SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TULODIV, 600 mg, 50 mg, 300 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of **TULODIV** contains 600 mg of abacavir (as abacavir sulphate), 50 mg of dolutegravir (as dolutegravir sodium) and 300 mg of lamivudine.

Contains sugar: Mannitol 145,400 mg (per tablet)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Beige coloured, oval shaped, biconvex film-coated tablets debossed with 'H' on one side and 'A60' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TULODIV 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 agents in **TULODIV**.

4.2 Posology and method of administration

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

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

TULODIV 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 professional information for these medicinal products.

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

Special Populations

Adults and adolescents

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

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 medicinal products or disease.

Renal impairment

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

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

Method of administration:

For oral use.

TULODIV can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to abacavir, dolutegravir or lamivudine, or to any of the components listed in section 6.1.
- Patients with moderate and severe hepatic impairment due to the abacavir component (see section 4.2 and 5.2).
- Patients with renal impairment with a creatinine clearance of < 50 ml/min due to the lamivudine component (see section 4.2 and 5.2).
- **TULODIV** is contraindicated in combination with dofetilide or pilsicainide.
- Metformin is contraindicated in patients taking **TULODIV**.
- **TULODIV** is contraindicated during first trimester of pregnancy and in mothers who are breastfeeding their infants.

4.4 Special warnings and precautions for use

Hypersensitivity to abacavir (see section 4.8)

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

Risk factors

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

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

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

Clinical description

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

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

Clinical management

Regardless of their HLA-B*5701 status, any patient developing signs or symptoms of hypersensitivity MUST contact their medical practitioner immediately for advice. If a hypersensitivity reaction is diagnosed TULODIV MUST be discontinued immediately. TULODIV, or any other medicinal product 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, **TULODIV** 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). **TULODIV**, or any other medicinal product containing abacavir, should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

An Alert Card with information for the patient about this hypersensitivity reaction is included in the **TULODIV** pack.

Special considerations following an interruption of **TULODIV** *therapy*

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

There have been infrequent reports of hypersensitivity reaction following re-introduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart **TULODIV** in these patients, this should be done only under direct medical supervision.

On 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 **TULODIV**, this must be done only if medical care can be accessed readily by the patient or others.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of abacavir in such patients who test positive for the 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 abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701 positive.
- Patients must also be informed that HLA-B*5701 negative patients can also experience abacavir hypersensitivity reaction. Therefore, ANY patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir **MUST CONTACT** their medical practitioner **IMMEDIATELY**.

- Patients who are hypersensitive to abacavir should be reminded that they must never take **TULODIV** or any other medicinal product containing abacavir again, regardless of their HLA-B*5701 status.
- In order to avoid restarting **TULODIV**, patients who have experienced a hypersensitivity reaction should be asked to return the remaining **TULODIV** tablets to the pharmacy.
- Patients who have stopped **TULODIV** for any reason and particularly due to possible adverse reactions or illness, must be advised to contact their medical practitioner before restarting.
- Each patient should be reminded to read the patient information leaflet included in the **TULODIV** 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.

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 **TULODIV** 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 **TULODIV** after the onset of hypersensitivity may result in a life-threatening reaction.

Myocardial infarction

In a reported prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous six months was correlated with an increased risk of myocardial infarction. As a precaution the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir and action taken to minimise all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

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

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.

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 **TULODIV** 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 **TULODIV**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Lactic acidosis/hyperlactataemia

Use of **TULODIV** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2-5 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 **TULODIV** to patients with known risk factors for liver disease.

Treatment with **TULODIV** 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 sign and symptoms.

Pancreatitis

Pancreatitis has been observed in some patients receiving **TULODIV**.

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **TULODIV** until diagnoses of pancreatitis is excluded.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of lamivudine is increased due to decreased clearance, hence a dose reduction of lamivudine is required whilst no dosage adjustment of dolutegravir or abacavir is necessary. Therefore, **TULODIV** should not be used in patients with a creatinine clearance less than 50 ml/min (see section 4.2, 4.3 and 5.2).

Liver disease

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

Patients co-infected with HIV and HBV who discontinue **TULODIV** 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.

