PROFESSIONAL INFORMATION FOR DAMICAVA

SCHEDULING STATUS

S4

HYPERSENSITIVITY REACTIONS:

Hypersensitivity to abacavir (see **section 4.8**).

In clinical studies conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5 % of subjects receiving abacavir developed a hypersensitivity reaction, which in some cases has proved fatal.

Risk factors:

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. In the prospective study CNA106030 (PREDICT-1), use of pre-therapy screening for the HLA-B*5701 allele and subsequently avoiding abacavir in patients with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7,8 % (66 of 847) to 3,4 % (27 of 803) ($p < 0,0001$) and the incidence of hypersensitivity reactions confirmed by skin patch testing from 2,7 % (23 of 842) to 0,0 % (0 of 802) ($p < 0,0001$). Based on this study, it is estimated that 48 % to 61 % of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0 % to 4 % of patients who do not have the HLA-B*5701 allele.

Clinicians should screen for carriage of the HLA-B*5701 allele in any HIV infected patient without prior exposure to abacavir. Screening is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see "**Special considerations following an interruption of abacavir therapy**"). Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended.

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision making. Even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Clinical description:

The hypersensitivity reaction is characterised by the appearance of symptoms indicating multi-organ involvement. The majority of patients have fever and/or rash as part of the syndrome.

Some of the other symptoms of hypersensitivity may include fatigue, malaise, gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localised). The symptoms of this hypersensitivity reaction can occur at any time during treatment with abacavir, but usually occur within the first six weeks of therapy. The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Clinical management:

Regardless of their HLA-B*5701 status, any patient developing signs or symptoms of hypersensitivity must contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed, DAMICAVA must be discontinued immediately. DAMICAVA, or

any other medicine containing abacavir, must never be restarted following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, DAMICAVA should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). DAMICAVA, or any other medicine containing abacavir, should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medicines.

Special considerations following an interruption of DAMICAVA therapy:

Regardless of a patient's HLA-B*5701 status, if therapy with any abacavir containing product has been discontinued and restarting therapy with DAMICAVA is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. If a hypersensitivity reaction cannot be ruled out, DAMICAVA or any other medicine containing abacavir should not be restarted.

There have been infrequent reports of hypersensitivity reaction following re-introduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart DAMICAVA in these patients, this should be done only under direct medical supervision. On very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to restart DAMICAVA, this must be done only if medical care can be accessed readily by the patient or others.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of abacavir in such patients who test positive for the HLAB*5701 allele is not recommended.

Essential patient information:

Prescribers must ensure that patients are fully informed regarding the following information on the hypersensitivity reaction:

- Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701 positive.
- Patients must also be informed that HLA-B*5701 negative patients can also experience abacavir hypersensitivity reaction. Therefore, ANY patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT their doctor IMMEDIATELY.
- Patients who are hypersensitive to abacavir should be reminded that they must never take DAMICAVA or any other medicine containing abacavir again, regardless of their HLA-B*5701 status.
- In order to avoid restarting DAMICAVA, patients who have experienced a hypersensitivity reaction should be asked to return the remaining DAMICAVA tablets to the pharmacy.
- Patients who have stopped DAMICAVA for any reason and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.

Each patient should be reminded to read the Patient Information Leaflet (PIL) included in the DAMICAVA pack.

1. NAME OF THE MEDICINE

DAMICAVA 600 mg/50 mg/300 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains abacavir sulfate equivalent to abacavir 600 mg, dolutegravir sodium equivalent to dolutegravir 50 mg and lamivudine 300 mg as active ingredients.

Contains sugar: mannitol (145 mg/tablet).

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

3. PHARMACEUTICAL FORM

Film-coated tablets.

DAMICAVA tablets are brown coloured, oval shaped, biconvex, film-coated tablet, debossed with "Cipla" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DAMICAVA is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 18 years of age, who are antiretroviral treatment-naïve or are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral medicines in DAMICAVA.

4.2. Posology and method of administration

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

DAMICAVA should not be administered to patients younger than 18 years.

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

Separate preparations of dolutegravir, abacavir or lamivudine should be administered in cases where discontinuation or dose adjustment is indicated. In such cases the medical practitioner should refer to the individual product information for these medicines. Since the recommended dose of dolutegravir is 50 mg twice daily for patients with resistance to integrase inhibitors, the use of DAMICAVA is not recommended for patients with integrase inhibitor resistance.

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

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

Special populations

Adults and adolescents weighing at least 40 kg:

The recommended dose is one tablet per day.

