PROFESSIONAL INFORMATION FOR

DAMICAVA PAED

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DAMICAVA PAED Dispersible tablets

WARNING

Hypersensitivity to abacavir

Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSR can be life-threatening and may be fatal, when not managed appropriately. The risk for abacavir HSR to occur is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

In clinical studies, conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5 % of subjects who received abacavir, as contained in DAMICAVA PAED, 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.

It is recommended that any HIV-infected patient without prior exposure to abacavir be screened for HLA-B*5701 allele. 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 DAMICAVA PAED 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 re-challenge 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. Most 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 DAMICAVA PAED**, 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 DAMICAVA PAED.

Clinical management

Regardless of their HLA-B*5701 status, any patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed, DAMICAVA PAED MUST be discontinued immediately. DAMICAVA PAED, 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 PAED 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 PAED, or any other medicine containing abacavir, should not be restarted even if a recurrence of symptoms occurs following re-challenge with alternative medication(s).

An Alert Card with information for the patient about the hypersensitivity reaction is included in the DAMICAVA PAED pack.

Special considerations following an interruption of DAMICAVA PAED therapy

Regardless of a patient's HLA-B*5701 status, if therapy with DAMICAVA PAED or any abacavir containing product has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. Patients who have discontinued DAMICAVA PAED due to possible adverse events or illness should be advised to consult their doctor before restarting treatment. **If a hypersensitivity reaction cannot be ruled out, DAMICAVA PAED or any other medicine containing abacavir should not be restarted.**

There have been infrequent reports of a 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 PAED in these patients, this should be done only under direct medical supervision.

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 PAED, 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 DAMICAVA PAED in patients of unknown HLA-B*5701 status who have previously tolerated DAMICAVA PAED. Re-initiation of DAMICAVA PAED in such patients who test positive for the HLA-B*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 the abacavir in DAMICAVA PAED 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 PAED or any other medicine containing abacavir again, regardless of their HLA-B*5701 status.

- in order to avoid restarting DAMICAVA PAED, patients who have experienced a hypersensitivity reaction should be asked to return the remaining DAMICAVA PAED tablets to the pharmacy.
- patients, who have stopped DAMICAVA PAED 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 package leaflet included in the DAMICAVA PAED pack. They should be reminded of the importance of removing the Alert Card included in the pack and keeping it with them always.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains abacavir sulfate 70,280 mg equivalent to abacavir 60 mg, dolutegravir sodium 5,262 mg equivalent to dolutegravir 5 mg and lamivudine 30 mg.

Excipient with known effect:

Contains sweetener: aspartame 9,5 mg/tablet.

Contains sugar: mannitol 14,5 mg/tablet.

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

3. PHARMACEUTICAL FORM

Dispersible tablets.

Pink coloured, oval shaped, biconvex, film-coated tablets debossed with “C” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DAMICAVA PAED is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in paediatric patients aged at least 3 months and weighing 6 kg to less than 25 kg.

4.2 Posology and method of administration

Posology

Paediatric population

Patients should be stabilised on individual medicines before being switched to DAMICAVA PAED.

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

DAMICAVA PAED can be taken with or without food.

DAMICAVA PAED is available as dispersible tablets for patients weighing at least 6 kg, and less than 25 kg.

The dispersible tablets should be dispersed in drinking water. When dispersed, the amount of water will depend on the number of tablets prescribed. The tablet should not be chewed, cut or crushed.

The recommended dose of DAMICAVA PAED dispersible tablets is determined according to weight and age and is presented in the table below.

DAMICAVA PAED should be taken once a day.

Table 1: DAMICAVA PAED

Body weight	**DAMICAVA PAED [a] number of tablets**	**Total daily dose**
6 kg to < 10 kg	3 tablets once daily	180 mg abacavir, 15 mg dolutegravir, and 90 mg lamivudine once daily
10 kg to < 14 kg	4 tablets once daily	240 mg abacavir, 20 mg dolutegravir, and 120 mg lamivudine once daily
14 kg to < 20 kg	5 tablets once daily	300 mg abacavir, 25 mg dolutegravir, and 150 mg lamivudine once daily
20 kg to < 25 kg	6 tablets once daily	360 mg abacavir, 30 mg dolutegravir, and 180 mg lamivudine once daily

[a] DAMICAVA PAED is a fixed-dose combination product containing 60 mg of abacavir, 5 mg of dolutegravir, and 30 mg of lamivudine.

Dose adjustment

DAMICAVA PAED is a fixed-dose tablet and should not be prescribed for patients requiring dose adjustments. Separate formulations for abacavir, dolutegravir and lamivudine are available in cases where discontinuation or dose adjustments of one of the actives is indicated or in patients experiencing dose limiting adverse events. In these cases, the medical practitioner should consult the professional information (PI) of the individual medicines.

Renal impairment

A dosage adjustment of lamivudine may be necessary in patients with mild renal impairment, due to a decreased clearance of lamivudine. However, a lamivudine dose reduction cannot be achieved with lamivudine in a fixed-dose combination as with DAMICAVA PAED. The use of

DAMICAVA PAED is contraindicated in patients with moderate (CrCl < 50 mL/min) and severe (CrCl < 30 mL/min) renal impairment (see **section 4.3**).

Hepatic impairment

A dose reduction of abacavir may be required in patients with mild hepatic impairment. As dose reduction is not possible with DAMICAVA PAED, the separate preparations of abacavir, dolutegravir and lamivudine should be used. DAMICAVA PAED is contraindicated in patients with moderate [Child Pugh B (score 7 - 9 points)] and severe [Child Pugh C (score 10 - 15 points)] hepatic impairment (see **sections 4.3** and **5.2**).

Method of administration

DAMICAVA PAED should be dispersed in water before administration. Please use the following procedure to disperse DAMICAVA PAED:

1. The number of tablets to be administered to the patient will be determined by his or her body weight (as shown in **Table 1** above).
2. Remove the number of tablets recommended for one dose from the bottle with dry hands.
3. The tablet(s) should be placed in a container and four teaspoonfuls (20 mL) of drinking water should be added per tablet.
4. The tablets should be swirled or stirred until completely dispersed. The suspension has a strawberry flavour.
5. The child should consume the entire quantity immediately.
6. The container should be rinsed with an additional small amount of drinking water and the child should drink the contents to ensure that the whole dose is taken.
7. The tablets should not be mixed with any liquid other than water.

