SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

DEZKAV (600 mg / 50 mg / 300 mg, film-coated tablets)

HYPERSENSITIVITY REACTIONS

Hypersensitivity to abacavir (see also 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. In some cases, this has proven 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 one study, 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 % to 3,4 % and the incidence of hypersensitivity reactions confirmed by skin patch testing from 2,7 % to 0,0 %. 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 abacavir treatment compared with 0 % to 4 % of patients who do not have the HLA-B*5701 allele. It is recommended that any HIV-infected patient without prior exposure to abacavir, be screened for HLA-B*5701 allele.

Clinicians should screen for carriage of the HLA-B*5701 allele in any HIV infection 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 below ‘Special considerations following an interruption of DEZKAV 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. 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 abdominal 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 allele status, any patient developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed DEZKAV MUST be discontinued immediate. DEZKAV, 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 DEZKAV should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnosis is possible (respiratory disease, flu-like illness, gastroenteritis or reactions to other medications). DEZKAV, or any 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 this hypersensitivity reaction is included in the DEZKAV pack.

Special consideration following an interruption of DEZKAV therapy:
Regardless of a patient's HLA-B*5701 status, if therapy with DEZKAV tablets has been discontinued for any reason and restarting therapy is under consideration, the reason for discontinuation must be established to assess whether the patient had any symptoms of a hypersensitivity reaction. **If a hypersensitivity reaction cannot be ruled out, DEZKAV**

tablets or any other medicine containing abacavir must 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 DEZKAV 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 DEZKAV tablets this must be done only if medical care 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 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 DEZKAV 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 an 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 DEZKAV tablets or any other medicine containing abacavir again, regardless of their HLA-B*5701 status.
- in order to avoid restarting DEZKAV tablets, patients who have experienced a hypersensitivity reaction should be asked to return the remaining DEZKAV tablets
- patients who have stopped DEZKAV tablets 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 included in the

DEZKAV pack. They should be reminded of the importance of removing the Alert Card included in the pack and keeping it with them at all times.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DEZKAV film-coated tablet contains:

Abacavir 600 mg

Dolutegravir 50 mg

Lamivudine 300 mg

Contains sugar: Mannitol 40 mg per tablet

3 PHARMACEUTICAL FORM

Film-coated tablets, peach to brown, oval, biconvex, bevelled edge tablets, debossed with M on one side of the tablet and ADL on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DEZKAV 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 DEZKAV.

4.2 Posology and method of administration

Posology

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

Adults and adolescents:

The recommended dose of DEZKAV in adults and adolescents weighing more than 40 kg is one tablet once daily.

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

DEZKAV is a fixed-dose tablet and should not be prescribed for patients requiring dosage

adjustments, such as those with creatinine clearance less than 50 ml/min. Separate preparations of dolutegravir, abacavir or lamivudine should be administered in cases where discontinuation or dose adjustment is indicated. In these 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 DEZKAV is not recommended for patients with integrase inhibitor resistance.

Special Populations:

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

Renal impairment:

Whilst no dosage adjustment of dolutegravir or abacavir is necessary in patients with renal impartment, a dose reduction of lamivudine is required due to decreased clearance. Therefore, DEZKAV should not be used in patients with a creatinine clearance less than 50 ml/min (see sections 5.2 and 4.3).

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 DEZKAV, the separate preparations of dolutegravir, abacavir or lamivudine should be used when this is deemed necessary. DEZKAV is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (see sections 5.2 and 4.3).

Paediatric population:

DEZKAV should not be used in children under the age of 18 years.

Method of administration

Oral use. DEZKAV can be taken with or without food (see section 5.2).

4.3 Contraindications

• DEZKAV is contraindicated in patients with known hypersensitivity to dolutegravir, abacavir or lamivudine or to any of the excipients of DEZKAV.
• DEZKAV is contraindicated in combination with dofetilide and pilsicainide.
• DEZKAV is contraindicated in moderate and severe hepatic impairment due to the abacavir component (see section 5.1).
• DEZKAV is contraindicated during pregnancy or in mothers who are breastfeeding their infants (see section 4.6).
• DEZKAV is contraindicated in patients with renal impairment with a creatinine clearance of <50 ml/min due to the lamivudine component (see section 5.1).
• Metformin is contraindicated in patients taking DEZKAV.