Medicine interactions

Caution should be given to co-administering medications (prescription and non-prescription) that may change the exposure of abacavir, dolutegravir, lamivudine or medications that may have their exposure changed by **TULODIV** (see section 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. Dolutegravir is recommended to be administered 2 hours before or 6 hours after these medicinal products (see section 4.5).

TULODIV is recommended to be administered 2 hours before or 6 hours after taking supplements or multivitamins containing calcium, iron or magnesium, or alternatively, administered with food (see section 4.5).

Metformin concentrations may be increased by **TULODIV**. Metformin is contraindicated in patients taking **TULODIV** (see section 4.3).

TULODIV should not be administered concurrently with other medicinal products containing any of the same active components (abacavir, dolutegravir, and/or lamivudine).

Since the recommended dose of dolutegravir is 50 mg twice daily for patients taking efavirenz, nevirapine, rifampicin and tipranavir/ritonavir, the use of **TULODIV** is not recommended for patients taking these medicines (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

Effect of dolutegravir, abacavir and lamivudine on the pharmacokinetics of other medicinal products

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

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

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

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

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

Effect of other medicinal products on the pharmacokinetics of dolutegravir, abacavir and lamivudine

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore medicines that induce these enzymes or transporters may theoretically decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Co-administration of dolutegravir and other medicines that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 1).

Efavirenz, nevirapine, rifampicin and tipranavir/ritonavir each reduced the plasma concentrations of dolutegravir significantly and require dolutegravir dose adjustment to 50 mg twice daily. Etravirine also reduced plasma concentrations, but the effect of etravirine was mitigated by co-administration of the CYP3A4 inhibitors lopinavir/ritonavir, darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir. Therefore no dolutegravir dose adjustment is necessary when co-administered with etravirine and either lopinavir/ritonavir, darunavir/ritonavir, or atazanavir/ritonavir. Another inducer, fosamprenavir in combination with ritonavir decreased plasma concentrations of dolutegravir but does not require a dosage adjustment of dolutegravir. A medicine interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, ritonavir, lopinavir/ritonavir, darunavir/ritonavir, rilpivirine, bocepravir, telaprevir, prednisone, rifabutin and omeprazole had no or a minimal effect on dolutegravir pharmacokinetics, therefore no dolutegravir dose adjustment is required when co-administered with these medicines.

The likelihood of metabolic interactions with abacavir and lamivudine is low. Abacavir and lamivudine are not significantly metabolised by CYP enzymes. The primary pathways of abacavir metabolism in human are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66 % of the administered dose. These metabolites are excreted in the urine. The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is renal.

Table 1 Medicine interactions

Concomitant medicine class: Medicine name	**Effect on concentration of TULODIV or concomitant medicine**	**Clinical comment**
HIV-1 antiviral medicines		
Non-nucleoside reverse transcriptase inhibitors		
Etravirine (ETR)	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % C_T ↓ 88 % ETR ↔	Etravirine decreased plasma dolutegravir concentration, which may result in loss of virologic response and possible resistance to dolutegravir. **TULODIV** should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57 % C_{max} ↓ 39 % C_T ↓ 75 % EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. Since the dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz the co-administration of efavirenz with **TULODIV** is not recommended.
Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. Since the dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine, the co-administration of nevirapine with **TULODIV** is not recommended.
Protease inhibitors		
Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 49 % C_T ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 %	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.

	C_T ↑ 121 % ATV ↔ RTV ↔	
Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % C_T ↓ 76 % TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. Since the dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir, the co-administration of tipranavir/ritonavir with **TULODIV** is not recommended.
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 in Phase III studies. No dose adjustment is necessary in INI-naïve patients.
Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Lopinavir/ritonavir (LPV + RTV)	DTG ↔ AUC ↔ C_{max} ↔ C_T ↔ LPV ↔ RTV ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ AUC ↓ 32 % C_{max} ↓ 11 % C_T ↓ 38 % DRV ↔ RTV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC ↑ 10 % C_{max} ↑ 7 % C_T ↑ 28 % LPV ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

	RTV ↔ ETR ↔	
Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % C_T ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors		
Tenofovir (TDV)	Dolutegravir ↔ TDV ↔	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other medicinal products		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with dolutegravir is contraindicated due to the potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration (see section 4.3).
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine St. John's wort	Dolutegravir ↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.
Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contraindicated in patients taking **TULODIV** (see section 4.3).
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % C_T ↓ 72 %	Rifampicin decreased dolutegravir plasma concentration. Since the dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin, the co-administration of rifampicin with **TULODIV** is not recommended.