4.3 Contraindications

DAMICAVA PAED is contraindicated in:

- Patients with known hypersensitivity to abacavir, dolutegravir or lamivudine or to any of the excipients used in the formulation of DAMICAVA PAED (see **section 6.1**)**.** Abacavir **must never** be restarted in a patient who has stopped therapy due to an abacavir hypersensitivity reaction.
- Patients with moderate [Child Pugh B (score 7 - 9 points)] and or severe [Child Pugh C (score 10 - 15 points)] hepatic impairment (see **section 5.2**).
- Patients with moderate (CrCl < 50 mL/min) or severe (CrCl < 30 mL/min) renal impairment.
- Patients weighing less than 6 kg, or 25 kg and more.
- Patients with phenylketonuria, as DAMICAVA PAED contains aspartame (see **section 4.4**).
- Pregnancy and lactation (see **section 4.6**).
- Combination with dofetilide and pilsicainide.
- Patients less than 3 months of age (see **section 4.1**).

4.4 Special warnings and precautions for use

Hypersensitivity reactions to abacavir (see also section 4.8)

Abacavir is associated with a risk for hypersensitivity reactions (HSR) (see **section 4.8**) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.

The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

Therefore, the following should be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.
- DAMICAVA PAED should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir containing regimen.
- **DAMICAVA PAED must be stopped without delay**, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with DAMICAVA PAED after the onset of hypersensitivity may result in a life-threatening reaction.
- After stopping treatment with DAMICAVA PAED for reasons of a suspected HSR, **DAMICAVA PAED or any other medicine containing abacavir must never be re-initiated**.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation and may include life-threatening hypotension and death.
- In order to avoid restarting abacavir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining DAMICAVA PAED tablets.
- **Clinical description of abacavir HSR***:*

  Abacavir HSR has been well characterised through clinical studies and during post-marketing follow-up.

  Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, **although these reactions may occur at any time during therapy.** Almost all HSR to abacavir include fever and/or rash. Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in **section 4.8 Description of selected adverse reactions**, including respiratory and gastrointestinal symptoms. Importantly, such symptoms **may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis**.

The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Patients who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re-initiating abacavir therapy (see **section 4.8 Description of selected adverse reactions**). Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

Hypersensitivity reactions to dolutegravir

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

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

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

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination anti-retroviral therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, cryptococcal meningitis, generalised and/or focal atypical mycobacterial infections and *Pneumocystis jiroveci* pneumonia (PJP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. 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. Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of DAMICAVA PAED therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy (referring to treatment guidelines) when starting dolutegravir-based therapy in hepatitis B co-

infected patients (see **section 4.8**).

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, high 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.

Interactions

Caution should be given to co-administering medicines (prescription and non-prescription) that may change the exposure of DAMICAVA PAED or medicines that may have their exposure changed by DAMICAVA PAED (see **sections 4.3** and **4.5**).

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

DAMICAVA PAED is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements, or alternatively, administered after food.

DAMICAVA PAED increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of DAMICAVA PAED with metformin, to maintain glycaemic control.

Opportunistic infections

Patients receiving DAMICAVA PAED or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV diseases. Regular monitoring of viral load and CD4 counts needs to be done.

Transmission of infection

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

Lactic acidosis/hyperlactataemia

Use of DAMICAVA PAED can result in potentially fatal lactic acidosis because of mitochondrial dysfunction. Clinical features are non-specific and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious signs of biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond 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 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, thyrotoxicosis 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 PAED to patients with known risk factors for liver

disease. Treatment with DAMICAVA PAED should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

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 signs and symptoms.

Pancreatitis

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

Patients with moderate to severe renal impairment

The clearance of lamivudine is decreased with renal impairment requiring a reduction in the dose of lamivudine which cannot be achieved with DAMICAVA PAED. If a dose reduction in mild renal impairment is needed patients should be switched to separate formulations or the actives to enable a reduction in the dose of lamivudine.

DAMICAVA PAED use is contraindicated in patients with moderate (CrCl < 50 mL/min) and severe (CrCl < 30 mL/min) renal impairment (see **section 4.3**).

Hepatic impairment

The unbound fraction of dolutegravir in the blood is doubled in patients with moderate hepatic impairment. DAMICAVA PAED is contraindicated in patients with moderate or severe hepatic impairment (Child Pugh grade C) (see **section 4.3**). The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir have not been studied.

DAMICAVA PAED use is contraindicated in patients with moderate [Child Pugh B (score 7 - 9 points)] or severe [(Child Pugh C (score 10 - 15 points)] hepatic impairment irrespective of the underlying cause (see **section 4.3**). Mild hepatic impairment may require a dose adjustment of abacavir which cannot be achieved with DAMICAVA PAED. Patients should be switched to separate formulations of the actives to enable a dose reduction of abacavir.

Use of DAMICAVA PAED can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). In case of concomitant antiviral therapy for hepatitis B or C, the relevant professional information (PI) of these medicines, should be consulted. 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.

Co-infection with hepatitis B or C

Provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN), the safety profile of dolutegravir in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT

abnormalities were higher in the subgroup with hepatitis B and/or C co-infection. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of DAMICAVA PAED therapy, particularly in those whose anti-hepatitis B therapy was withdrawn.

Patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If DAMICAVA PAED is discontinued in patients co-infected with hepatitis B virus, frequent monitoring of both liver function tests, and markers of HBV replication should be done.

Cardiovascular events

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

Myocardial infarction

There is some evidence of a possible association between abacavir use and an increased risk of myocardial infarction.