4.4 Special warnings and precautions for use

Warnings relevant to dolutegravir, abacavir and lamivudine are included in this section. There are no additional warnings relevant to DEZKAV.

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. Discontinue DEZKAV immediately if signs or symptoms of hypersensitivity reaction 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 DEZKAV 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 (see section 4.8). Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Liver disease

Use of DEZKAV can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of DEZKAV has not been established in patients with significant underlying liver disorders/diseases. DEZKAV is contraindicated in patients with moderate to severe hepatic impairment (see sections 4.3 and 5.2). In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant professional information leaflets for these medicines.

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.

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 DEZKAV 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 DEZKAV therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Immune Reconstitution Inflammatory Syndrome:

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

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection (see Patients co-infected with hepatitis B virus (HBV) later in this section and section 4.8).

Lactic acidosis / hyperlactataemia:

Use of DEZKAV can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Clinical features are non-specific and include nausea, vomiting, abdominal pain, generalised weakness, anorexia and sudden unexplained weight loss, and respiratory symptoms (dyspnoea and tachypnoea).

In patients with suspicious symptoms 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 DEZKAV to patients with known risk factors for liver disease. Treatment with DEZKAV 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-natal 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). Whether the neurological disorders are transient or permanent is currently unknown. Any foetus exposed in utero to nucleoside and nucleotide analogues, such as lamivudine and abacavir in DEZKAV, 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 or symptoms.

Patients with moderate to severe renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of DEZKAV is increased due to decreased clearance. The dose of DEZKAV should therefore be adjusted.

Cardiovascular events:

Although the available data from clinical and observational studies with abacavir show inconsistent results, several studies suggest an increased risk of cardiovascular events (notably myocardial infarction) in patients treated with abacavir. Therefore, when prescribing DEZKAV, action should be taken to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

In addition, alternative treatment options to the abacavir containing regimen should be considered when treating patients with a high cardiovascular risk.

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 DEZKAV 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 healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

Patients should be advised that antiretroviral therapy, including DEZKAV, 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.

Pancreatitis:

Pancreatitis has been observed in some patients receiving DEZKAV. Pancreatitis must be

considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of DEZKAV until diagnosis of pancreatitis is excluded.

Medicine interactions:

Caution should be given to co-administering medications (prescription and non-prescription) that may change the exposure of dolutegravir, abacavir, lamivudine or medications that may have their exposure changed by DEZKAV (see sections 4.3 and 4.5).

The 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. DEZKAV is recommended to be administered 2 hours before or 6 hours after these medicines (see section 4.5). DEZKAV 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).

Dolutegravir increase metformin concentrations. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance [CrCl] 45–59 mL/min). Metformin is contraindicated in patients taking DEZKAV (see section 4.3).

Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with etravirine (without boosted protease inhibitors), efavirenz, nevirapine, rifampicin, tipranavir/ritonavir, carbamazepine, phenytoin, phenobarbitone and St. John's wort, the use of DEZKAV is not recommended for patients taking these medicines (see section 4.5).

Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with etravirine (without boosted protease inhibitors), efavirenz, nevirapine, rifampicin, tipranavir/ritonavir, carbamazepine, phenytoin, phenobarbitone and St. John's wort, the use of DEZKAV is not recommended for patients taking these medicines (see section 4.5).

Medicine resistance:

Since the recommended dose of dolutegravir is 50 mg twice daily for patients with resistance to integrase inhibitors, the use of DEZKAV is not recommended for patients with integrase inhibitor resistance.

Important information about some of the ingredients of DEZKAV tablets:

DEZKAV tablets contain mannitol, which may have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

DEZKAV contains dolutegravir, abacavir and lamivudine, therefore any interactions identified for these individually are relevant to DEZKAV. No clinically significant medicine interactions are expected between dolutegravir, abacavir and lamivudine.

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

Dolutegravir is eliminated mainly through metabolism by uridine diphosphate glucuronosyl transferase (UGT) 1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). Co-administration of DEZKAV and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or P-gp may therefore increase dolutegravir plasma concentration. Medicines that induce those enzymes or transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir (see Table 1).