Missed dose:

If the patient misses a dose of DAMICAVA, the patient should take DAMICAVA as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Elderly:

There are limited data available on the use of dolutegravir, abacavir and lamivudine in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (see **section 5.2 - Special Patient Populations**). When treating

elderly patients, consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, concomitant medicine or disease.

Renal impairment:

Whilst no dosage adjustment of dolutegravir or abacavir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to decreased clearance. Therefore, DAMICAVA is contraindicated in patients with a creatinine clearance less than 50 mL/min (see **sections 4.3 and 5.2 - Special Patient Populations**).

Hepatic impairment:

A dose reduction of abacavir may be required for patients with mild hepatic impairment (Child-Pugh grade A). As dose reduction is not possible with DAMICAVA, the separate preparations of dolutegravir, abacavir or lamivudine should be used when administering treatment to such patients. DAMICAVA is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (see **sections 5.2 – Special populations and 4.3**).

Method of administration

Oral.

DAMICAVA can be taken with or without food.

4.3. Contraindications

DAMICAVA is contraindicated in:

- Patients with known hypersensitivity to dolutegravir, abacavir, lamivudine or to any other ingredient contained in DAMICAVA as listed in **section 6.1**.
- Combination with dofetilide or pilsicainide.

- Patients with moderate to severe hepatic insufficiency due to the abacavir component (see **section 5**).
- Patients with renal insufficiency with a creatinine clearance of < 50 mL/min due to the lamivudine component (see **section 5**).
- Patients who are also taking metformin (see **section 4.5**).

4.4. Special warnings and precautions for use

Safety and efficacy of the individual active ingredients in various antiretroviral regimens with similar dosages as contained in DAMICAVA have been established in clinical studies. However, safety and efficacy of the actives combined in a fixed drug combination (FDC) for the treatment of HIV, as in DAMICAVA have not been established in clinical studies.

All warnings included in this leaflet are relevant to the individual components, abacavir, lamivudine and dolutegravir. No additional warnings relevant to DAMICAVA are included.

Hypersensitivity to abacavir – refer to boxed warning.

Hypersensitivity to dolutegravir:

Hypersensitivity reactions have been reported with dolutegravir and were characterised by rash, constitutional findings and sometimes, organ dysfunction, including liver injury. DAMICAVA must be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with DAMICAVA after the onset of hypersensitivity may result in a life-threatening reaction.

Lactic acidosis/hyperlactataemia and severe hepatomegaly with steatosis:

Use of abacavir and lamivudine as in DAMICAVA can result in potentially fatal lactic acidosis and severe hepatomegaly with steatosis due to mitochondrial dysfunction. Clinical features indicative of lactic acidosis include nausea, vomiting, abdominal pain, dyspnoea, tachypnoea, fatigue and unexplained weight loss. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2 to 5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, and hyperthyroidism.
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients. Caution should be exercised when administering DAMICAVA to patients with known risk factors for liver disease. Treatment with DAMICAVA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis of hepatotoxicity.

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 patient with a raised lactate level. Blood for lactate assay should be heparinised and stored on ice. After recovery, NRTIs should be avoided. Seek expert advice on medicine selection. The above lactate values may not be applicable to paediatric patients. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of DAMICAVA alone or in combination.

Caution should be exercised when administering DAMICAVA particularly to those with known risk factors for liver disease. Treatment with DAMICAVA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Pancreatitis:

Pancreatitis has been observed in some patients receiving DAMICAVA. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of DAMICAVA until diagnosis of pancreatitis is excluded.

Renal insufficiency:

In patients with moderate to severe renal impairment, the terminal half-life of DAMICAVA is increased due to decreased clearance.

Hepatic impairment:

Use of DAMICAVA can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of DAMICAVA has not been established in patients with significant underlying liver disorders/diseases. 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. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

DAMICAVA is contraindicated in patients with moderate to severe hepatic impairment (see **section 5**).

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues 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 post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above), other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed in utero to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, 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.

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 antiretroviral 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, 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) 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.

Opportunistic infections:

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

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

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 package inserts for these medicines. Patients co-infected with HIV and HBV who discontinue DAMICAVA 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. Discontinuation of DAMICAVA therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

The risk of HIV transmission to others:

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

Cardiovascular events:

The risk of cardiovascular events is increased in abacavir containing medicines, including DAMICAVA. Patients with a high risk of cardiovascular events, should avoid using abacavir containing medicines, including DAMICAVA.

