SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

TRELAVUE Film-coated tablets

HYPERSENSITIVITY REACTIONS

Hypersensitivity to abacavir (see also SIDE EFFECTS).

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

Risk Factors:

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

Clinicians should screen for carriage of the HLA-B*5701 allele in any HIV infected patient without prior exposure to abacavir. Screening is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see “Special considerations following an interruption of abacavir

therapy"). Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended.

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

Clinical Description:

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

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

Clinical Management:

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

Special considerations following an interruption of TRELAVUE therapy:

Regardless of a patient's HLA-B*5701 status, if therapy with any abacavir containing product has been discontinued and restarting therapy with TRELAVUE 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, TRELAVUE 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 TRELAVUE 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 TRELAVUE, 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 doctor **IMMEDIATELY.**
- Patients who are hypersensitive to abacavir should be reminded that they must never take TRELAVUE or any other medicinal product containing abacavir again, regardless of their HLA-B*5701 status.
- In order to avoid restarting TRELAVUE, patients who have experienced a hypersensitivity reaction should be asked to return the remaining TRELAVUE tablets to the pharmacy.
- Patients who have stopped TRELAVUE for any reason and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.
- Each patient should be reminded to read the package leaflet included in the TRELAVUE 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.

COMPOSITION:

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

Excipients:

Tablet Core:

D-Mannitol, magnesium stearate, microcrystalline cellulose, povidone K29/32, sodium starch glycolate.

Tablet coating:

Opadry II Purple 85F90057 containing: Polyvinyl alcohol – part hydrolysed, titanium oxide, macrogol/PEG, talc, iron oxide black, iron oxide red.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

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. 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 Pharmacokinetic properties, Elimination). 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 subjects 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 (CLcr) was observed with dolutegravir within the first week of treatment. Dolutegravir had no significant effect on the glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF). *In vitro* studies suggest that the increases in serum creatinine observed in clinical studies are due to the nonpathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Pharmacokinetic properties:

The TRELAVUE tablet has been shown to be bioequivalent to dolutegravir single entity tablet with abacavir/lamivudine fixed dose combination tablet administered separately. There was no clinically significant effect of a high fat meal on the exposure of abacavir or lamivudine with dolutegravir; a high fat meal increased the C_{max} by 37 % and the AUC by 48 %. These results indicate that TRELAVUE 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 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 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 of between 30 to 44 %. The mean ratio of CSF/serum lamivudine concentrations 2 to 4 hours after oral administration was approximately 12 %.

***Metabolism*:**

Dolutegravir is 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 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 subjects comparable to that observed in adults who received dolutegravir 50 mg once daily (Table 1).

Table 1 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 have been obtained for dolutegravir, abacavir and lamivudine alone. TRELAVUE 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 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 not expected.

***Hepatically impaired*:**

Pharmacokinetic data has been obtained for dolutegravir, abacavir and lamivudine alone. Based on data obtained for abacavir, TRELAVUE 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. TRELAVUE 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 subjects with moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. 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 subjects with hepatitis B co-infection (see WARNINGS AND SPECIAL PRECAUTIONS for the use of TRELAVUE in patients co-infected with hepatitis B).

INDICATIONS:

TRELAVUE 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 TRELAVUE.

CONTRAINDICATIONS:

TRELAVUE is contraindicated in patients with known hypersensitivity to dolutegravir, abacavir or lamivudine, or to any of the excipients.

TRELAVUE is contraindicated in combination with dofetilide or pilsicainide.

TRELAVUE is contraindicated for patients with moderate and severe hepatic impairment due to the abacavir component (see PHARMACOLOGICAL ACTION).

TRELAVUE is contraindicated during pregnancy or in mothers who are breastfeeding their infants (see PREGNANCY AND LACTATION).

TRELAVUE is contraindicated in patients with renal impairment with a creatinine clearance of < 50 ml/min due to the lamivudine component (see PHARMACOLOGICAL ACTION).

Metformin is contraindicated in patients taking TRELAVUE.

WARNINGS AND SPECIAL PRECAUTIONS:

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

Hypersensitivity to abacavir – refer to Boxed Warning.

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.

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 below), 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 TRELAVUE.

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

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

Lactic acidosis/severe hepatomegaly with steatosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of abacavir and lamivudine. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms 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 agents 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).

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any patient with a raised lactate level. Blood for lactate assay should be heparinised and stored on ice. After recovery, NRTIs should be avoided. Seek expert advice on medicine selection.