The absorption of dolutegravir is reduced by certain anti-acid medicines (see Table 1).

Abacavir is metabolised by UGT (UGT2B7) and alcohol dehydrogenase; co-administration of inducers (e.g. rifampicin, carbamazepine and phenytoin) or inhibitors (e.g. valproic acid) of UGT enzymes or with compounds eliminated through alcohol dehydrogenase could alter abacavir exposure.

Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through the organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporters (MATE1 and MATE2-K). Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations, however the resulting increase was not clinically significant (see Table 1).

Dolutegravir is an OCT2 and MATE1 inhibitor; however, lamivudine concentrations were similar with or without co-administration of dolutegravir based on a cross study analysis, indicating that dolutegravir has no effect on lamivudine exposure in vivo. Lamivudine is also substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Although abacavir and lamivudine are substrates of BCRP and P-gp in vitro, given the high absolute bioavailability of abacavir and lamivudine, (see section 5.2), inhibitors of these efflux transporters are unlikely to result in a clinically relevant impact on abacavir or lamivudine concentrations.

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

In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on in vivo and/or in vitro data, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of any major enzyme or transporter such as CYP3A4, CYP2C9 and P-gp (for more information see section 5.2).

In vitro, dolutegravir inhibited the renal transporters OCT2 and MATE1. In vivo, a 10 – 14 % decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients. In vivo, dolutegravir may increase plasma concentrations of medicines in which excretion is dependent upon OCT2 or MATE-1 (e.g. metformin) (see Table 1).

In vitro, dolutegravir inhibited the renal uptake organic anion transporters (OAT)1 and OAT3. Based on the lack of effect on the in vivo pharmacokinetics of the OAT substrate tenofovir, in vivo inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied in vivo. Dolutegravir may increase plasma concentrations of medicines in which excretion is dependent upon OAT3.

In vitro, abacavir was an inhibitor of MATE1; the clinical consequences are not known. In vitro, lamivudine was an inhibitor of OCT1 and OCT2; the clinical consequences are not known. Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicines are listed in Table 1.

Interaction table

Interactions between dolutegravir, abacavir, lamivudine and co-administered medicines are listed in Table 1 (increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}"). The table should not be considered exhaustive but is representative of the classes studied.

Table 1: Interactions

Medicines by therapeutic areas	**Interaction geometric mean change (%)**	**Recommendations concerning co-administration**
Antiretroviral medicines		
Non-nucleoside reverse transcriptase inhibitors		
Etravirine without boosted protease inhibitors / Dolutegravir	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % C ↓ 88 % Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. Since the recommended dose of dolutegravir is 50 mg twice daily for patients taking etravirine without boosted protease inhibitors, DEZKAV is not recommended for patients taking etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir (see further below in table).
Lopinavir+ritonavir+ etravirine/ Dolutegravir	Dolutegravir ↔ AUC ↑ 11 % C_{max} ↑ 7 % C ↑ 28 % Lopinavir ↔ Ritonavir ↔ Etravirine ↔	No dose adjustment is necessary.
Darunavir+ritonavir+ etravirine/ Dolutegravir	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % C ↓ 36 % Darunavir ↔ Ritonavir ↔ Etravirine ↔	No dose adjustment is necessary.
Efavirenz/Dolutegravir	Dolutegravir ↓	

	AUC ↓ 57 % C_{max} ↓ 39 % C ↓ 75 % Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	Since the dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz, the co-administration of efavirenz with DEZKAV is not recommended (see section 4.4).
Nevirapine/Dolutegravir	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	Co-administration with nevirapine may 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 DEZKAV is not recommended.
Rilpivirine	Dolutegravir ↔ AUC ↑ 12 % C_{max} ↑ 13 % C ↑ 22 % Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Tenofovir	Dolutegravir ↔ AUC ↑ 1 % C_{max} ↓ 3 % C ↓ 8 % Tenofovir ↔	No dose adjustment is necessary when DEZKAV is combined with nucleoside reverse transcript inhibitors.