Myocardial infarction:

In a prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous six months was correlated with an increased risk of myocardial infarction. As a precaution the underlying risk of coronary heart disease should be considered when prescribing

antiretroviral therapies, including abacavir and action taken to minimise all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Medicine interactions:

Caution should be taken during co-administration of medicines that may change the exposure of dolutegravir, abacavir, lamivudine or medications that may have their exposure be changed by use of DAMICAVA (see **sections 4.3** and **4.5**)

Co-administration of dolutegravir 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) (see **section 4.5**).

Dolutegravir should not be co-administered with polyvalent cation-containing antacids. Dolutegravir is recommended to be administered 2 hours before or 6 hours after these medicines (see **section 4.5**). DAMICAVA is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements, or alternatively, administered with food (see **section 4.5**).

DAMICAVA may increase metformin concentrations. Therefore, metformin is contraindicated in patients that are on DAMICAVA treatment (see **sections 4.3** and **4.5**).

Co-administration of DAMICAVA with medicines containing any of its active components (abacavir, lamivudine and dolutegravir) is contraindicated. Since the recommended dose of dolutegravir is 50 mg twice daily for patients taking efavirenz, nevirapine, rifampicin and tipranavir/ritonavir, the use of DAMICAVA is not recommended for patients taking these medicines (see **section 4.5**).

Mannitol

DAMICAVA contains mannitol which may have an effect on the glycaemic control of patients with diabetes mellitus.

DAMICAVA may have a mild laxative effect.

4.5. Interaction with other medicines and other forms of interaction

Effect of dolutegravir, abacavir and lamivudine on the pharmacokinetics of other medicines.

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50} > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MRP2, or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters.

In medicine interaction studies, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, ritonavir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, bocepravir, telaprevir and oral contraceptives containing norgelgestromin and ethinyl estradiol.

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) (IC_{50} = 1,93 µM), multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6,34 µM) and MATE2-K (IC_{50} = 24,8 µM). Given dolutegravir's *in vivo* exposure, it has a low potential to affect the transport of MATE2-K substrates *in vivo*. *In vivo*, dolutegravir may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 or MATE1 (dofetilide, pilsicainide or metformin) (**see** Table 3).

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC_{50} = 2,12 µM) and OAT3 (IC_{50} = 1,97 µM). However, dolutegravir had no notable effect on the pharmacokinetics *in vivo* of the OAT substrates tenofovir and para aminohippurate, and therefore has low propensity to cause medicine interactions via inhibition of OAT transporters.

Abacavir and lamivudine do not inhibit or induce CYP enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6).

Effect of other medicines on the pharmacokinetics of dolutegravir, abacavir and lamivudine:

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp and BCRP; therefore, medicines that induce these enzymes or transporters may theoretically reduce dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Co-administration of dolutegravir and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 3).

Efavirenz, nevirapine, rifampicin and tipranavir/ritonavir each reduced the plasma concentrations of dolutegravir significantly, making it necessary to adjust the dolutegravir dose 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 dolutegravir 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 lowered plasma concentrations of dolutegravir but does not require a dosage adjustment of dolutegravir. A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, bocepravir, telaprevir, prednisone, rifabutin and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no dolutegravir dose adjustment is required when co-administered with these medicines.

The likelihood of metabolic interactions with abacavir and lamivudine is low. Abacavir and lamivudine are not significantly metabolised by CYP enzymes. The primary pathways of abacavir

metabolism in human are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66 % of the administered dose. These metabolites are excreted in the urine. The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicine administered concurrently should be considered, particularly when the main route of elimination is renal.

Table 3: Medical interactions with dolutegravir

Concomitant medicine class/name	**Effect on concentration of dolutegravir or concomitant medicine**	**Clinical comment**
HIV-1 antiviral medicines		
Non-nucleoside reverse transcriptase inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC ↓ 71 %, C_{max} ↓ 52 % C_{λ} ↓ 88 %. ETR ↔	Etravirine decreased plasma dolutegravir concentration, which may result in loss of virologic response and possible resistance to dolutegravir. DAMICAVA 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 % C_{λ} ↓ 75 %.	Efavirenz decreased dolutegravir plasma concentrations. Since the dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz,

Concomitant medicine class/name	Effect on concentration of dolutegravir or concomitant medicine	Clinical comment
	EFV ↔	the co-administration of efavirenz with DAMICAVA is not recommended.
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. Since the dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine, the co-administration of nevirapine with DAMICAVA is not recommended.
Protease inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 %, C_{max} ↑ 49 % C_{λ} ↑ 180 %. ATV ↔	Atazanavir increased dolutegravir plasma concentration. Dose adjustment is not required.
Protease inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 % C_{λ} ↑ 121 %.	Atazanavir/ritonavir increased dolutegravir plasma concentration. Dose adjustment is not required.