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 % C_T ↓ 7 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with **TULODIV**.
Prednisone	Dolutegravir ↔ AUC ↑ 11 % C_{max} ↑ 6 % C_T ↑ 17 %	No dose adjustment is necessary.
Methadone (40 to 90 mg once daily for 14 days/600 mg single dose, then 600 mg twice daily for 14 days)	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % C_T ↓ 1 % Abacavir AUC ↔ C_{max} ↓ 35 % Methadone CL/F ↑ 22 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with **TULODIV**. The changes in abacavir pharmacokinetics are not considered clinically relevant. The changes in methadone pharmacokinetics are not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.
Ethanol	Abacavir AUC ↑ 41 % Ethanol AUC ↔	Given the safety profile of abacavir, these findings are not considered clinically significant.
Trimethoprim/sulfamethoxazole (Co-trimoxazole) (160 mg/800 mg	Lamivudine: AUC ↑ 40 % Trimethoprim: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim or

once daily for 5 days/300 mg single dose)	Sulfamethoxazole: AUC ↔	sulfamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* (*P. carinii*) pneumonia and toxoplasmosis has not been studied. **TULODIV** should not be used for subjects with CLcr of < 50 ml/min (see section 4.3).
Emtricitabine	Interaction not studied.	Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these medicines in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.
Zalcitabine	Interaction not studied.	Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. **TULODIV** is therefore not recommended to be used in combination with zalcitabine.
Cladribine	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 **TULODIV** with cladribine is not recommended.
Ranitidine Cimetidine	Interaction not studied.	Clinically significant interaction unlikely. No dosage adjustment necessary.
Antacids containing polyvalent	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. **TULODIV** is recommended to be

cations (e.g., Mg, Al or Ca)		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 %	**TULODIV** 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 %	**TULODIV** is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Multivitamins (containing calcium, iron and magnesium)	Dolutegravir ↓ AUC ↓ 33 % C_{max} ↓ 35 % C_{24} ↓ 32 %	**TULODIV** is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Sorbitol solution (3,2 g, 10,2 g, 13,4 g)	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14 %; 32 %; 36 % C_{max} ↓ 28 %; 52 %, 55 %	When possible, avoid chronic coadministration of **TULODIV** with medicinal products 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 coadministration cannot be avoided.
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, CL/F = apparent clearance		

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 **TULODIV** in women of childbearing potential to exclude inadvertent (unintentional) use of **TULODIV** 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

Dolutegravir, lamivudine and abacavir were shown to cross the placenta in reproductive toxicity studies in animals.

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. The clinical relevance of transient elevations in serum lactate is unknown. There have also been reports of developmental delay, seizures and other neurological disease.

Abacavir and lamivudine may inhibit cellular DNA replication and abacavir has been shown to be carcinogenic in animal models (see section 5.3). The clinical relevance of these findings is unknown.

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.

Breastfeeding

HIV infected women should not breastfeed their infants in order to avoid transmission of HIV.

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 new born was 33

hours compared to 14 hours in the adults. There is insufficient information on the effects of dolutegravir in neonates/infants.

Abacavir is excreted into human milk. Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of abacavir and lamivudine when administered to babies less than three months old.

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.

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of **TULODIV** should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Hypersensitivity to abacavir (see section 4.4 Boxed warning)

In clinical studies conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5 % of subjects receiving abacavir developed a hypersensitivity reaction, which in some cases has proved fatal. This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever.

Symptoms can occur at any time while being treated with abacavir, but usually appear within the first six weeks of initiation of treatment (median time to onset 11 days).

The signs and symptoms of this hypersensitivity reaction are listed below.