Emtricitabine, didanosine, stavudine, zidovudine.	Interaction not studied	DEZKAV is not recommended for use in combination with emtricitabine containing medicines, since both lamivudine (in DEZKAV) and emtricitabine are cytidine analogues (i.e. risk for intracellular interactions, (see section 4.4).
Protease inhibitors		
Atazanavir/Dolutegravir	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 50 % C ↑ 180 % Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Atazanavir+ ritonavir/ Dolutegravir	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 34 % C ↑ 121 % Atazanavir ↔ Ritonavir ↔	No dose adjustment is necessary.
Tipranavir+ritonavir/ Dolutegravir	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % C ↓ 76 % Tipranavir ↔ Ritonavir ↔ (induction of UGT1A1 and CYP3A enzymes)	Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir, the co-administration of tipranavir/ritonavir with DEZKAV is not recommended.

Fosamprenavir+ ritonavir/ Dolutegravir	Dolutegravir↓ AUC ↓ 35 % C_{max} ↓ 24 % C ↓ 49 % Fosamprenavir↔ Ritonavir ↔ (induction of UGT1A1 and CYP3A enzymes)	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary.
Nelfinavir/Dolutegravir	Dolutegravir ↔ (Not studied)	No dose adjustment is necessary.
Lopinavir+ ritonavir/ Dolutegravir	Dolutegravir ↔ AUC ↓ 4 % C_{max} ↔ 0 % C_{24} ↓ 6 %	No dose adjustment is necessary.
Darunavir+ritonavir/ Dolutegravir	Dolutegravir ↓ AUC ↓ 22 % C_{max} ↓ 11 % C ↓ 38 % Darunavir ↔ Ritonavir ↔ (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Other antiviral medicines		
Boceprevir	Dolutegravir ↔ AUC ↑ 7 % C_{max} ↑ 5 % C ↑ 8 % Boceprevir ↔ (historical controls)	No dose adjustment is necessary.

Daclatasvir/Dolutegravir	Dolutegravir ↔ AUC ↑ 33 % C_{max} ↑ 29 % C ↑ 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.
Anti-infective medicines		
Trimethoprim/ sulfamethoxazole (Co-trimoxazole)/Abacavir	Interaction not studied	No DEZKAV dosage adjustment necessary, unless patient has renal impairment (see section 4.2).
Trimethoprim/ sulfamethoxazole (Co-trimoxazole)/ Lamivudine (160mg/800mg once dai for 5 days/300mg single dose)	Lamivudine: AUC ↑ 43 % C_{max} ↑ 7 % Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	
Antimycobacterials		

Rifampicin/Dolutegravir	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C ↓ 72 % (induction of UGT1A1 and CYP3A enzymes)	Since the dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin, the co-administration of rifampicin with DEZKAV is not recommended.
Rifabutin	Dolutegravir ↔ AUC ↓ 5 % C_{max} ↑ 16 % C ↓ 30 % (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Anticonvulsants		
Carbamazepine/ Dolutegravir	Dolutegravir ↓ AUC ↓ 49 % C_{max} ↓ 33 % C ↓ 73 %	Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine, DEZKAV is not recommended for patients taking carbamazepine.
Phenobarbitone / Dolutegravir Phenytoin/Dolutegravir Oxcarbazepine/ Dolutegravir	Dolutegravir↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected).	Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers, DEZKAV is not recommended for patients taking these metabolic inducers.
Antihistamines (histamine H2 receptor antagonists)		

Ranitidine	Interaction not studied. Clinically significant interaction unlikely.	No dosage adjustment necessary.
Cimetidine	Interaction not studied. Clinically significant interaction unlikely.	No dosage adjustment necessary.
Cytotoxics		
Cladribine/Lamivudine	Interaction not studied. *In vitro* lamivudine inhibits the intracellular 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.	Concomitant use of DEZKAV with cladribine is not recommended (see section 4.4).
Opioids		
Methadone/Abacavir (40 to 90mg once	Abacavir: AUC ↔	Methadone dosage adjustment likely not needed in majority of patients; occasionally

