AUSTRALIAN PRODUCT INFORMATION

TRIUMEQ (dolutegravir, abacavir and lamivudine) film-coated tablets

Abacavir, a component of TRIUMEQ tablets, is associated with hypersensitivity reactions, which can be life-threatening, and in rare cases fatal. TRIUMEQ tablets, or any other medicinal product containing abacavir (KIVEXA [abacavir/lamivudine], TRIZIVIR [abacavir/lamivudine/zidovudine] and ZIAGEN [abacavir]) MUST NEVER be restarted following a hypersensitivity reaction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

1 NAME OF THE MEDICINE

Dolutegravir (as sodium), abacavir (as sulfate) and lamivudine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TRIUMEQ film-coated tablets contain 50 mg of dolutegravir (as dolutegravir sodium), 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine. Product Information for TIVICAY (dolutegravir), ZIAGEN (abacavir), 3TC (lamivudine) and KIVEXA (abacavir and lamivudine) contain additional information.

Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

Abacavir sulfate is a white to off-white crystalline powder with a solubility of approximately 77 mg/mL in water at 25°C.

Lamivudine is a white to off-white crystalline solid which is highly soluble in water.

TRIUMEQ tablets also contain mannitol. For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Purple, film-coated, oval, biconvex tablets, debossed with ‘572 Trı’ on one side. Each film-coated tablet contains 50 mg of dolutegravir (as dolutegravir sodium), 600 mg of abacavir (as abacavir sulphate) and 300 mg of lamivudine.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRIUMEQ is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 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 (dolutegravir, abacavir or lamivudine) in TRIUMEQ.

4.2 DOSE AND METHOD OF ADMINISTRATION

Therapy should be initiated by a physician experienced in the management of HIV infection.

The recommended dose of TRIUMEQ in adults and adolescents weighing at least 40 kg is one tablet once daily, taken with or without food.

Because TRIUMEQ is a fixed dose tablet, it should not be prescribed for patients requiring dose adjustment:

- Adults or adolescents weighing < 40 kg
- Children < 12 years of age
- Patients with creatinine clearance < 30 mL/min
- Patients with mild hepatic impairment
- Patients resistant to integrase inhibitors

Populations

Children

Based on indications for use for TIVICAY [dolutegravir] and KIVEXA [abacavir/lamivudine], TRIUMEQ is indicated for use in adolescents aged 12 years and above (See Product Information for TIVICAY [dolutegravir] and KIVEXA [abacavir/lamivudine]).

TRIUMEQ is not recommended for treatment of children less than 12 years of age as the necessary dose adjustment cannot be made. Clinical data is currently not available for this combination. Physicians should refer to the individual product information for TIVICAY [dolutegravir], ZIAGEN [abacavir] and 3TC [lamivudine].

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 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

Risks and benefits of using TRIUMEQ in patients with renal impairment should be assessed by a physician experienced in the management of HIV infection and discussed with the patient.

Lamivudine exposure is significantly increased in patients with a creatinine clearance < 50 mL/min. 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 (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES – Special patient populations – Renally impaired).

Therefore, TRIUMEQ is not recommended for use in patients with a creatinine clearance less than 30 mL/min. If lamivudine dose adjustment is indicated, TRIUMEQ should be discontinued, and the individual components should be used to construct the treatment regimen.

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 TRIUMEQ, the separate preparations of dolutegravir, abacavir or lamivudine should be used when this is judged necessary. TRIUMEQ is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (see Section 5.2 PHARMACOKINETIC PROPERTIES - Special patient populations).

Separate preparations of dolutegravir, abacavir or lamivudine should be administered in cases where discontinuation or dose adjustment is indicated. In these cases the physician should refer to the individual product information for these medicinal products. A separate preparation of dolutegravir (TIVICAY) is available where a dose adjustment is required due to drug-drug interactions (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Women of childbearing potential and pregnancy

There is limited information on the use of TRIUMEQ in pregnancy. TRIUMEQ should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in pregnancy).

4.3 CONTRAINDICATIONS

TRIUMEQ is contraindicated in patients with known hypersensitivity to dolutegravir, abacavir or lamivudine, or to any of the excipients (see Section 6.1 LIST OF EXCIPIENTS).

TRIUMEQ must not be administered concurrently with medicinal products with narrow therapeutic windows, that are substrates or organic cation transporter 2 (OCT2), including but not limited to dofetilide, pilsicainide or fampridine (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The special warnings and precautions relevant to dolutegravir, abacavir and lamivudine are included in this section. There are no additional precautions and warnings relevant to TRIUMEQ.

Hypersensitivity reactions (see also Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Hypersensitivity reactions have been reported with the use of abacavir or dolutegravir, components of TRIUMEQ.

Abacavir

Hypersensitivity to abacavir is a multi-organ clinical syndrome which can occur at any time during treatment, but most often occurs within the first 6 weeks of therapy.

Signs or symptoms usually present in 2 or more of the following groups although hypersensitivity following the presentation of a single sign or symptom has been reported infrequently.

- fever
- rash
- gastrointestinal, including nausea, vomiting, diarrhoea, or abdominal pain
- constitutional, including generalised malaise, fatigue, or achiness
- respiratory, including dyspnoea, cough, or pharyngitis.

Hypersensitivity reactions may present similarly to pneumonia, bronchitis or pharyngitis, influenza-like illness or gastroenteritis.

- **Discontinue TRIUMEQ as soon as a hypersensitivity reaction is suspected**.
- **If hypersensitivity reaction cannot be ruled out, TRIUMEQ or any other medicinal product containing abacavir must not be restarted.**
- The risk is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir hypersensitivity reactions have been reported at a lower frequency in patients who do not carry this allele.
- **TRIUMEQ is not recommended for use in patients with the HLA-B*5701 allele or in patients who have had a suspected abacavir HSR while taking any medicinal product containing abacavir.**
- Testing for HLA-B*5701 status is recommended before initiating abacavir treatment and also before re-starting abacavir treatment in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.
- The diagnosis of hypersensitivity reaction is based on clinical judgment. **If a hypersensitivity reaction is suspected, TRIUMEQ must be stopped without delay, even in the absence of the HLA-B*5701 allele.** Delay in stopping treatment with abacavir after the onset of hypersensitivity may result in a life-threatening hypotension and death.
- Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity reaction have also experienced life-threatening reactions within hours of re-initiating abacavir therapy. Therefore, if a hypersensitivity reaction is ruled out, the reintroduction of TRIUMEQ or any other abacavir-containing product is recommended only if medical care can be readily accessed.

- Each patient should be reminded to read the Consumer Medicine Information. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.
- Patients who have experienced a hypersensitivity reaction should be instructed to dispose of their remaining TRIUMEQ tablets in order to avoid restarting abacavir.