Concomitant medicine class/name	Effect on concentration of dolutegravir or concomitant medicine	Clinical comment
	ATV ↔ RTV ↔	
Protease inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % C_{λ} ↓ 76 %. TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. Since the dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir, the co-administration of tipranavir/ritonavir with DAMICAVA is not recommended.
Protease inhibitor: Fosamprenavir/ritonavir (FPV + RTV)	Dolutegravir ↓ AUC ↓ 35 %, C_{max} ↓ 24 % C_{λ} ↓ 49 %. FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but reduced efficacy was not reported by clinical studies. No dose adjustment is necessary in INI-naïve patients.
Protease inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.

Concomitant medicine class/name	**Effect on concentration of dolutegravir or concomitant medicine**	**Clinical comment**
Protease inhibitor: Lopinavir/ritonavir (LPV + RTV)	Dolutegravir ↔ LPV ↔ RTV ↔ AUC ↔ C_{max} ↔ C_{λ} ↔	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 % C_{λ} ↓ 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)	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 % C_{λ} ↑ 28 % LPV ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Concomitant medicine class/name	Effect on concentration of dolutegravir or concomitant medicine	Clinical comment
	RTV ↔ ETR ↔	
Protease inhibitor: Darunavir/ritonavir + etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % C_{λ} ↓ 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 dolutegravir is contraindicated due to the potential life threatening toxicity caused by high dofetilide or pilsicainide concentration (see **section 4.3**).
Oxcarbazepine Phenytoin	Dolutegravir ↓	Co-administration may decrease dolutegravir plasma concentration and

Concomitant medicine class/name	Effect on concentration of dolutegravir or concomitant medicine	Clinical comment
Phenobarbital Carbamazepine St. John's wort		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. DAMICAVA is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 %	DAMICAVA is recommended to be administered 2 hours before or 6 hours after taking products containing calcium, or alternatively, administer with food.
Iron supplements	Dolutegravir ↓ AUC ↓ 54 %, C_{max} ↓ 57 % and C_{24} ↓ 56 %.	DAMICAVA is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is

Concomitant medicine class/name	Effect on concentration of dolutegravir or concomitant medicine	Clinical comment
		contra-indicated in patients taking DAMICAVA (see **section 4.3**).
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C_{λ} ↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. Since the dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin, the co-administration of rifampicin with DAMICAVA is not recommended.
Oral contraceptives (Ethyinyl estradiol (EE) and norgestromin NGMN)	Effect of dolutegravir: EE ↔ AUC ↑ 3 % C_{max} ↓ 1% C_{λ} ↑ by 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 % C_{λ} ↓ 7 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2%	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of

Concomitant medicine class/name	Effect on concentration of dolutegravir or concomitant medicine	Clinical comment
	C_{max} ↔ C_{λ} ↓ 1 %	methadone is necessary when co-administered with dolutegravir.

Abbreviations: ↑ = increased; ↓ = decreased; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration; C_{λ} = concentration at the end of the interval

Table 4: Abacavir-associated medicine interactions

Concomitant medicine class/name	Effect on concentration of abacavir or concomitant medicine	Clinical comment
Methadone (40 to 90 mg once daily for 14 days/600 mg single dose, then 600 mg twice daily for 14 days)	Abacavir AUC ↔ C_{max} ↓ 35 % Methadone CL/F ↑ 22 %	The changes in abacavir pharmacokinetics are not considered clinically relevant. The changes in methadone pharmacokinetics are not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.
Ethanol	Abacavir AUC ↑ 41 % Ethanol AUC ↔	Given the safety profile of abacavir, these findings are not considered clinically significant.

Abbreviations: ↑ = increased; ↓ = decreased; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration; CLF = apparent clearance

Table 5: Lamivudine-associated medicine interactions

Concomitant medicine class/name	**Effect on concentration of lamivudine or concomitant medicine**	**Clinical comment**
Trimethoprim/ sulfamethoxazole (cotrimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose).	Lamivudine: AUC ↑ 40 % Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔.	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see **section 4.2**). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* (*P. carinii*) pneumonia and toxoplasmosis has not been studied. DAMICAVA should not be used for subjects with CLcr of < 50 mL/min (see **section 4.3**).
Emtricitabine		Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicines are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase

Concomitant medicine class/name	Effect on concentration of lamivudine or concomitant medicine	Clinical comment
		gene (M184V) and therefore the therapeutic efficacy of these medicines in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed dose combinations.
Zalcitabine		Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. Concurrent use of DAMICAVA zalcitabine is therefore not recommended.