daily for 14 days/600mg single dose, then 600mg twice daily for 14 days)	C_{max} ↓ 35 % Methadone: CL/F ↑ 22 %	methadone re-titration may be required.
Retinoids		
Retinoid compounds (e.g. Isotretinoin)	Interaction not studied. Possible interaction given common pathway of elimination via alcohol dehydrogenase (abacavir- component).	Insufficient data to recommend dosage adjustment.
Miscellaneous		
Alcohol		
Ethanol/ Dolutegravir Ethanol/ Lamivudine Ethanol/Abacavir (0,7 g/kg single dose/600mg single dose)	Interaction not studied (Inhibition of alcohol dehydrogenase) Abacavir: AUC ↑ 41 % Ethanol: AUC ↔	No dosage adjustment necessary.
Sorbitol		
Sorbitol solution (3,2 g, 10,2 g, 13,4 g)/Lamivudine	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14 %; 32 %; 36 % C_{max} ↓ 28 %; 52 %, 55 %.	When possible, avoid chronic coadministration of DEZKAV with medicines containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

Antacids and supplements		
Magnesium/ aluminium-containing antacids/Dolutegravir	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacids should be taken well separated in time from the administration of DEZKAV (minimum 2 hours after or 6 hours before).
Calcium supplements/Dolutegravir	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 % (Complex binding to polyvalent ions)	Supplements or multivitamins containing calcium, iron or magnesium should be taken well separated in time from the administration of DEZKAV (minimum 2 hours after or 6 hours before).
Iron supplements/Dolutegravir	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 57% C_{24} ↓ 56 % (Complex binding to polyvalent ions)	
Multivitamins (containing calcium, iron and magnesium) /Dolutegravir	Dolutegravir ↓ AUC ↓ 33 % C_{max} ↓ 35 % C_{24} ↓ 32 %	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11 % C_{max} ↑ 6 % C ↑ 17 %	No dose adjustment is necessary.
Antidiabetics		
Metformin/Dolutegravir	Metformin ↑	A dose adjustment of metformin should be considered when starting and stopping

		coadministration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when co-administered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (section 4.4). Metformin is contraindicated in patients taking DEZKAV (see section 4.3).
Herbal products		
St. John's wort/Dolutegravir	Dolutegravir↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort, DEZKAV is not recommended.
Oral contraceptives		
Ethinyl estradiol (EE) and Norgestromin (NGMN)/Dolutegravir	Effect of dolutegravir: EE ↔ AUC ↑ 3 % C_{max} ↓ 1 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 %	Dolutegravir had no Pharmacodynamic effect on Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and progesterone. No dose adjustment of oral contraceptives is necessary when co-administered with DEZKAV.

Paediatric population

Interaction studies have only been performed in adults.

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 DEZKAV in women of childbearing potential to exclude inadvertent (unintentional) use of DEZKAV 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:

DEZKAV should not be used during pregnancy and lactation as teratogenicity has been observed in animal studies.

The safe use of DEZKAV in human pregnancy has not been established. Dolutegravir, lamivudine and abacavir were shown to cross the placenta in reproductive toxicity studies in animals.

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.

For patients co-infected with hepatitis B who are being treated with a lamivudine containing medicine such as DEZKAV and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

Elevations in serum lactate levels

There have been reports of elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs) such as abacavir and lamivudine (see Section 4.4). The clinical relevance of transient elevations in serum lactate is unknown. There have also been reports of developmental delay, seizures and other neurological disease.

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 < 4 % of maternal serum concentrations. Therefore, mothers breastfeeding their infants should not take DEZKAV.

Fertility:

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

female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Adverse effects such as fatigue and insomnia have been observed during treatment with DEZKAV and should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

DEZKAV contains dolutegravir, abacavir and lamivudine, therefore the adverse events associated with these may be expected.

The side effects listed below have been identified during post-approval use of abacavir, lamivudine and dolutegravir.