Dolutegravir

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue TRIUMEQ and other suspect agents 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 TRIUMEQ or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Clinically, it is not possible to determine whether a hypersensitivity reaction with TRIUMEQ would be caused by abacavir or dolutegravir. Therefore, never restart TRIUMEQ or any other abacavir- or dolutegravir-containing product in patients who have stopped therapy with TRIUMEQ due to a hypersensitivity reaction.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including 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).

Caution should be exercised when administering TRIUMEQ particularly to those with known risk factors for liver disease. Treatment with TRIUMEQ 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).

Fat loss or fat gain

Fat loss or fat gain has been reported during combination antiretroviral therapy. The long-term consequences of these events are currently unknown. A causal relationship has not been established.

Serum lipids and blood glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. 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 cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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 TRIUMEQ 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 TRIUMEQ 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 TRIUMEQ or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission of infection

While effective viral suppression with antriretroviral therapy has been proven to substantially reduce the risk of sexual transmissions, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Myocardial infarction

Several observational, epidemiological studies have reported an association with abacavir use and risk of myocardial infarction. Meta-analyses of randomised controlled trials have observed no excess risk of myocardial infarction with abacavir use. To date, there is no established biological mechanism to explain a potential increase in risk. In totality the available data from observational studies and from controlled clinical trials show inconsistency and therefore the evidence for a causal relationship between abacavir treatment and the risk of myocardial infarction is inconclusive.

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).

Patients with resistance to the integrase class (documented or clinically suspected)

TRIUMEQ alone is not recommended in patients with resistance associated with integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in TRIUMEQ is insufficient in these populations (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and TIVICAY [dolutegravir] Product Information).

Use in hepatic impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES - Special patient populations.

Use in renal impairment

Administration in subjects with moderate renal impairment

Patients with a creatinine clearance between 30 and 49 mL/min receiving TRIUMEQ may experience a 1.6-to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥ 50 mL/min. There are no safety data from randomised, controlled trials comparing TRIUMEQ to the individual components in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of haematologic toxicities (neutropenia and anaemia), although discontinuations due to neutropenia or anaemia each occurred in < 1% of subjects. Other lamivudine-related adverse events (such as gastro-intestinal and hepatic disorders) may occur.

Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive TRIUMEQ should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, per lamivudine prescribing information, is indicated, which cannot be achieved with TRIUMEQ. TRIUMEQ should be discontinued and the individual components should be used to construct the treatment regimen.

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES - Special patient populations.

Use in the 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 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.

Paediatric use

TRIUMEQ is not recommended for treatment of children less than 12 years of age as the necessary dose adjustment cannot be made. Clinical data is currently not available for this combination. Physicians should refer to the individual product information for TIVICAY [dolutegravir], ZIAGEN [abacavir] and 3TC [lamivudine].

Effects on laboratory tests

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Tables 5 and 6.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 TRIUMEQ.

Dolutegravir should not be co-administered with polyvalent cation-containing antacids. TRIUMEQ is recommended to be administered 2 hours before or 6 hours after these agents.

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

Dolutegravir increases metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control.

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

The recommended dose of dolutegravir is 50 mg twice daily when co-administered with etravirine (without boosted protease inhibitors), efavirenz, nevirapine, rifampicin, tipranavir/ritonavir, carbamazepine, phenytoin, phenobarbital and St. John's wort.

As TRIUMEQ contains dolutegravir, abacavir and lamivudine, any interactions that have been identified with these agents individually may occur with TRIUMEQ. Due to the different routes of metabolism and elimination, no clinically significant drug interactions are expected between dolutegravir, abacavir and lamivudine. In a cross study comparison, abacavir and lamivudine exposures were similar when given as TRIUMEQ compared to ABC/3TC alone.

Effect of TRIUMEQ on the pharmacokinetics of other agents

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 drug interactions via inhibition of OAT transporters.

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). *In vivo*, dolutegravir may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 or MATE1 (for example dofetilide, pilsicainide, fampridine or metformin) (see Table 1). Given dolutegravir's *in vivo* exposure, it has a low potential to affect the transport of MATE2-K substrates *in vivo*.

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 P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, organic cation transporter 1 (OCT1) multidrug resistance-associated protein 2 (MRP2), or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on these data, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

In drug 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, boceprevir, daclatasvir and oral contraceptives containing norgestimate and ethinyl estradiol.

Abacavir and lamivudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with other medicinal products metabolised by major P450 enzymes.

Abacavir and lamivudine demonstrate no or weak inhibition of the OATP1B3, BCRP and Pgp or MATE2-K. In addition, lamivudine demonstrates no or weak inhibition of the drug transporters MATE1 or OCT3 and abacavir demonstrates minimal inhibition of OCT1 and OCT2. Abacavir and lamivudine are therefore not expected to affect the plasma concentrations of drugs that are substrates of these enzymes or transporters.

Although abacavir is an inhibitor of MATE1 and lamivudine is an inhibitor of OCT1 and OCT2 *in vitro*, they have low potential to affect the plasma concentrations of substrates of these transporters at therapeutic drug exposures (up to 600 mg for abacavir or 300 mg for lamivudine).

Effect of other agents on the pharmacokinetics of TRIUMEQ

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore drugs 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 drugs that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 1).

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

Efavirenz, etravirine, nevirapine, rifampicin, carbamazepine and tipranavir in combination with ritonavir each reduced the plasma concentrations of dolutegravir significantly, and require dolutegravir dose adjustment to 50 mg twice daily. 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 drug interaction study with the UGT1A1 inhibitor, atazanavir, did not result in a clinically meaningful increase in the plasma concentrations of dolutegravir. Tenofovir, lopinavir/ritonavir, daclatasvir and darunavir/ritonavir had no or a minimal effect on dolutegravir pharmacokinetics, therefore no dolutegravir dose adjustment is required when co-administered with these drugs.

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 humans 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. *In vitro*, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, MRP2 or MRP4 therefore drugs that modulate these transporters are not expected to affect abacavir plasma concentrations.

Although abacavir and lamivudine are substrates of BCRP and Pgp *in vitro*, clinical studies demonstrate no clinically significant changes in abacavir pharmacokinetics when co-administered with lopinavir/ritonavir (Pgp and BCRP inhibitors) and inhibitors of these efflux transporters are unlikely to affect the disposition of lamivudine due to its high bioavailability. Lamivudine is an *in vitro* substrate of MATE1, MATE2-K and OCT2. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations; however, the resulting increase was of such magnitude that a dose adjustment is not recommended as it is not expected to have clinical significance. Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Selected drug interactions are presented in Tables 1, 2 and 3. Recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 1: Drug Interactions studied with dolutegravir

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Dolutegravir or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR) without boosted protease inhibitors	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% Cτ ↓ 88% ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of dolutegravir is 50 mg twice daily for patients taking etravirine without boosted protease inhibitors. As TRIUMEQ is a fixed dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered approximately 12 hours after TRIUMEQ. In this case the physician should refer to the individual product information for TIVICAY.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV+ETR)	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% LPV ↔ RTV ↔	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.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75% EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. As TRIUMEQ is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered approximately 12 hours after TRIUMEQ. In this case the physician should refer to

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Dolutegravir or Concomitant Drug**	**Clinical Comment**
		the individual product information for TIVICAY.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. As TRIUMEQ is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered approximately 12 hours after TRIUMEQ. In this case the physician should refer to the individual product information for TIVICAY.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% Cτ ↑ 180% ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV+RTV)	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121% ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% Cτ ↓ 76% TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. As TRIUMEQ is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered approximately 12 hours after TRIUMEQ. In this case the physician should refer to the individual product information for TIVICAY.