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

Gastrointestinal disorders: nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration
Respiratory, thoracic and mediastinal disorders: dyspnoea, cough, sore throat, adult respiratory distress syndrome, respiratory failure
General disorders and administrative site conditions: fever, fatigue, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Nervous system disorders: headache, paraesthesia
Blood and the lymphatic system disorders: lymphopenia
Hepato-biliary disorders: elevated liver function tests, hepatitis, hepatic failure
Musculoskeletal connective tissue and bone disorders: myalgia, rarely myolysis, arthralgia, elevated creatine phosphokinase
Renal and urinary disorders: elevated creatinine, renal failure.

Some patients with hypersensitivity were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in abacavir being continued or re-introduced, leading to a more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. If hypersensitivity reaction cannot be ruled out, **TULODIV**, or any other medicinal product containing abacavir should not be restarted.

The symptoms related to this hypersensitivity reaction worsen with continued therapy and usually resolve upon discontinuation of abacavir.

Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction may be more severe than on initial presentation and may include life-threatening hypotension and death. Regardless of their HLA-B*5701 status, patients who develop this hypersensitivity reaction must discontinue **TULODIV** and must never be rechallenged with **TULODIV**, or any other medicinal product containing abacavir.

There have been reports of hypersensitivity reactions following re-introduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal or a respiratory symptom).

Hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity reaction.

Many of the side effects listed occur commonly (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 **TULODIV** has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart abacavir, this must be done only under direct medical supervision (see section 4.4 Boxed Warning).

Table 2: Tabulated summary of adverse reactions associated with the combination of abacavir, dolutegravir and lamivudine

System Organ Class	**Frequency**	**Adverse reactions**
Blood and lymphatic systems disorders	Less frequent	neutropenia, anaemia, thrombocytopenia, pure red cell aplasia
Immune system disorders	Frequent	hypersensitivity
	Less frequent	immune reconstitution syndrome
Metabolism and nutrition disorders	Frequent	anorexia
	Less frequent	hypertriglyceridaemia, hyperglycaemia, lactic acidosis
Psychiatric disorders	Frequent	insomnia, abnormal dreams, depression, anxiety, nightmare, sleep disorder
	Less frequent	suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)
Nervous system disorders	Frequent	headache, dizziness, somnolence, lethargy
	Less frequent	peripheral neuropathy, paraesthesia
Respiratory, thoracic and mediastinal disorders	Frequent	cough, nasal symptoms

Gastrointestinal disorders	Frequent	nausea, diarrhoea, vomiting, flatulence, abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, gastro-oesophageal reflux disease, dyspepsia
	Less frequent	pancreatitis
Hepatobiliary disorders	Frequent	alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations
	Less frequent	hepatitis, acute hepatic failure, increased bilirubin
Skin and subcutaneous tissue disorders	Frequent	rash, pruritus, alopecia
	Less frequent	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Frequent	arthralgia, muscle disorders (including myalgia)
	Less frequent	rhabdomyolysis
General disorders and administration site conditions	Frequent	fatigue, asthenia, fever, malaise
Investigations	Frequent	Creatinine phosphokinase (CPK) elevations
	Less frequent	amylase elevations

Table 3: Tabulated summary of adverse reactions associated with the individual components of **TULODIV**

System Organ Class	**Frequency**	**Adverse reactions**		
		Abacavir	**Dolutegravir**	**Lamivudine**
Blood and lymphatic systems disorders	Less frequent			neutropenia, anaemia, thrombocytopenia
Immune system disorders	Frequent	hypersensitivity		
	Less frequent		hypersensitivity, immune reconstitution syndrome	

Metabolism and nutrition disorders	Frequent	anorexia		
Psychiatric disorders	Frequent		Insomnia, abnormal dreams	
Nervous system disorders	Frequent	headache	headache, dizziness	headache
Gastrointestinal disorders	Frequent	nausea, vomiting, diarrhoea	nausea, vomiting, diarrhoea, flatulence, abdominal pain, upper abdominal pain, abdominal discomfort	nausea, vomiting, diarrhoea, upper abdominal pain
Hepatobiliary disorders	Less frequent		hepatitis	Transient rise in liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	Frequent		rash, pruritis	rash
General disorders and administration site conditions	Frequent	fatigue, fever, lethargy	fatigue	fatigue, fever, malaise,

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 Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is currently limited experience with overdosage in dolutegravir.