Side effects based on post-marketing experience:

System organ class	**Abacavir**	**Lamivudine**	**Dolutegravir**
Blood and lymphatic systems disorders		pure red cell aplasia	
Immune system disorders			hypersensitivity, Immune Reconstitution Syndrome
Metabolism and nutrition disorders	hyperlactataemia lactic acidosis	hyperlactataemia lactic acidosis	Metabolism and nutrition disorders
Psychiatric disorders			insomnia, depression, suicidal ideation

			or suicide attempt
Nervous system disorders		paraesthesia, peripheral neuropathy has been reported although a causal relationship to treatment is uncertain	headache, dizziness, abnormal dreams
Gastrointestinal disorders	pancreatitis, but a causal relationship to abacavir is uncertain	rises in serum amylase, pancreatitis, although a causal relationship to lamivudine is uncertain	nausea, diarrhoea, vomiting, flatulence, upper abdominal pain, abdominal pain, abdominal discomfort
Hepatobiliary disorders			hepatitis
Skin and subcutaneous tissue disorders	rash (without systemic symptoms), erythema multiforme, stevens-johnson syndrome and toxic epidermal necrolysis	alopecia	rash, pruritus
Musculoskeletal and connective		arthralgia, muscle disorders rhabdomyolysis	

tissue disorders			
General disorders and administration site conditions			fatigue
Investigations			increased AST, ALT, CPK, bilirubin

a. Summary of the safety profile

The most frequently reported adverse reactions considered possibly or probably related to dolutegravir and abacavir/lamivudine were nausea, insomnia, dizziness and headache.

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 (see section 4.4).

Less frequent 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.

The most severe adverse event related to the treatment with dolutegravir and abacavir/lamivudine, seen in individual patients, was a hypersensitivity reaction that included rash and severe liver effects (see section Boxed warning, section 4.4 and Description of selected adverse reactions in this section).

b. Tabulated list of adverse reactions

The adverse reactions considered related to treatment with the components of DEZKAV and post-marketing experience are listed in Table 2 by body system, organ class and frequency.

Table 2: Tabulated summary of adverse reactions associated with the combination of

dolutegravir + abacavir/lamivudine including post-marketing experience; and adverse reactions to treatment with dolutegravir, abacavir and lamivudine and post-marketing experience when used with other antiretrovirals:

Frequency	**Adverse reaction**
Blood and lymphatic systems disorders:	
Less frequent:	neutropenia[1], anaemia[1], thrombocytopenia[1], pure red cell aplasia[1]
Immune system disorders:	
Frequent	hypersensitivity (see section 4.4)
Less frequent:	immune reconstitution syndrome (see section 4.4)
Metabolism and nutrition disorders:	
Frequent:	anorexia[1]
Less frequent:	hypertriglyceridaemia, hyperglycaemia, lactic acidosis[1]
Psychiatric disorders:	
Frequent:	insomnia, abnormal dreams, depression, anxiety[1], nightmare, sleep disorder
Less frequent	suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness), panic attack completed suicide (particularly in patients with a pre-existing history of depression or psychiatric illness)
Nervous system disorders:	
Frequent:	headache, dizziness, somnolence, lethargy[1]
Less frequent:	peripheral neuropathy[1], paraesthesia[1]
Respiratory, thoracic and mediastinal disorders:	
Frequent:	cough[1], nasal symptoms[1]
Gastrointestinal disorders:	
Frequent:	nausea, diarrhoea, vomiting, flatulence, abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, gastro-

	oesophageal reflux disease, dyspepsia
Less frequent:	pancreatitis[1]
Hepatobiliary disorders:	
Frequent:	alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations
Less frequent:	Hepatitis, acute hepatic failure[1], increased bilirubin[2]
Skin and subcutaneous tissue disorders:	
Frequent:	rash, pruritus, alopecia[1]
Less frequent:	erythema multiform[1], Stevens-Johnson syndrome[1], toxic epidermal necrolysis[1]
Musculoskeletal and connective tissue disorders:	
Frequent:	Arthralgia[1], muscle disorders[1](including myalgia[1])
Less frequent:	rhabdomyolysis[1]
General disorders and administration site conditions:	
Frequent:	Fatigue, asthenia, fever[1], malaise[1]
Investigations:	
Frequent:	CPK elevations, weight increased
Less frequent:	amylase elevations[1]
[1]This adverse reaction was identified from clinical studies or post-marketing experience for dolutegravir, abacavir or lamivudine when used with other antiretrovirals or post-marketing experience with DEZKAV. [2]In combination with increased transaminases.	