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Dolutegravir or Concomitant Drug**	**Clinical Comment**
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)	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔ Cτ ↓ 6% LPV RTV	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect the pharmacokinetics of lopinavir or ritonavir.
Protease Inhibitor: Darunavir/ritonavir (DRV+RTV)	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% Cτ ↓ 38%	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDF)	Dolutegravir ↔ AUC ↔ C_{max} ↓3% Cτ ↓ 8% Tenofovir ↔ AUC ↑ 12 % C_{max} ↑ 9% Cτ ↑ 19 %	Tenofovir 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.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir or Concomitant Drug**	**Clinical Comment**
		Dofetilide or pilsicainide co-administration with dolutegravir is contraindicated due to potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration.
Fampridine	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; coadministration has not been studied. Fampridine co-administration with TRIUMEQ is contraindicated.
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% $C\tau$ ↓ 73%	Carbamazepine decreased dolutegravir plasma concentration. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. As TRIUMEQ is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered approximately 12 hours after TRIUMEQ. In this case the physician should refer to the individual product information for TIVICAY.
Phenytoin Phenobarbital St. John's wort	Dolutegravir↓	Co-administration with these metabolic inducers has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. The effect of these metabolic inducers on dolutegravir exposure is likely similar to carbamazepine. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. As TRIUMEQ is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered approximately 12 hours after TRIUMEQ. In this case the physician should refer to the individual product information for TIVICAY.
Oxcarbazepine	Dolutegravir ↓	This interaction has not been studied. Although an inducer of CYP3A4, based on data from other inducers, a clinically

Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Dolutegravir or Concomitant Drug**	**Clinical Comment**
		significant decrease in dolutegravir is not expected. No dose adjustment is necessary.
Antacids containing polyvalent cations (e.g. Mg, Al)	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% C24 ↓ 74%	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. Dolutegravir 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% C24 ↓ 39%	TRIUMEQ 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% C24 ↓ 56%	TRIUMEQ is recommended to be administered 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin ↑ When co-administered with dolutegravir 50 mg QD: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50 mg BID: Metformin AUC ↑ 145 % C_{max} ↑ 111%	Co-administration of dolutegravir increased metformin plasma concentration. A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control.
Rifampicin	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% C_{τ} ↓ 72%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin. As TRIUMEQ is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered, approximately 12 hours after TRIUMEQ. In this case the

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir or Concomitant Drug**	**Clinical Comment**
		physician should refer to the individual product information for TIVICAY.
Oral contraceptives (Ethinyl estradiol (EE) and Norgestimate (NGM))	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 norgestimate 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.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.

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

Table 2: Drug Interactions studied with abacavir

Concomitant Drug Class: Drug Name	**Effect on Concentration of abacavir or Concomitant Drug**	**Clinical Comment**
Riociguat	Riociguat	*In vitro*, abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving TRIUMEQ led to an approximately three-fold higher riociguat AUC(0-∞) when compared to historical riociguat AUC(0-∞) reported in healthy subjects. Riociguat dose may need to be

		reduced, consult the riociguat product labelling for dosing recommendations and for interactions observed in patients receiving highly active antiretroviral therapy.
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 3: Drug Interactions studied with lamivudine

Concomitant Drug Class: Drug Name	**Effect on Concentration of lamivudine or Concomitant Drug**	**Clinical Comment**
Trimethoprim/sulfamethoxazole (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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION). 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* pneumonia (often referred to as PCP) and toxoplasmosis has not been studied. TRIUMEQ is not recommended for patients with CrCl of < 30 mL/min.
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 drugs in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.
Other Agents		
Sorbitol solution (3.2 g, 10.2 g, 13.4 g)	Single dose lamivudine oral solution 300 mg Lamivudine: [a]AUC ↓ 14%; 32%; 36% [b]C_{max} ↓ 28%; 52%; 55%	When possible, avoid chronic co-administration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration
[a]AUC (90% CI): 14% (9 - 20%); 32% (28 - 37%); 36% (32 - 41%); [b]C_{max} (90% CI): 28% (20 - 34%); 52% (47 - 57%); 55% (50 - 59%)

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of dolutegravir, abacavir or lamivudine on human male or female fertility. No studies on the effect on fertility in animals have been conducted with the dolutegravir/abacavir/lamivudine combination. Individually, dolutegravir, abacavir and lamivudine did not affect male or female mating or fertility in rats at doses associated with exposure levels approximately 44, 30 or 64 (respectively) higher than the exposures in humans at doses of 50 mg, 600 mg, and 300 mg (respectively).

Use in pregnancy

(Category B3)

There is limited data on the use of TRIUMEQ in pregnancy. TRIUMEQ should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

No studies on the effect on embryofetal development have been conducted with the dolutegravir/abacavir/lamivudine combination.

Summary

Data from two, ongoing birth outcome surveillance studies in Botswana and Eswatini which together include over 14,000 individuals evaluated during pregnancy show similar prevalence of neural tube defects among infants born to individuals taking dolutegravir at the time of conception compared to those born to individuals taking non-dolutegravir-containing regimens at conception or infants born to HIV-negative individuals.

There are insufficient human data on the use of dolutegravir during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. However, available human data from the Antiretroviral Pregnancy Registry (APR) do not indicate an increased risk of birth defects. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

The first interim analysis from an ongoing birth outcome surveillance study in Botswana identified an association between dolutegravir and an increased risk of neural tube defects when dolutegravir was administered at the time of conception and in early pregnancy. A subsequent analysis was conducted based on a larger cohort from the birth outcome surveillance study in Botswana and included over 9,460 individuals exposed to dolutegravir at conception, 23,664 individuals exposed to non-dolutegravir-containing regimens, and 170,723 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.11% (95% CI: 0.05-0.19). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.11%, 95% CI: 0.07-0.16%), or to HIV-negative individuals (0.06%, 95% CI: 0.05-0.08%).