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 DAMICAVA in women of childbearing potential to exclude inadvertent (unintentional) use of DAMICAVA 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 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 dolutegravir, the benefits and risks of continuing dolutegravir 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.

Dolutegravir 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.

Late onset neurological disorders relating to mitochondrial disfunction have been observed in infants/children who have been exposed in utero and/or postnatally to nucleoside analogues as contained in DAMICAVA (see **section 4.4**).

Breastfeeding

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

Dolutegravir is excreted 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 hr compared to 14 hr 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 dolutegravir on human male or female fertility. Animal studies indicate no effects of dolutegravir on male or female fertility (see **section 5.3**).

4.7. Effects on ability to drive and use machines

DAMICAVA may affect the ability to drive and use machines. Patients should ensure that they do not engage in driving or operating machines until they know how DAMICAVA affects them.

4.8. Undesirable effects

Hypersensitivity to abacavir (see also boxed warning):

In clinical studies conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5 % of subjects receiving abacavir developed a hypersensitivity reaction, which in some cases has proved fatal. This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever.

Symptoms can occur at any time while being treated with abacavir, but usually appear within the first six weeks of initiation of treatment (median time to onset 11 days). The signs and symptoms of this hypersensitivity reaction are listed below.

Skin and subcutaneous tissue disorders: rash (usually maculopapular or urticarial).

Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration.

Respiratory, thoracic and mediastinal disorders: dyspnoea, cough, sore throat, adult respiratory distress syndrome, respiratory failure.

General disorders and administrative site conditions: fever, fatigue, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis.

Nervous system disorders: headache, paraesthesia.

Blood and the lymphatic system disorders: lymphopenia

Hepato-biliary disorders: elevated liver function tests, hepatic failure.

Musculoskeletal connective tissue and bone disorders: myalgia, rarely rhabdomyolysis, arthralgia, elevated creatine phosphokinase.

Renal and urinary disorders: elevated creatinine, renal failure.

Some patients with hypersensitivity were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in abacavir being continued or re-introduced, leading to a more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. If hypersensitivity reaction cannot be ruled out, DAMICAVA, or any other medicine containing abacavir should not be restarted. The symptoms related to this hypersensitivity reaction worsen with continued therapy and usually resolve upon discontinuation of abacavir. Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction may be more severe than on initial presentation and may include life-threatening hypotension and death. Regardless of their HLA-B*5701 status, patients who develop this hypersensitivity reaction must discontinue DAMICAVA and must never be rechallenged with DAMICAVA, or any other medicine containing abacavir.

Most undesirable effects occurring frequently (nausea, vomiting, diarrhoea, fever, lethargy, rash) in patients are due to abacavir hypersensitivity. Therefore, patients with any of these symptoms

should be carefully evaluated for the presence of this hypersensitivity reaction. If DAMICAVA has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart abacavir, this must be done only under direct medical supervision (see Special considerations following an interruption of DAMICAVA therapy in boxed warning).

The undesirable effects observed for the combination of the three components of this medicine are generally consistent with the side effect profiles for the individual components dolutegravir, abacavir and lamivudine. However, the following common treatment-emergent undesirable effects were observed with the combination but were not listed in the prescribed information for any of the individual components.

- **Gastrointestinal disorders:** abdominal distension, gastro-oesophageal reflux disease, dyspepsia
- **Nervous system disorders:** somnolence
- **Psychiatric disorders:** depression, nightmare and sleep disorders
- **Metabolism and nutrition disorders:** hypertriglyceridaemia and hyperglycaemia

In addition, fatigue and insomnia were observed at greater frequency with the combination when compared with the individual components. The frequency category for fatigue and insomnia was frequent with the combination.

Undesirable effects associated with the DAMICAVA film-coated tablets:

MedDRA system organ class	**Frequency**	**Side effects**
Metabolism and nutrition disorders:	*Less frequent:*	Hypertriglyceridaemia and hyperglycaemia.

Psychiatric disorders:	*Frequent:*	Depression, nightmares, sleep disorder.
	Less frequent:	Insomnia, anxiety, suicidal ideation or suicide attempt.
Nervous system disorders:	*Frequent:*	Somnolence, lethargy.
Gastrointestinal disorders:	*Frequent:*	Abdominal distension, gastro-oesophageal reflux disease, dyspepsia.
General disorders and administrative site conditions:	*Frequent:*	Fatigue.
Investigations:	*Frequent:*	CPK elevations, ALT/AST elevations.