c. Description of selected adverse reactions

Hypersensitivity reactions

Both abacavir and dolutegravir are associated with a risk for hypersensitivity reactions (HSR), which were observed more commonly with abacavir. Hypersensitivity reaction observed for each of these medicines (described below) share some common features such as fever and/or rash with other symptoms indicating multi-organ involvement. Time to onset was typically 10 - 14 days

for both abacavir and dolutegravir-associated reactions, although reactions to abacavir may occur at any time during therapy. Treatment with DEZKAV must be stopped without delay if HSR cannot be ruled out on clinical grounds, and therapy with DEZKAV or other abacavir or dolutegravir containing medicines must never be re-initiated. Please refer to BOXED WARNING and section 4.4 for further details on patient management in the event of a suspected HSR to DEZKAV.

Dolutegravir hypersensitivity
Symptoms have included rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions.

Abacavir hypersensitivity
The signs and symptoms of this HSR 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 lymphatic system disorders:
Lymphopenia

Hepatobiliary disorders:
elevated liver function tests, hepatic failure
Musculoskeletal connective tissue and bone disorders:
myalgia, rarely myolysis, arthralgia, elevated creatinine phosphokinase

Renal and urinary disorders:
elevated creatinine, renal failure.
Symptoms related to this HSR worsen with continued therapy and can be life-threatening and in rare instance, have been fatal.

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. Similar 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 very rare 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).

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

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

Immune reactivation syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of CART, an

inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 96 weeks. In the SINGLE study 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.

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

Co-infection with Hepatitis B or C

In dolutegravir patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C coinfection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C coinfection for all treatment groups.

d. Paediatric population

There are no clinical study data on the effects of DEZKAV in the paediatric population. Individual components have been investigated in adolescents (12 to 17 years).

Based on limited available data with the dolutegravir single entity used in combination with other antiretroviral agents to treat adolescents (12 to 17 years), there were no additional types of adverse reactions beyond those observed in the adult population.

The individual preparations of abacavir and lamivudine have been investigated separately, and as a dual nucleoside backbone, in combination antiretroviral therapy to treat ART- naive and ART-experienced HIV- infected paediatric patients (data available on the use of abacavir and lamivudine in infants less than three months are limited). No additional types of adverse reactions have been observed beyond those characterised for the adult population.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms and signs:

In overdose, side effects can be precipitated and/or be of increased severity.

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.

There is currently limited experience with overdosage in dolutegravir. However, as dolutegravir is highly bound by plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors ATC code: J05AR13.

Pharmacological classification: A 20.2.8 Antiviral agents

Pharmacodynamic properties:

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 (t½ 71 hours)

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs) and are selective inhibitors of HIV-1 and HIV-2. Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective 5'-triphosphate (TP) which are the active moieties with

extended intracellular half-lives supporting once daily dosing (see section 5.2). Lamivudine-TP and carbovir-TP (the active triphosphate from 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.

Resistance

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

No integrase inhibitor (INI) resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment – naïve studies (SPRING-1, SPRING-2 and SINGLE studies). In the SAILING study for treatment experienced (and integrase naïve) patients (n = 354 in the dolutegravir arm), treatment emergent integrase resistance was observed in 2 of 9 subjects with virologic failure. In both cases, a unique R263K integrase substitution was observed, with a maximum fold change (FC) of 1,93.

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

Abacavir-resistant isolated of HIV-1 have been selected in vitro and in vivo and are associated with specific genotypic changes 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 IC50, 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 7-8-FC in abacavir susceptibility and combinations of three mutations were required to confer more than 8-FC in susceptibility.

HIV-1 resistance to lamivudine involves the development of a M184I or 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. M184V is associated with a low-level increase in abacavir resistance but does not confer clinical resistance for abacavir. Isolates resistant to abacavir may also show reduced sensitivity to lamivudine. The combination of abacavir/lamivudine has demonstrated decreased 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 decrease of 10-14 % in mean serum creatinine clearance (CLcr) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). In vitro studies suggest that the increases in creatinine observed in clinical studies are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

5.2 Pharmacokinetic properties

The DEZKAV tablet has shown to be bioequivalent to the abacavir/dolutegravir/lamivudine fixed dose combination tablet. There was no clinically significate effect of a high fat meal on the exposure of abacavir, lamivudine or dolutegravir; a high fat meat increased the C_{max} by 37 % and the AUC by 48 %. These results indicate that DEZKAV can be taken with or without food. The pharmacokinetic properties of dolutegravir, lamivudine and abacavir are described below.