The Eswatini birth outcome surveillance study includes 9,743 individuals exposed to dolutegravir at conception, 1,838 individuals exposed to non-dolutegravir-containing regimens, and 32,259 HIV-negative pregnant individuals. The prevalence of neural tube defects in infants delivered to individuals taking dolutegravir at conception was 0.08% (95% CI: 0.04-0.16%). The observed prevalence rate did not differ significantly from that of infants delivered to individuals taking non-dolutegravir-containing regimens (0.22%, 95% CI: 0.06-0.56%) or to HIV-negative individuals (0.08%, 95% CI: 0.06-0.12%). The observed prevalence of neural tube defects in infants delivered to individuals taking non-dolutegravir-containing regimens had a wide confidence interval due to low sample size.

Limitations of these birth outcome surveillance studies include insufficient data to determine if baseline characteristics were balanced between the study groups or to assess other factors such as the use of folic acid during the preconception or first trimester periods.

Antiretroviral Pregnancy Registry

The APR has received prospective reports of 1,506 exposures to dolutegravir-containing regimens during pregnancy resulting in live births, as of July 2023. These consist of 957 exposures during the first trimester, 549 exposures during the second/third trimester and included 32 and 29 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to dolutegravir-containing regimens in the first trimester was 3.3% (2.3%, 4.7%) and in the second/third trimester, 5.3% (3.6%, 7.5%).

In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%. The background risk for major birth defects for the treatment-indicated population is unknown.

In animal reproductive toxicity studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified.

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (50 times the 50 mg human clinical exposure when dolutegravir is administered in combination with abacavir and lamivudine, based on AUC).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation was associated with marked maternal toxicity but did not elicit developmental toxicity or teratogenicity (0.74 times the 50 mg human clinical exposure when dolutegravir is administered in combination with abacavir and lamivudine, based on AUC).

Dolutegravir readily crosses the placenta in humans. In pregnant women with HIV, the median (range) foetal umbilical cord concentrations of dolutegravir were 1.28 (1.21 to 1.28) fold greater compared with maternal peripheral plasma concentrations.

There is insufficient information on the effects of dolutegravir on neonate.

Data on abacavir and lamivudine

There have been reports of mild, transient 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). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lamivudine and abacavir were associated with findings in animal reproductive toxicity studies.

Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Developmental toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed when rats were treated with abacavir at doses of 648 mg/kg during organogenesis (approximately 31 times the human therapeutic exposure based on AUC, for a 600 mg dose in combination with dolutegravir and lamivudine at the recommended dose). In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 427 mg/kg per day. The offspring of female rats treated with abacavir at 427 mg/kg (beginning at embryo implantation and ending at weaning) showed increased incidence of still birth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations at doses up to 453 mg/kg (7 times the expected human exposure, based on AUC).

Lamivudine was not teratogenic in animal studies, but there were indications of an increase in early embryonic deaths in rabbits at exposure levels (based on C_{max} and AUC) comparable to or below those achieved in man. However, there was no evidence of

embryonic loss in rats at exposure levels of approximately 32 times the clinical exposure (based on C_{max}).

In humans, consistent with passive transmission of lamivudine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

The APR has received prospective reports of over 2,800 exposures to abacavir during pregnancy resulting in live births. These consist of over 1,450 exposures during the first trimester, over 1,350 exposures during the second/third trimester and included 47 and 41 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to abacavir in the first trimester was 3.2% (2.4%, 4.3%) and in the second/third trimester, 3.0% (2.2%, 4.1%).

The APR has received reports of over 13,000 exposures to lamivudine during pregnancy resulting in live births. These consist of over 5,600 exposures during the first trimester, over 7,500 exposures during the second/third trimester and included 173 and 219 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to lamivudine in the first trimester was 3.1% (2.6%, 3.6%) and in the second/third trimester, 2.9% (2.5%, 3.3%).

Mitochondrial dysfunction: nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These reactions are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Use in lactation

Health experts recommend that where possible HIV infected women do not breast-feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breastfeeding during antiretroviral therapy.

Dolutegravir is excreted in human milk in small amounts. In an open-label randomised study in which HIV-infected treatment-naïve pregnant women were administered a dolutegravir based regimen until two weeks post-partum, the median (range) dolutegravir breast milk to maternal plasma ratio was 0.033 (0.021 to 0.050).

In a study following repeat oral dose of either 150 mg lamivudine twice daily (given in combination with 300 mg zidovudine twice daily) or 300 mg lamivudine twice daily, lamivudine was excreted in human breast milk (0.5 to 8.2 microgram/mL) at similar

concentrations to those found in serum. In other studies, following repeat oral dose of 150 mg lamivudine twice daily (given either in combination with 300 mg zidovudine or as COMBIVIR or TRIZIVIR) the breast milk: maternal plasma ratio ranged between 0.6 and 3.3. In a study after repeat oral administration of 300 mg abacavir twice daily (given as TRIZIVIR), the breast milk: maternal plasma ratio was 0.9. No pharmacokinetic studies were conducted with abacavir once daily oral administration. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/mL and were not detectable in one of the studies (assay sensitivity 7 ng/mL). Most infants (8 out of 9) had non-detectable levels of abacavir (assay sensitivity 16 ng/mL). Intracellular carbovir and lamivudine triphosphate (active metabolites of abacavir and lamivudine) levels in breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compounds measured is unknown.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of dolutegravir, abacavir or lamivudine, on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated given the pharmacology of these medicinal products. The clinical status of the patient and the adverse event profile of TRIUMEQ should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

TRIUMEQ contains dolutegravir, abacavir and lamivudine, therefore the adverse events associated with these may be expected. For many of the adverse events listed it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process.

Description of selected adverse effects

Hypersensitivity (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

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

Dolutegravir hypersensitivity

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

Abacavir hypersensitivity

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

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however, reactions have occurred without rash or fever. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin:	**Rash** (usually maculopapular or urticarial)
Gastrointestinal tract:	**Nausea, vomiting, diarrhoea, abdominal pain**, mouth ulceration
Respiratory tract:	**Dyspnoea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous:	**Fever, fatigue, malaise,** oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/psychiatry:	**Headache**, paraesthesia
Haematological:	Lymphopenia
Liver/pancreas:	**Elevated liver function tests**, hepatic failure
Musculoskeletal:	**Myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology:	Elevated creatinine, renal failure

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

For details of clinical management in the event of a suspected abacavir HSR, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Many of the adverse events 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 TRIUMEQ 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 TRIUMEQ therapy in Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adverse drug reactions 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, < 1/1000) and very rare (< 1/10,000), including isolated reports.

Clinical trial data

Clinical safety data with TRIUMEQ are limited. The adverse reactions observed for the combination of DTG + ABC/3TC in analysis of pooled data from Phase IIb to Phase IIIb clinical trials were generally consistent with the adverse reaction profiles for the individual components dolutegravir, abacavir and lamivudine.