Table 6: Reported adverse events associated with individual components of the DAMICAVA

System organ class	**Dolutegravir**	**Abacavir**	**Lamivudine**
Blood and lymphatic system disorder			*Less frequent:* neutropenia, anaemia, thrombocytopenia.
Immune system disorders	*Less frequent*: hypersensitivity. (see **section 4.4**)	*Frequent*: medicine Hypersensitivity. (see **section 4.4**).	

	immune reconstitution syndrome (see **section 4.4**).		
Metabolism and nutrition disorders	*Frequent*: weight gain.	*Frequent*: anorexia.	
Psychiatric disorders	*Frequent*: insomnia, abnormal dreams.		
Nervous system disorders	*Frequent*: headache, dizziness.	*Frequent*: headache.	*Frequent*: headache.
Gastrointestinal disorders	*Frequent*: nausea, diarrhoea, vomiting, flatulence, abdominal pain, upper abdominal pain, abdominal discomfort.	*Frequent*: nausea, vomiting, diarrhoea.	*Frequent*: nausea, vomiting, upper abdominal pain, diarrhoea.
Hepatobiliary disorders	*Less frequent*: hepatitis.		*Less frequent*: transient rises in liver enzymes (AST, ALT).
Skin and subcutaneous system disorders	*Frequent*: rash, pruritus.		*Frequent*: rash.

General disorders and administration site conditions	*Frequent*: fatigue.	*Frequent*: fever, lethargy, fatigue.	*Frequent*: fever, malaise, fatigue.

Changes in laboratory chemistries:

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 96 weeks. A mean change from baseline of 12,6 µmol/L was observed after 96 weeks of treatment. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see **section 5.1 – Effects on renal function**). Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see **section 5.2 - Metabolism**). Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with dolutegravir therapy.

The undesirable effects listed in Table 7 below have been identified during post-approval use of abacavir and lamivudine. No dolutegravir or DAMICAVA post marketing data are available.

Table 7: Undesirable effects based on reported post-marketing data

System organ class	Abacavir	Lamivudine
Blood and lymphatic system disorder		Pure red cell aplasia.
Metabolism and nutrition disorders	Hyperlactataemia, lactic acidosis (see **section 4.4**)	Hyperlactataemia, lactic acidosis (see **section 4.4**)

System organ class	Abacavir	Lamivudine
Nervous system disorders		Paraesthesiae, peripheral neuropathy has been reported although a causal relationship to treatment is uncertain.
Gastrointestinal disorders	Pancreatitis, but a causal relationship to abacavir is uncertain.	Increases in serum amylase, pancreatitis, although a causal relationship to lamivudine is uncertain.
Skin and subcutaneous system disorders	Rash (without systemic symptoms), Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.	Alopecia.
Musculoskeletal and connective tissue disorders		Arthralgia, muscle disorders *Less frequent*: Rhabdomyolysis.

There have been post marketing reports of weight gain with the use of dolutegravir.

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 “Adverse drug reaction and quality problem reporting form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problemreporting-form/ or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9. Overdose

Signs and symptoms:

Data are limited with regards to dolutegravir overdosage.

Treatment:

The patient should be treated symptomatically and supportively with appropriate monitoring as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 20.2.8 Antiviral agents

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infections, combinations

ATC code: J05AR13

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. Biochemical assays of strand transfer using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2,7 nM and 12,6 nM *in vitro*, dolutegravir dissociates slowly from the active site of the wild type-integrase DNA complex ($T_{1/2}$ 71 hours).

Abacavir and lamivudine are selective nucleoside reverse transcriptase inhibitors (NRTIs) of HIV-1 and HIV-2. Abacavir and lamivudine are metabolised sequentially by intracellular kinases to their respective triphosphate (TP) active moieties, namely carbovir-TP (the active TP form of abacavir) and lamivudine-TP with extended intracellular half-lives supporting once daily dosing (see **section 5.2 - Elimination**). Lamivudine TP and carbovir TP act as both substrates and inhibitors of HIV reverse transcriptase (RT). However, the monophosphate forms are responsible for the antiviral activity. The monophosphate forms are incorporated into the DNA chain, which results in termination of viral DNA replication. The TP forms have been shown to have less affinity for host cell DNA polymerases.

Resistance *in vivo* (dolutegravir): integrase naïve patients

No integrase inhibitor-resistant mutations or treatment emergent resistance to the NRTI backbone therapy were reported in clinical studies of treatment-naïve patients with dolutegravir given at daily doses of 50 mg. There are reports of treatment emergent integrase resistance in treatment experienced (but integrase naïve) patients. A unique R263K integrase substitution was observed in these treatment experienced patients that developed integrase resistance, with a maximum fold change (FC) of 1,93.