As a precaution the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including DAMICAVA PAED and action taken to minimise all modifiable risk factors (e.g., hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Excipients

DAMICAVA PAED contains 9,5 mg aspartame in each dispersible tablet, which is equivalent to 3,393 mg/100 mg. Aspartame is a source of phenylalanine. It may be harmful if the patient has

phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction with other medicines and other forms of interaction

Dolutegravir

Effect of DAMICAVA PAED on the pharmacokinetics of other medicines

In vitro, DAMICAVA PAED 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, OATP1B1, OATP1B3, OCT1 or MRP2. *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, DAMICAVA PAED is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters [e.g., reverse transcriptase and protease inhibitors, opioid analgesics, antidepressants, statins, azole antifungals (such as fluconazole, itraconazole, clotrimazole), proton pump inhibitors (such as esomeprazole, lansoprazole, omeprazole), anti-erectile dysfunction medicines (such as sildenafil, tadalafil, vardenafil), acyclovir, valacyclovir, sitagliptin, adefovir].

DAMICAVA PAED did not have a clinically relevant effect on the pharmacokinetics of the following: tenofovir, methadone, efavirenz, lopinavir, atazanavir, darunavir, etravirine, fosamprenavir, rilpivirine, boceprevir, telaprevir, daclatasvir and oral contraceptives containing norgestimate and ethinyl oestradiol.

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 (IC50 = 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* DAMICAVA PAED may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 (dofetilide, pilsicainide or metformin) (see **Table 2: Dolutegravir medicine interactions – Other medicines**).

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 *in vivo* pharmacokinetics of the OAT substrates tenofovir and para-aminohippurate and therefore has low propensity to cause interactions via inhibition of OAT transporters.

Effect of other medicines on the pharmacokinetics of DAMICAVA PAED

DAMICAVA PAED is eliminated mainly through metabolism by UGT1A1. DAMICAVA PAED is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore, medicines that induce those enzymes may theoretically decrease dolutegravir plasma concentration and reduce the therapeutic effect of DAMICAVA PAED.

Co-administration of DAMICAVA PAED and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see **Table 2**).

In vitro, dolutegravir is not a substrate of human organic anion transporting polypeptide (OATP)1B1, OATP1B3, or OCT1, therefore medicines that solely modulate these transporters are not expected to affect dolutegravir plasma concentration.

Efavirenz, nevirapine, rifampicin and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly and require dolutegravir dose adjustment to the recommended dose.

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

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. Since DAMICAVA PAED is a fixed-dose combination product of abacavir, dolutegravir and lamivudine, dose adjustment of dolutegravir is not possible.

Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of DAMICAVA PAED. Caution is warranted and clinical monitoring is recommended when these combinations are given in integrase inhibitor (INI)-resistant patients (see **Table 2: Dolutegravir medicine interactions – HIV-1 antiviral medicines**).

A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no DAMICAVA PAED dose adjustment is required when co-administered with these medicines.

Table 2: Dolutegravir medicine interactions

Concomitant medicine class: Medicine name	**Effect on concentration of DAMICAVA PAED or concomitant medicine**	**Clinical comment**
HIV-1 antiviral medicines		
Non-nucleoside reverse transcriptase inhibitor: etravirine (ETR) without boosted protease inhibitor	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % Cτ ↓ 88 % ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of dolutegravir should be given when co-administered with etravirine without boosted protease inhibitors. Since DAMICAVA PAED is a fixed-dose combination product of abacavir, dolutegravir and lamivudine, dose adjustment of dolutegravir is not possible. Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir in INI-resistant patients.
Protease inhibitor: lopinavir/ritonavir + etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC ↑ 11 % C_{max} ↑ 7 % Cτ ↑ 28 % LPV ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dolutegravir dose adjustment is necessary.

	RTV ↔	
Protease inhibitor: darunavir/ritonavir + etravirine	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % Cт ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dolutegravir dose adjustment is necessary.
Non-nucleoside reverse transcriptase inhibitor: efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57 % C_{max} ↓ 39 % Cт ↓ 75 % EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir should be given when co-administered with efavirenz. Since DAMICAVA PAED is a fixed-dose combination product of abacavir, dolutegravir and lamivudine, dose adjustment of dolutegravir is not possible. Alternative combinations that do not include efavirenz should be used where possible in INI-resistant patients.
Non-nucleoside reverse transcriptase inhibitor: nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than

		that of efavirenz. The recommended dose of dolutegravir should be given when co-administered with nevirapine. Since DAMICAVA PAED is a fixed dose combination product of abacavir, dolutegravir and lamivudine, dose adjustment of dolutegravir is not possible. Alternative combinations that do not include nevirapine should be used where possible in INI-resistant patients.
Protease inhibitor (PI): atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 50 % C_T ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dolutegravir dose adjustment is necessary.
Protease inhibitor: atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 % C_T ↑ 121 % ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dolutegravir dose adjustment is necessary.
Protease inhibitor: tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 %	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of dolutegravir

	C_T ↓ 76 % TPV ↔ RTV ↔	should be given when co-administered with tipranavir/ritonavir. Since DAMICAVA PAED is a fixed dose combination product of abacavir, dolutegravir and lamivudine, dose adjustment of dolutegravir is not possible. Alternative combinations that do not include tipranavir/ritonavir should be used where possible in INI resistant patients.
Protease inhibitor: fosamprenavir/ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24 % C_T ↓ 49 % FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy. No dolutegravir dose adjustment is necessary in INI-naïve patients. Alternative combinations that do not include fosamprenavir/ritonavir should be used where possible in INI resistant patients.
Protease inhibitor: nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No

		dolutegravir dose adjustment is necessary.
Protease inhibitor: lopinavir/ritonavir (LPV+RTV)	DTG ↔ AUC ↓ 4 % C_{max} ↔ ↓ 6 % LPV ↔ RTV ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dolutegravir dose adjustment is necessary.
Protease inhibitor: darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ AUC ↓ 22 % C_{max} ↓ 11 % Cт ↓ 38 % DRV ↔ RTV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dolutegravir dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitor: tenofovir (TDV)	Dolutegravir ↔ AUC ↔ C_{max} ↓3 % Cт ↓ 8 % TDV ↔ AUC ↑ 12 % C_{max} ↑ 9 % Cт ↑ 19 %	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dolutegravir dose adjustment is necessary.
Protease inhibitor: darunavir/ritonavir + etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % Cт ↓ 36 %	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant

	DRV ↔ RTV ↔	extent. No dolutegravir 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 DAMICAVA PAED is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see **section 4.3**).
Carbamazepine	Dolutegravir ↓ AUC ↓ 49 % C_{max} ↓ 33 % Cт ↓ 73 %	Carbamazepine decreased dolutegravir plasma concentration. The recommended dose of dolutegravir should be given when co-administered with carbamazepine. Since DAMICAVA PAED is a fixed-dose combination product of abacavir, dolutegravir and lamivudine, dose adjustment of dolutegravir is not possible. Alternatives to

		carbamazepine should be used where possible for INI-resistant patients.
Phenytoin Phenobarbitone St. John's wort	Dolutegravir ↓	Co-administration with these metabolic inducers has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of these metabolic inducers on dolutegravir exposure is likely similar to carbamazepine. The recommended dose of dolutegravir should be given when co-administered with these metabolic inducers. Since DAMICAVA PAED is a fixed dose combination product of abacavir, dolutegravir and lamivudine, dose adjustment of dolutegravir is not possible. Alternative combinations that do not include these metabolic inducers should be used where possible in INI-resistant patients.
Oxcarbazepine	Dolutegravir ↓	This interaction has not been studied. Although an inducer of CYP3A4, based on data from other inducers, a clinically significant decrease in

		dolutegravir is not expected. No dolutegravir dose adjustment is necessary.
Antacids containing polyvalent cations (e.g., Al or Ca)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. DAMICAVA PAED 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 PAED 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 % C_{24} ↓ 56 %	DAMICAVA PAED is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin ↑ When co-administered with dolutegravir Metformin	Co-administration of dolutegravir increased metformin plasma concentration. A dose adjustment of metformin should be considered when

	AUC ↑ 145 % C_{max} ↑ 111 %	starting and stopping co-administration of DAMICAVA PAED with metformin, to maintain glycaemic control.
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C_T ↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir should be given when co-administered with rifampicin. Since DAMICAVA PAED is a fixed-dose combination product of abacavir, dolutegravir and lamivudine, dose adjustment of dolutegravir is not possible. Alternatives to rifampicin should be used where possible for INI-resistant patients.
Oral contraceptives [ethinyl estradiol (ee) and norgestromin (NGMN)]	Effect of dolutegravir: EE ↔ AUC ↑ 3 % C_{max} ↓ 1 % C_T ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 %	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 DAMICAVA PAED.

	C_T ↓ 7 %	
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % C_T ↓ 1 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with DAMICAVA PAED.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33 % C_{max} ↑ 29 % C_T ↑ 45 % Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.

Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max}= maximum observed concentration, C_T = concentration at the end of dosing interval.

Abacavir and lamivudine

As DAMICAVA PAED contains abacavir and lamivudine, any interactions that have been identified with these medicines individually may occur with DAMICAVA PAED. Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine.

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for P450 mediated interactions with other medicines involving abacavir are low. The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Lamivudine does not inhibit the cytochrome

P450 isoform. The possibility of interactions with other medicines should be considered if lamivudine is co-administered with medicines that are known to be excreted via the kidneys.

Interactions relevant to abacavir

Ethanol

Concomitant use of alcohol with abacavir, a constituent of DAMICAVA PAED can alter the metabolism of abacavir, increasing exposure to abacavir by 41 %.

Methadone

Co-administration of abacavir with methadone showed a reduction in abacavir C_{max} and a one-hour delay in T_{max} but AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant, however occasionally methadone dose titration may be required.

Interactions relevant to lamivudine

Zalcitabine

Lamivudine (as contained in DAMICAVA PAED), may inhibit intracellular phosphorylation of zalcitabine when used concurrently. Therefore, DAMICAVA PAED must not be used concomitantly with zalcitabine.

Trimethoprim

The effect of co-administration of lamivudine as contained in DAMICAVA PAED with higher doses of cotrimoxazole used for the treatment of *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided.

DAMICAVA PAED should not be taken with any other medicines containing lamivudine. The list below should not be considered exhaustive but is representative of the classes studied.

Table 3: Abacavir and lamivudine medicine interactions

Medicines by therapeutic area	**Interaction: Geometric mean change (%) (Possible mechanism)**	**Recommendation concerning co-administration**
ANTI-INFECTIVE PRODUCTS		
Trimethoprim/sulfamethoxazole (cotrimoxazole)/abacavir	Interaction not studied.	No DAMICAVA PAED dosage adjustment necessary, unless patient has renal impairment.
Trimethoprim/sulfamethoxazole (cotrimoxazole)/lamivudine	Lamivudine: AUC ↑ 40 % Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	When concomitant administration with cotrimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided.
CYTOTOXICS		
Cladribine/lamivudine	Interaction not studied. *In vitro* lamivudine inhibits the intracellular	Therefore, the concomitant use of lamivudine with cladribine is not recommended.

	phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine.	
OPIOIDS		
Methadone/abacavir	Abacavir: AUC ↔ C_{max} ↓ 35 % Methadone: CL/F ↑ 22 %	Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms and methadone doses should be adjusted accordingly.
Methadone/lamivudine	Interaction not studied	
RETINOIDS		
Retinoid compounds (e.g. isotretinoin)/abacavir	Interaction not studied. Possible interaction given	Insufficient data to recommend dosage adjustment.

	common pathway of elimination via alcohol dehydrogenase.	
Retinoid compounds (e.g. isotretinoin)/lamivudine	Interaction not studied.	
ANTIVIRALS		
Ribavirin/abacavir	Interaction not studied. Though evidence is conflicting, co-administration of abacavir and ribavirin has been associated with a lower response rate to ribavirin-containing hepatitis C treatment.	If possible, abacavir should be substituted by another NRTI (e.g. tenofovir) when co-treating with ribavirin.
Lopinavir and ritonavir/abacavir	In a pharmacokinetic study, co-administration of abacavir once daily with	Insufficient data to recommend dosage adjustment.

	lopinavir/ritonavir led to a decrease in abacavir plasma AUC. The clinical relevance of this is unknown.	
Tipranavir and ritonavir/abacavir	Co-administration of abacavir and tipranavir + ritonavir decreased the plasma AUC of abacavir by approximately 40 %. The clinical relevance is unknown.	Insufficient data to recommend dosage adjustment.
Didanosine/abacavir Didanosine/lamivudine Zidovudine/abacavir	Interaction not studied.	No dose adjustment necessary.
Zidovudine/lamivudine Zidovudine 300 mg single dose/lamivudine 150 mg single dose	Lamivudine: AUC ↔ Zidovudine: AUC ↔	
Emtricitabine/lamivudine		Due to similarities, DAMICAVA PAED should not be administered

		concomitantly with other cytidine analogues, such as emtricitabine.
MISCELLANEOUS		
Ethanol/abacavir	Abacavir: AUC ↑41 % Ethanol: AUC ↔ (Inhibition of alcohol dehydrogenase)	No dosage adjustment is necessary.
Ethanol/lamivudine	Interaction not studied.	