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

Treatment naïve patients

The safety assessment of TRIUMEQ is primarily based on the analyses of 48 and 96 week data from a randomised, international, multicentre, double-blind, active-controlled trial, SINGLE (ING114467) and supported by data in treatment-naïve patients from SPRING-2 (ING113086) and FLAMINGO (ING114915).

In SINGLE (ING114467), 833 patients were randomised and received at least 1 dose of either dolutegravir 50 mg with fixed-dose abacavir sulfate and lamivudine once daily (n = 414) or fixed-dose efavirenz-emtricitabine-tenofovir (EFV/TDF/FTC) once daily (n = 419). Through 96 weeks, the rate of adverse events leading to discontinuation was 3% in patients receiving dolutegravir + ABC/3TC and 12% in patients receiving EFV/TDF/FTC once daily.

In SPRING-2 (ING113086), 411 patients received dolutegravir once daily versus 411 who received raltegravir 400 mg twice daily, both in combination with investigator-selected nucleoside reverse transcriptase inhibitor (NRTI) background regimen (either ABC/3TC or TDF/FTC). Of these patients, 169 in the group receiving dolutegravir and 164 in the group receiving raltegravir were receiving KIVEXA [abacavir/lamivudine] as the background regimen. Through 96 weeks, the rate of adverse events leading to discontinuation in these patients was 3% in patients receiving dolutegravir and 2% in patients receiving raltegravir.

In FLAMINGO (ING114915), 243 patients received dolutegravir once daily versus 242 patients who received darunavir 800 mg/ritonavir 100 mg once daily, both in combination with investigator-selected NRTI background regimen (either ABC/3TC or TDF/FTC). There were 484 patients included in the efficacy and safety analyses. Of these patients, 79 in the group receiving dolutegravir and 80 in the group receiving darunavir were receiving ABC/3TC as the background regimen. Through 48 weeks, the rate of adverse events leading to discontinuation in these patients were 4% in patients receiving dolutegravir and 4% in patients receiving darunavir.

Treatment-emergent adverse reactions of moderate to severe intensity observed in ≥ 2% of patients in either treatment arm of SINGLE are provided in Table 4.

Table 4: Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and ≥ 2% Frequency in Treatment Naïve Patients in SINGLE (ING114467)

Body System/ Preferred Term	48-Week		96-Week	
	DTG + ABC/3TC Once Daily (N = 414)	EFV/TDF/FTC Once Daily (N = 419)	DTG + ABC/3TC Once Daily (N = 414)	EFV/TDF/FTC Once Daily (N = 419)
Psychiatric				
Insomnia	3%	2%	3%	2%
Depression	< 1%	1%	1%	2%
Abnormal dreams	< 1%	2%	< 1%	2%
Nervous System				
Dizziness	< 1%	5%	< 1%	5%
Headache	2%	2%	2%	2%
Gastrointestinal				
Nausea	< 1%	3%	< 1%	3%
Diarrhea	< 1%	2%	< 1%	2%
General Disorders				
Fatigue	1%	1%	2%	2%
Skin and Subcutaneous Tissue				
Rash	< 1%	3%	< 1%	3%
Ear and Labyrinth				
Vertigo	0	2%	0	2%

N = Number of patients in each treatment group; EFV/TDF/FTC = efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg

The adverse reactions observed in the subset of patients who received dolutegravir + ABC/3TC in SPRING-2 and FLAMINGO were generally consistent with those seen for the overall patient population participating in these trials.

Treatment experienced patients

In SAILING, 719 patients were randomised and received either dolutegravir once daily (n = 357) or raltegravir 400 mg twice daily (n = 362) with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. There were 715 patients included in the efficacy and safety analyses. At 48 weeks, the rate of adverse events leading to discontinuation was consistent with that seen in the overall treatment naïve patient population.

Less common adverse reactions observed in clinical trials

The following adverse reactions occurred in ≤ 2% of treatment naïve or treatment experienced patients in any one trial. These events have been included because of their seriousness and/or assessment of potential causal relationship.

Gastrointestinal disorders: Abdominal pain, abdominal distention, abdominal discomfort, dyspepsia, flatulence, gastroesophageal reflux disease, upper abdominal pain, vomiting.

General disorders: Fever, lethargy.

Hepatobiliary disorders: Hepatitis.

Immune system disorders: Hypersensitivity, immune reconstitution syndrome.

Metabolism and nutrition disorders: Anorexia, hypertriglyceridemia.

Musculoskeletal disorders: Arthralgia.

Nervous: Somnolence.

Psychiatric: Suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness). Nightmare and sleep disorder.

Skin and subcutaneous tissue disorders: Pruritus.

Laboratory abnormalities: treatment naïve subjects

Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in ≥ 2% of subjects in SINGLE are presented in Table 5. The mean change from baseline observed for selected lipid values is presented in Table 6.

Table 5: Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment Naïve Patients in SINGLE (ING114467)

	48 Week		96 Week	
Laboratory Parameter Preferred Term	**DTG + ABC/3TC Once Daily (N = 414)**	**EFV/TDF/FTC Once Daily (N = 419)**	**DTG + ABC/3TC Once Daily (N = 414)**	**EFV/TDF/FTC Once Daily (N = 419)**
ALT				
Grade 2 (> 2.5-5.0 x ULN)	2%	5%	2%	5%
Grade 3 to 4 (> 5.0 x ULN)	< 1%	< 1%	< 1%	< 1%
AST				
Grade 2 (> 2.5-5.0 x ULN)	2%	3%	3%	3%
Grade 3 to 4 (> 5.0 x ULN)	0	2%	< 1%	3%
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	4%	2%	4%	2%
Grade 3 to 4 (≥ 10.0 x ULN)	3%	5%	5%	7%
Hyperglycemia				
Grade 2 (6.95-13.88 mmol/L)	7%	5%	7%	5%
Grade 3 to 4 (> 13.88 mmol/L)	1%	< 1%	2%	< 1%
Lipase				
Grade 2 (> 1.5-3.0 x ULN)	8%	7%	9%	10%
Grade 3 to 4 (> 3.0 ULN)	3%	2%	4%	3%
Total neutrophils				
Grade 2 (0.75-0.99 x 10^9)	2%	4%	3%	5%
Grade 3 to 4 (< 0.75 x 10^9)	2%	3%	2%	3%

ULN = Upper limit of normal; N = Number of patients in each treatment group; EFV/TDF/FTC = efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg

Table 6: Mean Change From Baseline in Fasted Lipid Values in Treatment Naïve Subjects in SINGLE (ING114467)

Laboratory Parameter Preferred Term	48 Week		96 Week	
	DTG + ABC/3TC Once Daily (N = 414)	EFV/TDF/FTC Once Daily (N = 419)	DTG + ABC/3TC Once Daily (N = 414)	EFV/TDF/FTC Once Daily (N = 419)
Cholesterol (mmol/L)	0.441	0.622	0.615	0.724
HDL cholesterol (mmol/L)	0.135	0.206	0.138	0.194
LDL cholesterol (mmol/L)	0.219	0.339	0.384	0.465
Triglycerides (mmol/L)	0.200	0.210	0.200	0.195

N = Number of patients in each treatment group; EFV/TDF/FTC = efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg

The rates of laboratory abnormalities and mean change in fasted lipid values remained generally similar between the 48- and 96-week data evaluation in SINGLE.