Resistance *in vitro and in vivo* (abacavir and lamivudine)

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and *in vivo* and are associated with specific mutations in the RT codon region (codons M184V, K65R, L74V and Y115F). During *in vitro* abacavir selection, the M184V mutation occurred first and resulted in about a two-fold

increase in IC_{50}, below the abacavir clinical cut-off of 4,5-FC. Continued passage in increasing concentrations of medicine resulted in selection for double RT mutants 65R/184V and 74V/184V or triple RT mutant 74V/115Y/184V. Two mutations conferred a 7- to 8-FC in abacavir susceptibility and combinations of three mutations were required to confer more than an 8-FC in susceptibility.

HIV-1 lamivudine resistance involves the development of a M184I or M184V amino acid change close to the active site of the viral RT. This variant has emerged in both *in vitro* and *in vivo* in HIV-1 patients receiving lamivudine-containing antiretroviral therapy. M184V mutants have reduced susceptibility to lamivudine and diminished viral replicative capacity *in vitro*. M184V mutation is associated with a low-level increase in abacavir resistance but does not confer clinical resistance for abacavir. Abacavir-resistant isolates may also show reduced sensitivity to lamivudine. The abacavir/lamivudine combination has demonstrated reduced susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, and to viruses with L74V plus the M184V/I substitution.

Effects on renal function

A 10 to 14 (Format) % reduction in mean serum creatinine clearance (CLcr) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on the glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). *In vitro* studies suggest that the increases in serum 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.

5.2. Pharmacokinetic properties

Studies have demonstrated bioequivalence between DAMICAVA and dolutegravir single entity tablet administered together with abacavir/lamivudine fixed dose combination tablet. There was

no clinically significant effect of a high fat meal on the exposure of abacavir or lamivudine with dolutegravir; a high fat meal increased the C_{max} by 37 % and the AUC by 48 %. These results show that DAMICAVA can be taken with or without food.

Absorption

After oral administration, dolutegravir, abacavir and lamivudine are absorbed. The absolute bioavailability of dolutegravir has not been established. The absolute bioavailability of oral abacavir and lamivudine in adults is 83 % and 80 to 85 %, respectively. The mean time to maximal serum concentrations (T_{max}) is about 2 to 3 hours (post dose for tablet formulation) for dolutegravir, 1,5 hours for abacavir and 1,0 hour for lamivudine. The geometric mean steady state pharmacokinetic parameters observed following multiple oral doses of once daily dolutegravir 50 mg are 53,6 µg.h/mL for AUC_{24}, 3,67 µg/mL for C_{max}, and 1,11 µg/mL for C_{24}. Following a single oral dose of 600 mg of abacavir, the mean C_{max} is 4,26 µg/mL and the mean AUC_{∞} is 11,95 µg.h/mL. Multiple oral doses of lamivudine 300 mg administered for a period of 7 days resulted in mean steady state C_{max} is 2,04 µg/mL and the mean AUC_{24} is 8,87 µg.h/mL.

Distribution

Following oral administration of dolutegravir, the apparent volume of distribution Vd/F was found to be 12,5 L, approximately. Intravenous administration of abacavir and lamivudine showed that the mean apparent volume of distribution is 0,8 and 1,3 L/kg, respectively.

In vitro studies have shown that dolutegravir is approximately 99,3 % bound to human plasma proteins. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma medicine-related radioactivity concentration ratios averaged between 0,441 to 0,535 indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0,2 to 1,1 % in healthy subjects,

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.

In vitro studies indicate that abacavir plasma protein binding ranges from low to moderate (approximately 49 %) at therapeutic concentrations.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and shows low plasma protein binding (less than 36 %).

Dolutegravir, abacavir and lamivudine are present in cerebrospinal fluid (CSF). CSF:plasma concentration ratio of dolutegravir ranged from 0,11 to 2,04 %. Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44 %. The mean ratio of CSF/serum lamivudine concentrations 2 to 4 hours after oral administration was approximately 12 %.

Metabolism

Dolutegravir is mainly metabolised by UGT1A1 with a minor CYP3A component (9,7 % of total dose administered in a human mass balance study). Dolutegravir is the principal 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 the faeces. It is not known 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 as ether glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose).