Abbreviations: ↑ = Increase; ↓= decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration; CL/F = apparent oral clearance.

Potent enzymatic inducers such as rifampicin, phenobarbitone and phenytoin may, via their effects on UDP glucuronyl transferases, decrease the plasma concentrations of abacavir. The magnitude of any such effects, as well as their possible clinical consequences, are unknown.

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 PAED in women of childbearing potential to exclude inadvertent (unintentional) use of DAMICAVA PAED 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

The use of DAMICAVA PAED is contraindicated in pregnancy (see **section 4.3**). The safety of DAMICAVA PAED in human pregnancy has not been established and an increased risk of birth defects cannot be excluded.

Both lamivudine and abacavir crossed the placenta in reproductive toxicity studies in animals. Early embryonic deaths occurred with lamivudine in rabbits at systemic exposures comparable to that achieved in humans. Abacavir demonstrated toxicity to the developing embryo and foetus in rats which resulted amongst others, in foetal oedema, skeletal variations/malformations, early intrauterine deaths and still births.

Mitochondrial dysfunction has been reported with the use of nucleoside analogues. Abacavir and lamivudine in combination should not be initiated during pregnancy, due to the risk of a hypersensitivity reaction to abacavir and possible mitochondrial damage to foetus (see **section 4.3**).

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

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

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 postnatally to nucleoside analogues (see **section 4.4**).

Breastfeeding

Women on treatment with DAMICAVA PAED should not breastfeed their infants (see **section 4.3**).

Lamivudine, dolutegravir and probably also abacavir, are excreted into the breast milk of lactating mothers. It is recommended that HIV-infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

There is insufficient information on the effects of dolutegravir in neonates/infants.

Fertility

Studies in animals showed that neither abacavir nor lamivudine had any effect on fertility.

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

4.7 Effects on ability to drive and use machines

DAMICAVA PAED may affect the ability to drive and use machines.

Patients should not drive and use machines until they know how treatment with DAMICAVA PAED affects them.

4.8 Undesirable effects

a) Summary of safety profile

Abacavir and lamivudine

Many of the adverse reactions listed in the table below occur frequently (nausea, vomiting, diarrhoea, fever, lethargy, rash) in patients with abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity reaction. If DAMICAVA PAED has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart a medicine containing abacavir, the possibility of a hypersensitivity reaction should be borne in mind and these patients should be closely monitored for signs and symptoms. Cases of erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported where abacavir hypersensitivity could not be ruled out. In such cases medicines containing abacavir should be permanently discontinued.

Abacavir hypersensitivity (see also **section 4.4**)

The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or post-marketing surveillance. Those reported **in at least 10 % of patients** with a hypersensitivity reaction are in **bold** text.

Skin

Rash (usually maculopapular or urticarial).

Gastrointestinal tract

Nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration.

Respiratory tract

Dyspnoea, cough, sore throat, adult respiratory distress syndrome, respiratory failure.

Miscellaneous

Fever, lethargy, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis.

Neurological/psychiatry

Headache, paraesthesia.

Haematological

Lymphopenia.

Liver/pancreas

Elevated liver function tests, hepatitis, hepatic failure.

Musculoskeletal

Myalgia, rarely myolysis, arthralgia, elevated creatine phosphokinase.

Urology

Elevated creatinine, renal failure.

Rash (81 % vs 67 % respectively) and gastrointestinal manifestations (70 % vs 54 % respectively) were more frequently reported in children compared to adults.

Some patients with hypersensitivity reactions were initially thought to have gastroenteritis, respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. This delay in diagnosis of hypersensitivity has resulted in abacavir being continued or re-introduced, leading

to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases.

Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, although these reactions may occur at any time during therapy. Close medical supervision is necessary during the first two months, with consultations every two weeks.

It has been suggested that intermittent therapy may increase the risk of developing clinically significant hypersensitivity reactions. Consequently, patients should be advised of the importance of taking DAMICAVA PAED regularly.

Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction is usually more severe than on initial presentation and may include life-threatening hypotension and death.

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity prior to stopping abacavir. The most common isolated symptom of a hypersensitivity reaction was a skin rash. On occasion, hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity reaction. In both cases, if a decision is made to restart abacavir this must be done in a setting where medical assistance is readily available.

b) Tabulated summary of adverse reactions

Dolutegravir

MedDRA system organ class	**Frequency**	**Side effects**
Immune system disorders	*Less frequent*	Hypersensitivity (see **section 4.4**), immune reconstitution syndrome (see **section 4.4**).
Psychiatric disorders	*Frequent*	Insomnia, abnormal dreams, depression, anxiety.
	Less frequent	Suicide ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness.
Nervous system disorders	*Frequent*	Headache, dizziness.
Gastrointestinal disorders	*Frequent*	Nausea, diarrhoea, vomiting, flatulence, upper abdominal pain.
	Less frequent	Abdominal pain, abdominal discomfort.
Hepatobiliary disorders	*Less frequent*	Hepatitis.
Skin and subcutaneous tissue disorders	*Frequent*	Rash, pruritus.
General disorders and administration site conditions	*Frequent*	Fatigue.

The safety profile was similar across the treatment-naïve, treatment-experienced (and integrase-naïve) and integrase-resistant patient populations.

Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 48 weeks. In treatment-naïve patients a mean change from baseline of 9,96 µmol/L (range: -53 µmol/L to 54,8 µmol/L) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment experienced patients. 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 for dolutegravir and raltegravir (but not efavirenz). 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**).

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise have also been reported with dolutegravir therapy.