Laboratory abnormalities observed in the subset of subjects who received dolutegravir + ABC/3TC in SPRING-2 and FLAMINGO were generally consistent with observations in SINGLE.

Laboratory abnormalities: Treatment experienced patients:

Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 96 weeks. In SINGLE, a mean change from baseline of 12.6 µmol/L was observed after 96 weeks of treatment. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Effects on renal function).

Small increases in total bilirubin were observed on dolutegravir and raltegravir (but not efavirenz) arms in the clinical trials. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see Section 5.2 PHARMACOKINETIC PROPERTIES - Metabolism).

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

Paediatric population

There are no clinical study data on the effects of TRIUMEQ in the paediatric population. Individual components have been investigated in adolescents aged 12 to 18.

Based on limited available data with the dolutegravir single entity used in combination with other antiretroviral agents to treat adolescents (12 to less than 18 years of age), there were no additional types of adverse reactions beyond those observed in the adult population.

The individual preparations of ABC and 3TC have been investigated separately, and as a dual nucleoside backbone, in combination antiretroviral therapy to treat ART-naïve and ART-

experienced HIV-infected paediatric patients (data available on the use of ABC and 3TC in children less than three months are limited). No additional types of undesirable effects have been observed beyond those characterised for the adult population.

Abacavir sulfate and lamivudine

Laboratory abnormalities observed in clinical trials of abacavir (in combination with other antiretroviral treatment) were anaemia, neutropenia, thrombocytopenia, low white blood cell count, elevated liver chemistries (AST, ALT, alkaline phosphatase, bilirubin), and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical trials of 3TC (in combination with other antiretroviral treatment) were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

Post-marketing data

In addition to the adverse reactions included from clinical trial data, the adverse reactions listed in Table 7 have been identified during post-approval use of dolutegravir, abacavir and lamivudine or dolutegravir/abacavir/lamivudine fixed dose combination. These events have been chosen for inclusion due to a potential causal connection to dolutegravir, abacavir and/or lamivudine.

Table 7: Adverse reactions based on post-marketing experience

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

System organ class	Dolutegravir	Abacavir	Lamivudine
Post marketing events observed with dolutegravir/abacavir/lamivudine fixed dose combination			
Hepatobiliary disorders	Rare: acute hepatic failure		

[1]Lactic acidosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms and signs

There is currently limited experience with overdosage in dolutegravir.

Limited experience of single higher doses (up to 250 mg in healthy patients) revealed no specific symptoms or signs, apart from those listed as adverse reactions.

No specific symptoms or signs have been identified following acute overdose with abacavir or lamivudine, apart from those listed as adverse reactions.

Treatment

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

If overdose occurs, the patient should be treated 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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC50 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 (t½ 71 hours).

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs), and are potent, selective inhibitors of HIV-1 and HIV-2 replication. 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 PHARMACOKINETIC PROPERTIES - Excretion). 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.

Pharmacodynamic effects

In a randomised, dose-ranging trial, HIV-1 infected patients treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean declines from baseline to day 11 in HIV-1 RNA of 1.5, 2.0, and 2.5 log10 for dolutegravir 2 mg, 10 mg, and 50 mg once daily, respectively. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Antiviral activity of dolutegravir in cell culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild type HIV-1 in peripheral blood mononuclear cells (PBMC) and MT4 cells with mean IC50s of 0.5 nM to 2.1 nM.

In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse clade B isolates, dolutegravir demonstrated antiviral potency similar to laboratory strains, with a mean IC50 of 0.52 nM.

When tested in PBMC assays against a panel consisting of 24 HIV-1 clinical isolates [group M (clade A, B, C, D, E, F and G) and group O] and 3 HIV-2 clinical isolates, the geometric mean IC50 was 0.20 nM and IC50 values ranged from 0.02 to 2.14 nM for HIV-1, while the geometric mean IC50 was 0.18 nM and IC50 values ranged from 0.09 to 0.61 nM for HIV-2 isolates.

Antiviral activity in combination with other antiviral agents

The antiviral activity of dolutegravir in vitro was not antagonistic with abacavir. No antagonistic effects in vitro were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine).

In vitro data with dolutegravir combined with lamivudine are not available.

The antiviral activity of dolutegravir in vitro was not antagonistic with the integrase inhibitor (INI) raltegravir; the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitor (NRTI) abacavir, the protease inhibitors (PIs) amprenavir or lopinavir; the CCR5 co-receptor antagonist maraviroc, or the fusion inhibitor enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor adefovir, or inhibited by the antiviral ribavirin.

Effect of human serum and serum proteins

The protein adjusted IC90 (PA-IC90) in PBMCs for dolutegravir was estimated to be 64 ng/mL. Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve subjects was 1.20 microgram/mL, 19 times higher than the estimated PA-IC90.

Plasma protein binding studies in vitro indicate that abacavir binds only low to moderately (~49%) to human plasma proteins at therapeutic concentrations.

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

Resistance in vitro (dolutegravir)

Dolutegravir-resistant viruses were selected in studies of potential resistance using different wild type strains and clades of HIV-1. Amino acid substitutions that emerged during passaging included E92Q, G193E, G118R, S153F or Y, and R263K, and were associated with decreased susceptibility to dolutegravir of up to 11-fold.

In resistance development studies starting with the single raltegravir resistance mutants Q148H, Q148K or Q148R, additional mutations detected during passage with dolutegravir included E138K/Q148K, E138K/Q148R, Q140S/Q148R and G140S/Q148R, which all exhibited greater than ten-fold reductions in sensitivity to dolutegravir.