Abacavir undergoes hepatic metabolism with less than 2 % of the administered dose being renally excreted as unchanged compound. The main metabolic pathways in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66 % of the administered dose. These metabolites are excreted in the urine. Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared

unchanged by renal excretion. The likelihood of metabolic interactions with lamivudine is low due to the minor extent of hepatic metabolism (less than 10 %).

Elimination

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 0,56 L/hr. The mean half-life of abacavir is about 1,5 hours. The geometric mean terminal half-life of intracellular carbovir-TP at steady-state is 20,6 hours. Multiple oral doses of abacavir 300 mg twice a day resulted in no significant accumulation of abacavir. Abacavir is metabolised hepatically with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir represent about 83 % of the administered abacavir dose in the urine. The remainder is eliminated in the faeces. The observed lamivudine half-life of elimination is 5 to 7 hours. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was prolonged to 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/h/kg, predominantly by renal clearance (greater than 70 %) via the organic cationic transport system.

Special populations

Paediatric population

Studies in treatment-experienced HIV-1 infected children aged between 12 and 18 years old have demonstrated that once daily doses of dolutegravir 50 mg resulted in comparable exposure to that observed in adult patients who also received dolutegravir 50 mg once per day (see Table 1).

Table 1: Pharmacokinetic parameters in adolescents

Age/ weight	**Dolutegravir dose**	**Dolutegravir pharmacokinetic parameters**		
		$AUC_{(0-24)}$	**C_{max} µg/mL**	**C_{24}**

		µg.hr/mL		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 who weighed 37 kg received 35 mg once daily.				

There is limited data in adolescents receiving a daily dose of 600 mg of abacavir and 300 mg of lamivudine. Pharmacokinetic parameters are comparable to those reported in adults.

The elderly

Pharmacokinetic data for dolutegravir, abacavir and lamivudine in subjects of > 65 years old are limited.

Renal insufficiency

DAMICAVA should not be used in patients with creatinine clearance of less than 50 mL/min because the dose of lamivudine needs to be lowered even though dose adjustments for dolutegravir and abacavir are not required. Studies indicate that lamivudine plasma concentrations are elevated in patients with impaired renal function due to decreased clearance, necessitating dose reduction the lamivudine component. Therefore, the separate preparation of lamivudine should be used to treat these patients.

Abacavir undergoes hepatic metabolism, with approximately 2 % of the administered dose excreted unchanged in the urine. Pharmacokinetics of abacavir in patients with end-stage renal disease are similar to those with normal renal function.

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. There are no clinically significant differences in dolutegravir pharmacokinetics between patients with

normal renal function and those with severe renal function. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Pharmacokinetic data based on separate studies with abacavir, dolutegravir and lamivudine have been obtained. According to data obtained with abacavir, DAMICAVA is not recommended in patients with moderate to severe hepatic impairment.

Abacavir undergoes hepatic metabolism, primarily. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). The results indicated that the mean increase in abacavir exposure and half-life were 1,89 and 1,58 fold, respectively. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased. It may be necessary to lower the abacavir dosage in patients with mild hepatic impairment. The separate preparation of abacavir should therefore be used to treat these patients. There are no pharmacokinetic data for use of abacavir in moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to be variable and substantially increased in these patients. Therefore, DAMICAVA is not recommended in patients with moderate and severe hepatic impairment.

Data obtained for lamivudine in patients with moderate to severe hepatic impairment and for dolutegravir in patients with moderate hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction. Dolutegravir is primarily metabolised and eliminated by the liver. Studies have shown that dolutegravir exposure in patients with moderate liver impairment (Child-Pugh category B) was not significantly affected by a single dose of dolutegravir 50 mg. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in drug metabolising enzymes

There is no evidence that common polymorphisms in drug metabolising enzymes affect dolutegravir pharmacokinetics to a clinically meaningful extent.

Co-infection with Hepatitis B or C

Population pharmacokinetics analysis demonstrated that dolutegravir exposure was not clinically affected by hepatitis C virus co-infection. DAMICAVA pharmacokinetics have not been studied in subjects with hepatitis B co-infection (see **section 4.4**).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Sodium starch glycollate

Opadry II complete system 85F565121 Brown film-coating:

Iron oxide red

Iron oxide yellow

Macrogol

Polyvinyl alcohol (partly hydrolysed)

Talc

Titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store in the original container at or below 30 °C.

6.5. Nature and contents of container

DAMICAVA tablets are marketed in packs of 30's in white HDPE containers fitted with child resistant caps that contain a heat seal liner and 2 g silica gel bags.

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

52/20.2.8/0452

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

First authorisation: 14 April 2020

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

22 March 2024

This product has been manufactured under licence from the “Medicines Patent Pool”.