Absorption:

Dolutegravir, abacavir and lamivudine are absorbed following oral administration. The absolute bioavailability of dolutegravir has not been established. The absolute bioavailability of oral abacavir and lamivudine in adults is 83 % and 80 – 85 % respectively. The mean time to maximal serum concentrations (T_{max}) is about at 2 to 3 hours (post dose for the tablet formulation) for dolutegravir, 1,5 hours for abacavir and 1 hour for lamivudine.

Following multiple oral doses of dolutegravir 50 mg once daily, the geometric mean steady state pharmacokinetic parameter estimates are 56,6 ug.h/ml for AUC_{24}, is 8,87 ug.h/ml.

Distribution:

The apparent volume of distribution of dolutegravir (following oral administration of suspension formulation, Vd/F) is estimate at 12,5 l. Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0,8 and 1,3 l/kg respectively.

Dolutegravir is highly bound (approximately 99,3 %) to human plasma proteins based on *in vitro* data. Binding or 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 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. Plasma protein binding studies in vitro indicate that abacavir binds only low to moderately (approximately 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 %).

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 between 30 to 44 %. The mean ratio to CSF/serum lamivudine concentration 2 to 4 hours after oral administration was approximately 12 %.

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 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 is primarily metabolised by the liver 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 predominantly 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:

Dolutegravir has a terminal half-life of ~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. Following multiple oral doses of abacavir 300 mg twice daily, 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. For patients receiving lamivudine 300 mg once daily, the terminal half-life of lamivudine-TP was prolonged to 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/hr/kg, predominantly by renal clearance (greater that 70 %) via the organic cationic transport system.

Special patient populations:

Adolescents:

A paediatric study on 10 antiretroviral treatment-experienced HIV-1 infected adolescents aged 12 to 18 years of age showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir 50 mg once daily. (Table 6)

Table 6: Adolescent pharmacokinetic parameters (n=10)

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

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

Limited data are available 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.

Elderly:

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

Renally impaired:

Pharmacokinetic data has been observed for dolutegravir, abacavir and lamivudine alone. DEZKAV should not be used in patients with creatinine clearance of less than 50 mL/min because, whilst no dosage adjustment of dolutegravir or abacavir is necessary in patients with renal impairment, dose reduction is required for the lamivudine component. Therefore, the separate preparation of lamivudine should be used to treat these patients.

Studies with lamivudine show that plasma concentrations (AUC) are increased in patient with renal dysfunction due to decreased clearance.

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.

Renal clearance of unchanged medicine is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (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. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are expected.

Hepatically impaired:

Pharmacokinetic data has been observed for dolutegravir, abacavir and lamivudine alone. Based on data obtained for abacavir, DEZKAV is not recommended in patients with moderate to severe hepatic impairment.

Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh grade A). 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. Dosage reduction of abacavir may be required in patients with mild hepatic impairment. The separate preparation of abacavir should

therefore be used to treat these patients. The pharmacokinetics of abacavir have not been studies in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to be variable and substantially increased in these patients. DEZKAV is not recommended in patients with moderate to 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. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh grade 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 drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent.

Co-infection with Hepatitis B or C:

Population PK analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited pharmacokinetic data on subjects with hepatitis B co-infection (see Section 4.4 for the use of DEZKAV in patients co-infected with hepatitis B).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, sodium starch glycolate, Opadry II brown (polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide red, black iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Store in the original package to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant.

6.5 Nature and contents of container

DEZKAV will be packed in blue round HDPE bottle with a blue child resistant closure and silica gel sachet.

Packs of 30's and/or 90's.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd
4 Brewery Street
Isando
1600
Republic of South Africa

8. REGISTRATION NUMBER

62/20.2.8/0382

9. DATE OF FIRST AUTHORISATIN/RENEWAL OF THE AUTHORISATION

30 September 2025

10. DATE OF REVISION OF TEXT