The above lactate values may not be applicable to paediatric patients. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of TRELAVUE alone or in combination.

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

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, elevated serum lipid and blood glucose levels have been observed either separately or together in some patients (see SIDE EFFECTS).

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.

Immune Reconstitution Syndrome:

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or atypical focal mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of 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 SIDE EFFECTS).

Patients co-infected with hepatitis B virus (HBV):

Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy when starting therapy with TRELAVUE in hepatitis B co-infected patients.

Clinical study and marketed use of lamivudine, have shown that some patients with chronic HBV disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If TRELAVUE is discontinued in patients co-infected with HBV, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Opportunistic infections:

Patients receiving TRELAVUE may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV diseases.

Transmission of infection:

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

Myocardial Infarction:

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

Medicine Interactions:

Caution should be 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 TRELAVUE (see CONTRAINDICATIONS and INTERACTIONS).

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 INTERACTIONS).

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 agents (see INTERACTIONS).

TRELAVUE is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements, or alternatively, administered with food (see INTERACTIONS).

Metformin concentrations may be increased by TRELAVUE. Metformin is contraindicated in patients taking TRELAVUE (see CONTRAINDICATIONS).

TRELAVUE should not be administered concurrently with other medicinal products containing any of the same active components (dolutegravir, abacavir, 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 TRELAVUE is not recommended for patients taking these medicines (see INTERACTIONS).

Effects on ability to drive and use machines:

There have been no studies to investigate the effect of TRELAVUE on driving performance or the ability to operate machinery. The clinical status of the patient and the adverse event profile of TRELAVUE should be borne in mind when considering the patient's ability to drive or operate machinery.

INTERACTIONS:

Effect of Dolutegravir, Abacavir and Lamivudine on the Pharmacokinetics of Other Agents:

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50} > 50 µM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1,

MRP2, or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, dolutegravir is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or transporters.

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

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

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

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

Effect of Other Agents 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 3).

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 3 Medicine Interactions studied with dolutegravir

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of dolutegravir or Concomitant Medicine**	**Clinical Comment**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR)	Dolutegravir ↓ AUC ↓ 71 % C_{max} ↓ 52 % Cτ ↓ 88 % ETR ↔	Etravirine decreased plasma dolutegravir concentration, which may result in loss of virologic response and possible resistance to dolutegravir. TRELAVUE should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57 % C_{max} ↓ 39 % Cτ ↓ 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 TRELAVUE is not recommended.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. Since the dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine, the co-administration of nevirapine with TRELAVUE is not recommended.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91 % C_{max} ↑ 49 % Cτ ↑ 180 % ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV + RTV)	Dolutegravir ↑ AUC ↑ 62 % C_{max} ↑ 33 % Cτ ↑ 121 %	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of dolutegravir or Concomitant Medicine**	**Clinical Comment**
	ATV ↔ RTV ↔	
Protease Inhibitor: Tipranavir/ritonavir (TPV + RTV)	Dolutegravir ↓ AUC ↓ 59 % C_{max} ↓ 47 % Cτ ↓ 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 TRELAVUE is not recommended.
Protease Inhibitor: Fosamprenavir/ ritonavir (FPV + RTV)	Dolutegravir ↓ AUC ↓ 35 % C_{max} ↓ 24 % Cτ ↓ 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.
Protease Inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV + RTV)	DTG ↔ AUC ↔ C_{max} ↔ Cτ ↔ LPV ↔ RTV ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir (DRV/RTV)	Dolutegravir ↓ AUC ↓ 32 % C_{max} ↓ 11 % Cτ ↓ 38 % DRV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of dolutegravir or Concomitant Medicine	Clinical Comment
	RTV ↔	
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDV)	Dolutegravir ↔ TDV ↔	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC ↑ 10 % C_{max} ↑ 7 % Cτ ↑ 28 % LPV ↔ RTV ↔ ETR ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC ↓ 25 % C_{max} ↓ 12 % Cτ ↓ 36 % DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Agents		
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 CONTRAINDICATIONS).
Oxcarbazepine Phenytoin Phenobarbital Carbamazepine	Dolutegravir↓	Co-administration may decrease dolutegravir plasma concentration and has not been studied. Co-administration with these metabolic inducers should be avoided.