The patient should be treated symptomatically and supportively with appropriate monitoring as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 20.2.8 Antiviral agents
Antivirals for systemic use, antivirals for treatment of HIV infections, combinations. ATC code: J05AR13

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2,7 nM and 12,6 nM *in vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex ($t_{½}$ 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 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 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.

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

No integrase inhibitor-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 participants with virologic failure. In both cases, a unique R263K integrase substitution was observed, with a maximum FC of 1,93.

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

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and *in vivo* and are associated with specific 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 IC_{50}, below the abacavir clinical cut-off of 4,5-FC. Continued passage in increasing concentrations of medicine resulted in selection for double RT mutants 65R/184V and 74V/184V or triple RT mutant 74V/115Y/184V. Two mutations conferred a 7- to 8-FC in abacavir susceptibility and combinations of three mutations were required to confer more than an 8-FC in susceptibility.

HIV-1 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 (CL_{cr}) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on the glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). *In vitro* studies suggest that the increases in serum creatinine observed in clinical studies are due to the non-pathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

5.2 Pharmacokinetic properties

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 to 85 % respectively. The mean time to maximal serum concentrations (t_{max}) is about 2 to 3 hours (post dose for tablet formulation) for dolutegravir, 1,5 hours for abacavir and 1,0 hours for lamivudine.

Following multiple oral doses of dolutegravir 50 mg once daily, the geometric mean steady state pharmacokinetic parameter estimates are 53,6 µg.h/ml for AUC_{24}, 3,67 µg/ml for C_{max}, and 1,11 µg/ml for C_{24}. Following a single oral dose of 600 mg of abacavir, the mean C_{max} is 4,26 µg/ml and the mean AUC_{∞} is 11,95 µg.h/ml. 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

The apparent volume of distribution of dolutegravir (following oral administration of suspension formulation, Vd/F) is estimated 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 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 participants, approximately 0,4 to 0,5 % in participants with moderate hepatic impairment, and 0,8 to 1,0 % in participants 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 of between 30 to 44 %. The mean ratio of CSF/serum lamivudine concentrations 2 to 4 hours after oral administration was approximately 12 %.

Biotransformation

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). 53 % 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. 31 % 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 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

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 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. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was prolonged to 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/h/kg, predominantly by renal clearance (greater than 70 %) via the organic cationic transport system.

Special patient populations

Children

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 resulted in dolutegravir exposure in adolescent participants comparable to that observed in adults who received dolutegravir 50 mg once daily (Table 4).

Table 4 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 participants of > 65 years old are limited.

Renally impaired

Pharmacokinetic data have been obtained for dolutegravir, abacavir and lamivudine alone. **TULODIV** 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 patients 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 participants with severe renal impairment (CL_{cr} < 30 ml/min). No clinically important pharmacokinetic differences between participants with severe renal impairment (CL_{cr} < 30 ml/min) and matching healthy participants were observed. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Hepatically impaired

Pharmacokinetic data has been obtained for dolutegravir, abacavir and lamivudine alone. Based on data obtained for abacavir, **TULODIV** is not recommended in patients with moderate and 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 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. 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 studied in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to be variable and substantially increased in these patients. **TULODIV** is therefore not recommended in patients with moderate and severe hepatic impairment.

Data obtained for lamivudine in patients with moderate to severe hepatic impairment and for dolutegravir in patients with moderate hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction. Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 participants 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. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in drug metabolising enzymes

There is no evidence that common polymorphisms in drug metabolising enzymes 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 participants with hepatitis B co-infection (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Magnesium stearate
Mannitol
Microcrystalline cellulose
Povidone
Sodium starch glycolate

Film coating:

Ferrosoferric oxide/black iron oxide (E172)
Iron oxide red (E172)
Iron oxide yellow (E172)
Macrogol/polyethylene glycol (E1521)
Polyvinyl alcohol – part hydrolysed (E1203)
Talc (E553b)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

28, 30, 84, 90 and 180 film-coated tablets are packed in high density polyethylene (HDPE) containers with a silica gel canister and closed with a child-resistant plastic cap with a pulp liner.

10 x 10 tablets are packed in blister strips composed of PVC/aluminium and plain aluminium lidding foil.

Not all packs and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

57/20.2.8/0108

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 June 2025

10. DATE OF REVISION OF THE TEXT

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