Resistance in vivo (dolutegravir): integrase inhibitor naïve patients

No INI-resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment-naïve studies [SPRING-1 (ING112276), SPRING-2 (ING113086), SINGLE (ING114467), FLAMINGO (ING114915) and ARIA (ING117172) studies]. In the SAILING study for treatment experienced (and integrase naïve) patients (n = 354 in the dolutegravir arm), treatment emergent integrase substitutions were observed at Week 48 in 4 of 17 patients with virologic failure in the dolutegravir arm. Of these four, 2 patients had a unique R263K integrase substitution, with a maximum FC of 1.93, 1 patient had a polymorphic V151V/I integrase substitution, with maximum FC of 0.92, and 1 patient had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Resistance in vitro and in vivo (abacavir and lamivudine)

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral RT. This variant arises both in vitro and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity in vitro. Studies in vitro indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Genetic analysis of isolates from patients failing an abacavir-containing regimen demonstrated that reverse transcriptase amino acid residue 184 was consistently the most frequent position for NRTI resistance-associated mutations (M184V or M184I). The second

most frequent mutation was L74V. Mutations Y115F and K65R were uncommon. Viral resistance to abacavir develops relatively slowly in vitro and in vivo, requiring multiple mutations to reach an eight-fold increase in IC50 over wild-type virus, which may be a clinically relevant level.

Cross-resistance

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors. Viruses containing abacavir and lamivudine resistance-associated mutations, namely, M184V, L74V, Y115F and K65R, exhibit cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in vitro and in patients. The M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine and the K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the L74V plus the M184V/I mutation, viruses with K65R with or without the M184V/I mutation, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

Effects on electrocardiogram

In a randomised, placebo-controlled, cross-over trial, 42 healthy patients received single dose oral administrations of placebo, dolutegravir 250 mg suspension (exposures approximately 3-fold of the 50 mg once-daily dose at steady state), and moxifloxacin (400 mg, active control) in random sequence. Dolutegravir did not prolong the QTc interval for 24 hours post dose. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) was 1.99 msec (1-sided 95% upper CI: 4.53 msec).

Similar studies were not conducted with either abacavir or lamivudine.

Effects on renal function

The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated in an open-label, randomized, 3 arm, parallel, placebo-controlled study in 37 healthy patients, who were administered dolutegravir 50 mg once daily (n = 12), 50 mg twice daily (n = 13) or placebo once daily (n = 12) for 14 days. A modest decrease in CrCl was observed with dolutegravir within the first week of treatment, consistent with that seen in clinical studies. Dolutegravir at both doses had no significant effect on GFR or ERPF. These data support in vitro studies which suggest that the small increases in 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.

Clinical trials

TRIUMEQ is a film-coated tablet containing an integrase inhibitor (dolutegravir) and two NRTIs (abacavir and lamivudine).

Antiretroviral naïve patients

The efficacy of TRIUMEQ is supported by data from two randomized, controlled trials in antiretroviral treatment-naïve patients, SINGLE (ING114467) and ARIA (ING117172) and other trials in treatment-naïve patients (refer to the TIVICAY [dolutegravir] PI).

In SINGLE (ING114467), 833 patients were randomised and received at least one dose of either dolutegravir 50 mg once daily with fixed-dose abacavir sulphate and lamivudine or fixed dose efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC). At baseline, median patient age was 35 years, 16% were female, 32% non-white, 7% had hepatitis C co-infection and 4% were CDC Class C, these characteristics were similar between treatment groups.

Virologic outcomes (including outcomes by key baseline covariates) are described below.

Table 8: Virologic Outcomes of Randomised Treatment of SINGLE (ING114467) at 48 Weeks (Snapshot algorithm – missing or discontinuation = failure)

	48 Weeks	
	DTG + ABC/3TC Once Daily N=414	**EFV/TDF/FTC Once Daily N=419**
Virologic Success HIV-1 RNA < 50 copies/mL	88%	81%
Treatment Difference*	7.4% (95% CI: 2.5%, 12.3%)	
Virologic non response†	5%	6%
No virologic data at Weeks 48 window	7%	13%
Reasons		
Discontinued study/study drug due to adverse event or death‡	2%	10%
Discontinued study/study drug for other reasons§	5%	3%
Missing data during window but on study	0	<1%
HIV-1 RNA< 50 copies/mL by baseline covariates		
Baseline Plasma Viral Load (copies/mL)	n / N (%)	n / N (%)
≤ 100,000	253 / 280 (90%)	238 / 288 (83%)
> 100,000	111 / 134 (83%)	100 / 131 (76%)
Baseline CD4+ (cells/ mm^3)		
< 200	45 / 57 (79%)	48 / 62 (77%)
200 to < 350	143 / 163 (88%)	126 / 159 (79%)
≥ 350	176 / 194 (91%)	164 / 198 (83%)
Gender		
Male	307 / 347 (88%)	291 / 356 (82%)
Female	57 / 67 (85%)	47 / 63 (75%)
Race		
White	255 / 284 (90%)	238 / 285 (84%)
African-American/African Heritage/Other	109 / 130 (84%)	99 / 133 (74%)
Age (years)		
< 50	319 / 361 (88%)	302 / 375 (81%)
≥ 50	45 / 53 (85%)	36 / 44 (82%)

* Adjusted for baseline stratification factors.
† Includes patients who discontinued prior to Week 48 for lack or loss of efficacy and patients who are ≥50 copies in the 48 week window.
‡ Includes patients who discontinued due to an adverse event or death at any time point from Day 1 through the Week 48 analysis window if this resulted in no virologic data on treatment during the analysis window.
§ Includes reasons such as withdrew consent, loss to follow-up, moved, protocol deviation.
Notes: ABC/3TC = abacavir 600 mg, lamivudine 300 mg
EFV/TDF/FTC = efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg
N = Number of patients in each treatment group

In the primary 48 weeks analysis in the SINGLE study, the proportion of patients with virologic suppression (HIV-1 RNA < 50 copies/mL using a missing or discontinuation = failure analysis) in the dolutegravir + ABC/3TC arm (88%), was superior to the EFV/TDF/FTC arm (81%), p = 0.003. Similar treatment difference was observed in patients defined by baseline HIV-RNA level (< or > 100,000 copies/mL). The median time to viral suppression was 28 days in the group receiving dolutegravir + ABC/3TC and 84 days in the EFV/TDF/FTC arm (p < 0.0001). The adjusted mean change in CD4+ T cell count from baseline were 267 cells/mm3 in the group receiving dolutegravir + ABC/3TC and 208 cells/mm3 for the EFV/TDF/FTC arm in SINGLE at 48 week [adjusted difference between

arm (with 95% CI), 58.9 cells (33.4 cells to 84.4 cells), p < 0.001]. Both the time to viral suppression and change from baseline analyses were pre-specified and adjusted for multiplicity.

At 96 weeks, 80% of study participants on the dolutegravir + ABC/3TC regimen were virologically suppressed (< 50 copies/mL using a missing or discontinuation = failure analysis) vs. 72% of participants on EFV/TDF/FTC [difference and 95% CI; 8.0% (+2.3% to +13.8%)]. The higher responses on dolutegravir + ABC/3TC were driven by withdrawals due to AEs and missing data. At 144 weeks in the open-label phase, virologic suppression was maintained, the dolutegravir + ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3 (2.0, 14.6).