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of dolutegravir or Concomitant Medicine**	**Clinical Comment**
St. John's wort		
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Dolutegravir ↓ AUC ↓ 74 % C_{max} ↓ 72 % C_{24} ↓ 74 %	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. TRELAVUE is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39 % C_{max} ↓ 37 % C_{24} ↓ 39 %	TRELAVUE 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 %	TRELAVUE is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin ↑	Co-administration of dolutegravir increased metformin plasma concentration. Metformin is contraindicated in patients taking TRELAVUE (see CONTRAINDICATIONS).
Rifampicin	Dolutegravir ↓ AUC ↓ 54 % C_{max} ↓ 43 % $C\tau$ ↓ 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 TRELAVUE is not recommended.

Concomitant Medicine Class: Medicine Name	Effect on Concentration of dolutegravir or Concomitant Medicine	Clinical Comment
Oral contraceptives (Ethinyl estradiol (EE) and Norgestromin (NGMN))	Effect of dolutegravir: EE ↔ AUC ↑ 3 % C_{max} ↓ 1 % Cτ ↑ 2 % Effect of dolutegravir: NGMN ↔ AUC ↓ 2 % C_{max} ↓ 11 % Cτ ↓ 7 %	Dolutegravir did not change ethinyl estradiol and norgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2 % C_{max} ↔ 0 % Cτ ↓ 1 %	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when co-administered with dolutegravir.

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

Table 4 Medicine Interactions studied with abacavir

Concomitant Medicine Class: Medicine Name	Effect on Concentration of abacavir or Concomitant Medicine	Clinical Comment

Methadone (40 to 90 mg once daily for 14 days/600 mg single dose, then 600 mg twice daily for 14 days)	Abacavir AUC ↔ C_{max} ↓ 35 % Methadone CL/F ↑ 22 %	The changes in abacavir pharmacokinetics are not considered clinically relevant. The changes in methadone pharmacokinetics are not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.
Ethanol	Abacavir AUC ↑ 41 % Ethanol AUC ↔	Given the safety profile of abacavir, these findings are not considered clinically significant.
Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration, CL/F = apparent clearance		

Table 5 Medicine Interactions studied with lamivudine

Concomitant Medicine Class: Medicine Name	**Effect on Concentration of lamivudine or Concomitant Medicine**	**Clinical Comment**
Trimethoprim/sulfa-methoxazole (Co-trimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑ 40 % Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see DOSAGE AND DIRECTIONS FOR USE). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* (*P. carinii*) pneumonia and toxoplasmosis has not been studied. TRELAVUE should not be used for subjects with CLcr of < 50 ml/min (see CONTRAINDICATIONS).
Emtricitabine		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

Concomitant Medicine Class: Medicine Name	Effect on Concentration of lamivudine or Concomitant Medicine	Clinical Comment
		may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.
Zalcitabine		Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. TRELAVUE is therefore not recommended to be used in combination with zalcitabine.

PREGNANCY AND LACTATION:

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

The safe use of TRELAVUE in human pregnancy has not been established. 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.

Lactation:

HIV infected women should not breastfeed their infants in order to avoid transmission of HIV. It is expected that abacavir and dolutegravir will be secreted into human milk. Lamivudine is excreted in human milk at similar concentrations to those found in serum. Therefore, mothers breastfeeding their infants should not use TRELAVUE.

DOSAGE AND DIRECTIONS FOR USE:

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

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

TRELAVUE can be taken with or without food.

TRELAVUE 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 medicinal products.

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

Populations:

Adults and adolescents:

The recommended dose of TRELAVUE 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 Pharmacokinetic properties – Special Patient Populations). 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, TRELAVUE should not be used in patients with a creatinine clearance less than 50 ml/min (see Pharmacokinetic properties – Special Patient Populations and CONTRAINDICATIONS).

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 TRELAVUE, the separate preparations of dolutegravir, abacavir or lamivudine should be used when this is judged necessary. TRELAVUE is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (see Pharmacokinetic properties – Special Patient Populations and CONTRAINDICATIONS).

SIDE EFFECTS:

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

Hypersensitivity to abacavir (see also Boxed Warning).

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

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

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

The signs and symptoms of this hypersensitivity reaction are listed below. Those reported in at least 10 % of patients with a hypersensitivity reaction are in **bold text.**

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

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

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

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

Nervous system disorders: **headache,** paraesthesia

Blood and the lymphatic system disorders: lymphopenia

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

Musculoskeletal connective tissue and bone disorders: **myalgia,** rarely 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, TRELAVUE, 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 TRELAVUE and must never be rechallenged with TRELAVUE, 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 TRELAVUE has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart abacavir, this must be done only under direct medical supervision (see Special considerations following an interruption of TRELAVUE therapy in Boxed Warning).

