration in comparison with that which causes cell toxicity.

Lamivudine is a nucleoside analogue of 2'-deoxycytosine that exerts its antiviral effects by acting as a DNA chain terminator. The active anabolite of lamivudine, lamivudine 5'-triphosphate, is formed from phosphorylation by intracellular kinases and competes with naturally occurring cytidine triphosphate for incorporation into DNA. Lamivudine is a

selective inhibitor of HIV-1 and HIV-2 replication. Lamivudine is a potent inhibitor of the reverse transcriptase (RT) enzymes of HIV-1, with *in vitro* IC_{50} in different cell lines with different HIV-1 strains ranging from 0,002 to 1,14 mM and IC_{50} against HBV of 0,1 mM with limited cell toxicity at concentrations > 1000-fold those effective against HIV. It is also active against zidovudine resistant clinical isolates of HIV.

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.

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

Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells.

Lamivudine resistance to HIV-1 is due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine residue to either isoleucine or valine.

Antiviral activity in cell culture

Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentrations of drug necessary to effect viral replication by 50 percent (EC_{50}) values of 0,5 nM (0,21 ng/mL) to 2,1 nM (0,85 ng/mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0,52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M [clades A - G], and 3 in group O) with EC_{50} values ranging

from 0,02 nM to 2,14 nM for HIV-1. Dolutegravir EC_{50} values against three HIV-2 clinical isolates in PBMC assays ranged from 0,09 nM to 0,61 nM.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC_{50} values were in the range of 3 to 15,000 nM (1 nM = 230 ng/mL). The EC_{50} values of lamivudine against different HIV-1 clades (A - G) and group O viruses ranged from 1 to 120 nM, and against HIV-2 isolates from 3 to 120 nM in PBMCs.

Antiviral activity in combination with other antiviral medicines

Neither dolutegravir nor lamivudine were antagonistic to all tested anti-HIV medicines.

Effect of human serum

In 100 % human serum, the mean fold shift for dolutegravir activity is 75 fold, resulting in protein adjusted IC_{90} of 0,064 µg/mL. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36 %).

Effects on renal function

In the first week of treatment, a small decrease (10 to 14 %) in mean serum creatinine clearance may be observed. Dolutegravir has no significant impact on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). The increases in creatinine are due to non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

5.2 Pharmacokinetic properties

Dolutegravir

There are no significant differences between dolutegravir pharmacokinetics in healthy subjects compared to those of HIV-infected patients.

The PK variability of dolutegravir is between low to moderate.

Absorption

Dolutegravir is absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose. 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, dolutegravir exposure appears dose proportional from 25 to 50 mg.

The absolute bioavailability of dolutegravir has not been established.

Food effect

Food increases the extent and slows the rate of the absorption of dolutegravir. Bioavailability of dolutegravir depends on the meal content: low, moderate and high fat meals increase dolutegravir $AUC_{(0-\infty)}$ by 34 %, 41 % and 66 %; increase C_{max} by 46 %, 52 %, and 67 %; prolong T_{max} to 3, 4 and 5 hours from 2 hours under fasting conditions, respectively.

Distribution

Dolutegravir is highly bound to human plasma (approximately 99,3 %). The apparent volume of distribution is estimated to be 12,5 L. Binding of dolutegravir to plasma proteins is independent of concentration. Dolutegravir has minimal association of radioactivity with blood cellular components.

Free fraction of dolutegravir 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).

Dolutegravir is present in the female and male genital tract.

Biotransformation

Dolutegravir is primarily metabolised by UGT1A1 with a minor CYP3A component. Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). 53 % of the total oral dose is excreted unchanged in the 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. 31 % of the total dose is excreted in urine, represented by ether glucuronide of dolutegravir (18,9 % of the 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 elimination half-life of dolutegravir is approximately 7 hours.

Special populations

Elderly

Pharmacokinetic data for dolutegravir in subjects older than 65 years of age are limited.

Renal impairment

Renal clearance of unchanged medicine is a minor pathway of elimination of dolutegravir. There are no clinically significant differences in the pharmacokinetics of patients with severe renal impairment and that of healthy subjects.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. While no dosage adjustment of dolutegravir is required in mild to moderate hepatic impairment, the effect of dolutegravir pharmacokinetics in patients with severe hepatic impairment has not been studied.

Polymorphism in metabolising enzymes

There is no evidence that common polymorphisms in metabolising enzymes alter dolutegravir pharmacokinetics to a clinically relevant extent.

Gender and race

Gender and race have no clinically relevant effects on the pharmacokinetics of dolutegravir.

Co-infection with hepatitis B or C

Infection with hepatitis C has no clinically relevant effect on exposure to dolutegravir. Data on the effect of hepatitis B are limited.

Adolescents

The pharmacokinetics of dolutegravir in adolescents is comparable to that of adults. However, due to the lack of data, dolutegravir is not recommended in patients younger than 18 years of age.

Lamivudine:

Absorption

Lamivudine is well absorbed from the gastrointestinal tract and the bioavailability in adults is normally between 80 % and 85 %. Following oral administration, the mean time (T_{max}) to maximum serum concentrations (C_{max}) is about an hour.

Food effect

No dose adjustment is needed when lamivudine is co-administered with food as the bioavailability is not altered. There is, however, a delay in T_{max} and a reduction in C_{max}.

Distribution

The mean volume of distribution of lamivudine is 1,3 L/kg.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin.

Lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio of CSF to serum lamivudine concentration 2 to 4 hours after oral administration was approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Biotransformation

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. The likelihood of metabolic medicine interactions with lamivudine is low due to the small extent of hepatic metabolism.

Elimination

The mean terminal half-life of lamivudine is 5 to 7 hours.

Special populations

Renal impairment

Lamivudine elimination is affected by renal impairment, whether it is disease or age related. Plasma concentrations (AUC) of lamivudine are increased in patients with renal dysfunction due to decreased clearance.

Hepatic impairment

Lamivudine pharmacokinetics are not significantly affected by hepatic impairment.

Interaction with trimethoprim

An interaction with trimethoprim, a component of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. However, a dose adjustment is not required unless the patient also has renal impairment.

Gender and race

Gender and race have no clinically relevant effects on the pharmacokinetics of lamivudine.

Co-infection with hepatitis B or C

Data on the effect of hepatitis B are limited.

Pregnancy

Following oral administration, lamivudine pharmacokinetics in pregnancy are similar to that of non-pregnant adults.

5.3 Preclinical safety data

No data are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Colloidal silicon dioxide
- Mannitol
- Microcrystalline cellulose
- Opadry Gray YS-1-17506-A
- Povidone
- Sodium starch glycolate
- Sodium stearyl fumarate.

Contents of the film-coating (Opadry Gray):

- Ferrosoferric oxide/Black iron oxide
- Hypromellose 3mPas
- Hypromellose 6mPas
- Macrogol
- Polysorbate 80
- Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C in the original container.

6.5 Nature and contents of container

LOMIDA is packed in a 50 cc white round high density polyethylene (HDPE) bottle with 33 mm blue child resistant cap. Pack sizes are 28’s and 30’s.

6.6 Special precautions for disposal and other handling

No special requirements.

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

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20 February 2024

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