Paediatric population

Based on limited available data in children and adolescents (6 to less than 18 years of age), there were no additional types of adverse reactions beyond those observed in the adult population.

Abacavir and lamivudine

MedDRA system organ class	Abacavir	Lamivudine
Blood and lymphatic system disorders		*Less frequent:* Anaemia, neutropenia, thrombocytopenia.
Immune system disorders	*Frequent:* Hypersensitivity.	

Metabolism and nutrition disorders	*Frequent*: Anorexia.	
Nervous system disorders	*Frequent:* Headache.	*Frequent:* Headache.
Gastrointestinal disorders	*Frequent:* Nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration.	*Frequent:* Nausea, vomiting, diarrhoea, upper abdominal pain.
Hepatobiliary disorders		*Less frequent:* Transient rises in liver enzymes.
Skin and subcutaneous tissue disorders		*Frequent:* Rash.
General disorders and administration site conditions	*Frequent:* Fever, lethargy, fatigue.	*Frequent:* Fever, fatigue, malaise.

Post-marketing data

Dolutegravir

MedDRA system organ Class	Frequency	Side effects
Hepatobiliary disorders	*Frequency* unknown	Acute hepatic failure (acute hepatic failure has been reported in a dolutegravir-containing regimen. The contribution of dolutegravir in these cases is unclear).

Musculoskeletal and connective tissue disorders	*Frequency unknown*	Arthralgia, myalgia.
Investigations	*Frequency unknown*	Weight increased.

Abacavir and lamivudine

In addition to the adverse events included from clinical trial data, the following adverse events listed in the table below have been identified during post-approval use of abacavir and lamivudine. These events have been chosen for inclusion due to a potential causal connection to abacavir and/or lamivudine.

MedDRA system organ Class	**Abacavir**	**Lamivudine**
Blood and lymphatic system disorders		*Frequency unknown:* Pure red cell aplasia.
Metabolism and nutrition disorders	*Frequency unknown:* Hyperlactataemia, lactic acidosis.	*Frequency unknown:* Hyperlactataemia, lactic acidosis.
Nervous system disorders	*Frequency unknown:* Headache.	*Frequency unknown:* Paraesthesia, peripheral neuropathy has been reported although a causal relationship to treatment is uncertain.
Gastrointestinal disorders	*Frequency unknown:* Pancreatitis, although causal	*Frequency unknown:* Rise in serum amylase, pancreatitis,

	relationship to abacavir is uncertain.	although causal relationship to lamivudine is uncertain.
Skin and subcutaneous tissue disorders	*Frequency unknown:* Rash, usually maculopapular or urticarial (without systemic symptoms), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.	*Frequency unknown:* Alopecia.
Musculoskeletal and connective tissue disorders		*Frequency unknown:* Arthralgia, muscle disorders, rhabdomyolysis.

c) Description of selected adverse reactions

*Hypersensitivity (see **section 1 boxed Warning** and **section 4.4**)*

Abacavir hypersensitivity reaction (HSR) has been identified as a common adverse reaction with abacavir therapy. The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or post-marketing surveillance. Those reported in at least 10 % of patients with a hypersensitivity reaction are in bold text.

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. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

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.

Hepatobiliary disorders

Elevated liver function tests, hepatic failure.

Musculoskeletal connective tissue and bone disorders

Myalgia, rarely myolysis, arthralgia, elevated creatine phosphokinase.

Renal and urinary disorders

Elevated creatinine, renal failure.

Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR is usually more severe than on initial presentation and may include life-threatening hypotension and death. Reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see above) prior to stopping abacavir; and on occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

For details of clinical management in the event of a suspected abacavir HSR see **section 1 boxed Warning**.

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

Symptoms and signs

In overdose, side effects can be precipitated and/or be of increased severity. No specific symptoms or signs have been identified following acute overdose with abacavir or lamivudine, apart from those listed as side effects.

Treatment

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

If overdose occurs the patient should be monitored for evidence of toxicity. Treatment is symptomatic and supportive. 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.

There is no specific treatment for an overdose of dolutegravir. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. 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 Antivirals

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

ATC code: J05AR13

Dolutegravir

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. *In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t ½ 71 hours).

Resistance in vitro

Isolation from wild type HIV-1: Viruses highly resistant to dolutegravir were not observed during

HIV-1 passage. During wild type HIV-1 passage in the presence of dolutegravir integrase substitutions observed were S153Y and S153F with FCs ≤ 4,1 for strain IIIB, or E92Q with FC = 3,1 and G193E with FC = 3,2 for strain NL432. Additional passage of wild type subtype B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T.

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

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

Clinical isolates from raltegravir treatment virologic failure subjects: Seven hundred and five raltegravir resistant clinical isolates were analysed for susceptibility to dolutegravir. Dolutegravir has a < 10 FC against 93,9 % of the 705 clinical isolates.

Resistance in vivo: integrase inhibitor-naïve patients

No integrase inhibitor (INI)-resistant mutations or treatment-emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg film-coated tablets once daily in treatment-naïve studies. In treatment-experienced (and integrase-naïve) patients, treatment emergent integrase resistance was observed in subjects with virologic failure. A unique R263K integrase substitution was observed, with a maximum FC of 1,93.

Resistance in vivo: integrase inhibitor-resistant patients

Dolutegravir (plus optimised background therapy) was examined in subjects with pre-existing INI-resistance. Twenty-six subjects experienced virologic failure. Of these, 25 had paired baseline and PDVF resistance data for analysis and 13/25 (52 %) had treatment-emergent mutations. Treatment-emergent mutations or mixtures of mutations observed were E92Q, T97A, E138K/A, G140S, Y143H, S147G, Q148H/K/R, and N155H. Eleven of the 13 subjects with virus exhibiting treatment-emergent mutations harboured Q148 pathway virus present at baseline or historically.

Children

The pharmacokinetic parameters, safety, tolerability and efficacy of dolutegravir was evaluated in combination regimens in HIV-1 infected infants, children and adolescents.

Approximately 61 % of children and adolescents (12 to less than 18 years of age) treated with dolutegravir once daily plus OBR achieved viral load less than 50 copies/mL.