Side effects for dolutegravir, abacavir or lamivudine are listed in the tables below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000) and very rare (< 1/10 000), including isolated reports.

Clinical Trial Data:

Clinical safety data with TRELAVUE are limited. The side effects observed for the combination of the three components of this medicine in analysis of pooled data from clinical trials were generally consistent with the side effect profiles for the individual components dolutegravir, abacavir and lamivudine. However, the following common treatment-emergent side effects were observed with the combination but were not listed in the prescriber information for any of the individual components:

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

In addition, fatigue and insomnia were observed at a greater frequency with the combination when compared with the individual components. The frequency category for fatigue and insomnia was 'very common' with the combination (previously 'common' with each individual component or with dolutegravir, respectively).

There was no difference between the combination and the individual components in severity for any observed side effects.

Table 6 Adverse reactions associated with the individual components of TRELAVUE based on clinical study experience.

System organ class	Dolutegravir	Abacavir	Lamivudine
Blood and lymphatic systems disorders			Uncommon: neutropenia, anaemia, thrombocytopenia
Immune system disorders	Uncommon: hypersensitivity (see WARNINGS AND SPECIAL PRECAUTIONS), immune reconstitution syndrome (see WARNINGS AND SPECIAL PRECAUTIONS)	Common: medicine hypersensitivity (see WARNINGS AND SPECIAL PRECAUTIONS)	
Metabolism and nutrition disorders		Common: anorexia	

System organ class	Dolutegravir	Abacavir	Lamivudine
Psychiatric disorders	Common: insomnia, abnormal dreams		
Nervous system disorders	Very common: headache Common: dizziness	Common: headache	Common: headache
Gastrointestinal disorders	Very common: nausea, diarrhoea Common: vomiting, flatulence, abdominal pain, upper abdominal pain, abdominal discomfort	Common: nausea, vomiting, diarrhoea	Common: nausea, vomiting, upper abdominal pain, diarrhoea
Hepatobiliary disorders	Uncommon: hepatitis		Uncommon: transient rises in liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	Common: rash, pruritus		Common: rash
General disorders and administration site conditions	Common: fatigue	Common: fever, lethargy, fatigue	Common: fatigue, malaise, fever

Changes in laboratory chemistries*:*

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 96 weeks. A mean change from baseline of 12,6 µmol/l was observed after 96 weeks of treatment. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see Pharmacodynamic properties - Effects on Renal Function).

Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir. These changes are not considered clinically relevant as they likely reflect

competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see Pharmacokinetic properties - Metabolism).

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

Post-marketing data:

In addition to the side effects included from clinical trial data, the side effects listed in Table 7 below have been identified during post-approval use of abacavir and lamivudine. No dolutegravir or TRELAVUE post-marketing data are available.

Table 7 Side effects based on post-marketing experience

System organ class	Abacavir	Lamivudine
Blood and lymphatic systems disorders		pure red cell aplasia
Metabolism and nutrition disorders	hyperlactataemia [1]lactic acidosis	hyperlactataemia [1]lactic acidosis
Nervous system disorders		paraesthesiae, peripheral neuropathy has been reported although a causal relationship to treatment is uncertain
Gastrointestinal disorders	pancreatitis, but a causal relationship to abacavir is uncertain	rises in serum amylase, pancreatitis, although a causal relationship to lamivudine is uncertain
Skin and subcutaneous tissue disorders	rash (without systemic symptoms) erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	alopecia
Musculoskeletal and connective tissue disorders		arthralgia, muscle disorders rhabdomyolysis

[1]Lactic acidosis (see WARNINGS AND SPECIAL PRECAUTIONS)

Redistribution/accumulation of body fat has been observed in some patients receiving combination antiretroviral therapy (see WARNINGS AND SPECIAL PRECAUTIONS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms and Signs:

There is currently limited experience with overdosage in dolutegravir.

Treatment:

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

IDENTIFICATION:

Purple, biconvex, oval, film-coated tablets, debossed with “572 Trı” on one side.

PRESENTATION:

TRELAVUE tablets are packed into opaque, white High Density Polyethylene (HDPE) bottles and closed with white polypropylene child resistant closures, with a polyethylene faced induction heat seal liner. A silica gel desiccant is included in each bottle. The HDPE bottle is pigmented white with titanium dioxide and is packed into an outer cardboard carton.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Store in the original package to protect from moisture. Keep bottle tightly closed. Do not remove the desiccant.

REGISTRATION NUMBER:

49/20.2.8/0097

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Registration date: 21 April 2016

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