Similarly, approximately 61 % of children (6 to less than 12 years of age) treated with dolutegravir plus OBR, achieved viral load less than 50 copies/mL.

Effects on renal function

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

Abacavir and lamivudine

Abacavir and lamivudine are nucleoside analogue reverse transcriptase inhibitors (NRTIs) and are selective inhibitors of human immunodeficiency virus-1 (HIV-1) and HIV-2.

Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective triphosphate (TP) which are the active moieties. Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT).
However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Abacavir shows synergy *in vitro* in combination with amprenavir, nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, zalcitabine, stavudine and lamivudine. HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral RT. This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. Studies *in vitro* indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the RT codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo*, requiring multiple mutations

to reach an eight-fold increase in IC_{50} over wild type virus, which may be a clinically relevant level. Isolates resistant to abacavir might also show reduced sensitivity to lamivudine, zalcitabine, tenofovir, emtricitabine and/or didanosine, but remain sensitive to zidovudine and stavudine.

Cross-resistance between abacavir and lamivudine and antiretrovirals from other classes e.g. protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI), is unlikely. Clinical isolates with three or more mutations associated with NRTIs are unlikely to be susceptible to abacavir. Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral medicines. Zidovudine, stavudine, abacavir and tenofovir maintain their antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation.

5.2 Pharmacokinetic properties

Dolutegravir

Dolutegravir pharmacokinetic parameters are similar between healthy and HIV-infected subjects. The PK variability of dolutegravir is between low to moderate. In studies in healthy subjects, between-subject CVb % for AUC and C_{max} ranged from ~20 to 40 % and C_T from 30 to 65 % across studies. The between-subject PK variability of dolutegravir was higher in HIV-infected subjects than healthy subjects. Within-subject variability (CVw %) is lower than between-subject variability.

The relative bioavailability of dispersible tablets is approximately 1,6-fold higher as compared to film-coated tablets. Thus, a 30 mg dolutegravir dose administered as six 5 mg dispersible tablets will have similar exposure to a 50 mg DTG dose administered as film-coated tablet(s). Similarly, a 25 mg dolutegravir dose administered as five 5 mg dispersible tablets, will provide comparable exposure to a 40 mg dolutegravir dose administered as four 10 mg film-coated tablets.

Absorption

Dolutegravir is absorbed following oral administration, with median T_{max} at 2 to 3 hours post dose for the tablet formulation. The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 to 100 mg; however, increase in dolutegravir exposure appears dose proportional from 25 mg to 50 mg.

Dolutegravir may be administered with or without food. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate and high fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 34 %, 41 %, and 66 %, increased C_{max} by 46 %, 52 %, and 67 %, prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases are not clinically significant.
The absolute bioavailability of dolutegravir has not been established.

Distribution

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins based on *in vitro* data. The apparent volume of distribution (following oral administration of suspension formulation, Vd/F) is estimated at 12,5 L. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma 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, 0,8 to 1,0 % in subjects with severe renal impairment, and 0,5 % in HIV-1 infected patients.

Dolutegravir is present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18

ng/mL (comparable to unbound plasma concentration, and above the IC_{50}); CSF: plasma concentration ratio of dolutegravir ranged from 0,11 to 0,66 %. Dolutegravir concentrations in CSF exceeded the IC_{50}, supporting the median reduction from baseline in CSF HIV-1 RNA of 2,1 log after 2 weeks of therapy (see **section 5.1**).

Metabolism

Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component (9,7 % of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged medicine is low (< 1 % of the dose). Fifty-three percent of total oral dose is excreted unchanged in 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. Thirty-one percent of the total oral dose is excreted in the urine, represented by either glucuronide of dolutegravir (18,9 % of total dose), N-dealkylation metabolite (3,6 % of total dose) and a metabolite formed by oxidation at the benzylic carbon (3,0 % of total dose).

Elimination

Dolutegravir has a terminal half-life of ~14 hours and an apparent clearance (CL/F) of 0,56 L/hr.

Special patient populations

Children

The pharmacokinetics of dolutegravir film-coated and dispersible tablets in HIV-1 infected infants, children and adolescents aged ≥ 4 weeks to < 18 years were evaluated. Steady state plasma exposure at weight band doses are summarised in Table 5.

Table 5: Summary of DTG PK parameters following administration of DTG at weight band doses in paediatric HIV-1 infected subjects

Weight band (kg)	Dolutegravir dosage form	Once daily dose (mg)	PK parameter Geometric mean (% CV)		
			C_{max} (µg/mL)	AUC_{0-24h} (µg*h/mL)	C_{24h} (ng/mL)
3 to < 6	DT	5	3,80 (34)	49,37 (49)	962 (98)
6 to < 10[b]	DT	10	5,68 (38)	85,49 (32)	1821 (41)
6 to < 10[c]	DT	15	5,27 (50)	57,17 (76)	706 (177)
10 to < 14	DT	20	5,99 (33)	68,75 (48)	977 (100)
14 to < 20	DT	25	5,97 (42)	58,97 (44)	725 (75)
≥ 20	DT[d]	30	7,16 (26)	71,53 (26)	759 (73)
	FCT	50	4,92 (40)	54,98 (43)	778 (62)
Target: Geometric mean (range)				**46 (37 - 134)**	**995 (697 - 2260)**

DT = dispersible tablet

FCT = film-coated tablet

[a.] The bioavailability of dolutegravir DT is ~1,6-fold *dolutegravir* FCT.

[b.] < 6 months of age

[c.] ≥ 6 months of age

[d.] ≥ 20 to < 25 kg weight band

Renal impairment

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of a single 50 mg dose of dolutegravir film-coated tablets was performed in subjects with severe renal impairment (CLcr < 30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr < 30 mL/min) and matching healthy subjects were observed. AUC, C_{max}, and C_{24} of dolutegravir were decreased by 40 %, 23 %, and 43 %, respectively, compared with those in matched healthy subjects. No dosage adjustment is necessary for patients with renal impairment. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatic impairment

Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. No dosage adjustment is necessary for patients with mild hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in metabolising enzymes

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

Co-infection with hepatitis B or C

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

Abacavir and lamivudine in adults

Absorption

Abacavir and lamivudine are rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir and lamivudine in adults is 83 % and 80 to 85 %, respectively and is not affected by food. The mean time to maximal serum concentrations (T_{max}) is about 1,5 hours and 1,0 hour for abacavir and lamivudine, respectively. 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 mg.h/mL. Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days the mean steady-state C_{max} is 2,04 µg/mL and the mean AUC_{24} is 8,87 µg.h/mL.

Distribution

Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0,8 and 1,3 L/kg, respectively. Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~ 49 %) to human plasma proteins at therapeutic concentrations. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36 %). This indicates a low likelihood for interactions with other medicines through plasma protein binding displacement.

Data show that abacavir and lamivudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44 %. The observed values of the peak concentrations are 9-fold greater than the IC_{50} of abacavir of 0,08 µg/mL or 0,26 µM when abacavir is given at 600 mg twice daily. The mean

ratio of CSF/serum lamivudine concentrations 2 to 4 hours after oral administration was approximately 12 %. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Metabolism

Abacavir mainly undergoes hepatic metabolism with less than 2 % of the administered dose being renally excreted as unchanged compound. The primary pathways of metabolism 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 small extent of hepatic metabolism (less than 10 %).

Elimination

The mean half-life of abacavir is about 1,5 hours. Following multiple oral doses of abacavir 300 mg twice a day, there is no significant accumulation of abacavir.

Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for 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. 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 patient populations

Hepatically impaired

Pharmacokinetic data has been obtained for abacavir and lamivudine alone. Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). The results showed that there was a mean increase of 1,89-fold in the abacavir AUC and 1,58-fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased. A dose reduction of abacavir may be needed in patients with mild hepatic impairment which cannot be done with abacavir in a fixed-dose combination, as in DAMICAVA PAED. A separate abacavir formulation should be used.

DAMICAVA PAED is contraindicated in moderate to severe liver impairment as abacavir pharmacokinetics have not been studied in this population (see **section 4.3)**.

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

Renally impaired

Pharmacokinetic data have been obtained for abacavir and lamivudine alone. Abacavir is primarily metabolised by the liver, with approximately 2 % of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore, dose reduction is not required in patients with renal impairment.

Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. A lamivudine dose reduction may be required with mild renal impairment which cannot be done with lamivudine in a fixed dose combination. A separate lamivudine formulation should be used. DAMICAVA PAED is contraindicated in

moderate renal impairment (CrCl < 50 mL/min) and severe renal impairment (CrCl < 30 mL/min) (see **section 4.3**).

Paediatric population

Abacavir

The overall pharmacokinetic parameters in children are comparable to adults, with greater variability in plasma concentrations. Dosing according to weight bands for abacavir is based primarily on pharmacokinetic modelling. Higher (with possible safety implications) or lower (with possible efficacy implications) exposures to abacavir can occur in some paediatric patients due to greater variability of abacavir plasma concentrations and where dosing is according to weight bands, since accurate dosing cannot be achieved with the fixed-dose combination of actives as in DAMICAVA PAED. Therefore, children should be closely monitored for abacavir toxicities.

The use of abacavir in infants less than 6 weeks is contraindicated.

Lamivudine

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55 – 65 %) of lamivudine was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age approaching adult values around 12 years of age. Higher (with possible safety implications) or lower (with possible efficacy implications) exposures to lamivudine may occur in some paediatric patients due to dosing according to weight bands, reduced absolute bioavailability and increased clearance in younger children, since accurate dosing cannot be achieved with the fixed-dose combination of actives as in DAMICAVA PAED.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Aspartame

Calcium sulphate dihydrate

Colloidal silicon dioxide

Crospovidone

Ferric oxide red

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Sodium starch glycolate

Strawberry cream flavour permaseal (containing waxy maize maltodextrin, propylene glycol, nature-identical flavouring substances, modified waxy maize starch, natural flavouring substances)

Film-coat: Opadry II 85F240128 Pink

Iron oxide red (E172)

Iron oxide yellow (E172)

Macrogol (E1521)

Polyvinyl alcohol (E1203)

Talc (E553b)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a dry place at or below 30 °C.

Store in the original container in order to protect from moisture.

Keep the bottle tightly closed.

Do not remove the desiccant.

6.5 Nature and contents of container

DAMICAVA PAED is packed in 28's and 30's in a 50 cc white, round, HDPE bottle with 33 mm screw cap with a liner printed "SFYP" in black, containing a 2 g silica gel bag, with or without a cardboard carton.

DAMICAVA PAED is packed in 84's and 90's in a 75 cc white, HDPE bottle with 38 mm screw cap with a liner printed "SFYP" in black, containing a 2 g silica gel bag, with or without a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

57/20.2.8/0509

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 14 May 2024

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

Not applicable.

This product has been manufactured under licences from the Medicines Patent Pool and ViiV Healthcare. Any other use is not authorised.

Appendix A:

DAMICAVA PAED Alert Card

(Front of Card)

ALERT CARD

Important information about DAMICAVA PAED

Always carry this card

with you.

Patients taking abacavir, contained in DAMICAVA PAED, may develop a hypersensitivity reaction (serious allergic reaction) which **can be life threatening** if treatment with DAMICAVA PAED is continued. **If your child has a skin rash OR one or more symptoms from at least TWO of the following groups**:

- Fever
- Shortness of breath, sore throat or cough.
- Nausea or vomiting or diarrhoea or abdominal pain.
- Severe tiredness or achiness or generally feeling unwell.

(Back of Card)

CALL YOUR CHILD'S DOCTOR IMMEDIATELY. He or she will advise you whether your child should discontinue treatment or not. If your child has discontinued DAMICAVA PAED due to this reaction, your child must never take abacavir containing products again as within hours your child may experience a life-threatening lowering of his/her blood pressure or death.

You should immediately contact your child's doctor if you think he/she is having a hypersensitivity reaction to DAMICAVA PAED.

Write your doctor's details below:

Doctor:……. Tel: .....

If your child's doctor is not available, you must urgently seek alternative medical advice, e.g. the emergency unit at the nearest hospital.

For general information enquiries on DAMICAVA PAED, contact Cipla Medpro (Pty) Ltd:

Customer Care: 080 222 6662

Email: drugsafetysa@cipla.com