Antiretroviral naïve female patients

In ARIA (ING117172), a randomised, open-label, active-controlled, multicentre, parallel group, non-inferiority study; 499 HIV-1 infected ART naïve adult women were randomised 1:1 to receive either; dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg FDC (DTG/ABC/3TC); or atazanavir 300 mg plus ritonair 100 mg plus tenofovir disproxil fumarate/ emtricitabine 300 mg/200 mg (ATV+RTV+TDF/FTC FDC), all administered once daily. Demographic characteristics were similar across treatment groups; at baseline the median patient age was 37 years, 45% of patients were white and 42% of African American/African Heritage, 93% tested negative for hepatitis C (HCV) infection and 84% were in CDC Class A.

At 48 weeks, overall virologic suppression (HIV-1 RNA <50 copies/mL) in the DTG/ABC/3TC FDC group (82%) was shown to be statistically superior to the ATC+RTV+TDF/FTC FDC group (71%). The adjusted difference in proportion was 10.5, 95% CI (3.1% to 17.8%) [p=0.005].

Antiretroviral experienced patients

The efficacy of TRIUMEQ in antiretroviral treatment experienced patients is supported by data from STRIIVING (201147). In addition, the efficacy of dolutegravir, in combination with at least two active background regimens in treatment-experienced, INI-naïve subjects is supported by data from SAILING (ING111762) (refer to the TIVICAY [dolutegravir] PI).

In STRIIVING (201147) a 48-week, randomised, open-label, active controlled, multicentre, non-inferiority study; 555 HIV-1 infected, virologically suppressed (HIV-1 RNA <50 c/mL) subjects were randomly assigned (1:1) to continue their current ART regimen (2 NRTIs plus either a PI, NNRTI, or INI), or switch to DTG/ABC/3TC FDC once daily (Early Switch).

The majority of patients in the intent-to-treat exposed (ITT-E) population were white (65%) and male (86%); the median age was 45 (range 22-80) years. At baseline, 31% of patients had CD4+ counts of <500 cell/mm3. Overall, most patients had negative test results at screening for HBV and HCV infection (93%), were in CDC Class A (73%), and identified homosexual activity as an HIV risk factor (72%).

Virologic suppression (HIV-1 RNA <50 copies/mL) in the DTG/ABC/3TC FDC group (85%) was statistically non-inferior to the current ART groups (88%) at 24 weeks. The adjusted difference in proportion [DTG/ABC/3TC vs current ART] was 3.4%; 95% CI: [-9.1, 2.4]. After

24 weeks all remaining patients switched to DTG/ABC/3TC FDC (Late Switch). Similar levels of virologic suppression were maintained in both the Early and Late Switch groups at 48 weeks.

Children

In a Phase I/II 48 week multicentre, open-label study (P1093/ING112578), the pharmacokinetic parameters, safety, tolerability and efficacy of dolutegravir was evaluated in combination regimens in HIV-1 infected infants, children and adolescents.

At 24 weeks, 16 of 23 (69%) adolescents (12 to less than 18 years of age) treated with dolutegravir once daily (35 mg n = 4, 50 mg n = 19) plus optimised background regimen achieved viral load less than 50 copies/mL.

5.2 PHARMACOKINETIC PROPERTIES

TRIUMEQ has been shown to be bioequivalent to dolutegravir single entity tablet with abacavir/lamivudine fixed dose combination tablet administered separately. This was demonstrated in a single dose, 2-way crossover bioequivalence study of TRIUMEQ (fasted) versus 1 x 50 mg dolutegravir tablet, plus 1 x 600 mg abacavir/300 mg lamivudine tablet (fasted) in healthy patients (n = 62). In a separate cohort there was no clinically significant effect of a high fat meal on the exposure of dolutegravir, lamivudine or abacavir. These results indicate that TRIUMEQ can be taken with or without food.

The pharmacokinetic properties of dolutegravir, lamivudine and abacavir are described below.

Absorption

Dolutegravir is rapidly absorbed following oral administration [see TIVICAY [dolutegravir] PI, Section 5.2 PHARMACOKINETIC PROPERTIES - Absorption]. The absolute bioavailability of dolutegravir has not been established [see TIVICAY [dolutegravir] PI, Section 5.2 PHARMACOKINETIC PROPERTIES - Absorption]. The mean time to maximal serum concentrations (tmax) is about 2 to 3 hours (post dose for tablet formulation) for dolutegravir [see TIVICAY [dolutegravir] PI, Section 5.2 PHARMACOKINETIC PROPERTIES - Absorption]. Following multiple oral doses of dolutegravir 50 mg once daily, the geometric mean steady state pharmacokinetic parameter estimates are 53.6 microgram.h/mL for AUC24, 3.67 microgram/mL for Cmax, and 1.11 microgram/mL for C24 based on population pharmacokinetic analysis in treatment-naïve subjects.

Abacavir is rapidly absorbed following oral administration. The absolute bioavailability of oral abacavir is 83%. Following a single oral dose of 600 mg of abacavir, the mean Cmax is 4.26 microgram/mL and the mean AUC∞ is 11.95 microgram.h/mL.

Lamivudine is rapidly absorbed following oral administration. The absolute bioavailability of oral lamivudine in adults is 80 to 85% respectively. Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days the mean steady-state Cmax is 2.04 microgram/mL and the mean AUC24 is 8.87 microgram.h/mL.

Distribution

The apparent volume of distribution of dolutegravir (following oral administration of suspension formulation, Vd/F) is estimated at 12.5 L. 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 drug-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 patients, approximately 0.4 to 0.5% in patients with moderate hepatic impairment, and 0.8 to 1.0% in patients with severe renal impairment and 0.5% in HIV-1 infected patients.

Intravenous studies with abacavir showed that the mean apparent volume of distribution is 0.8. Plasma protein binding studies in vitro indicate that abacavir binds only low to moderately (approximately 49%) to human plasma proteins at therapeutic concentrations.

Intravenous studies with lamivudine showed that the mean apparent volume of distribution is 1.3 L/kg. 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). In 12 treatment-naïve patients receiving a regimen of dolutegravir plus abacavir/lamivudine for 16 weeks, dolutegravir concentration in CSF averaged 16.2 ng/mL at Week 2 and 12.6 ng/mL at Week 16, ranging from 3.7 to 23.2 ng/mL (comparable to unbound plasma concentration; 16.8 ng/mL at week 2 and 23 ng/mL at week 16, ranging from 3.81 to 32.1 ng/mL).

CSF:plasma concentration ratio of dolutegravir ranged from 0.11 to 2.04%. Dolutegravir concentrations in CSF exceeded the IC50 (0.52 nM = 0.2 ng/mL), supporting the median reduction from baseline in CSF HIV-1 RNA of 2.2 log after 2 weeks and 3.4 log after 16 weeks of therapy.

Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44%. The observed values of the peak concentrations are 9 fold greater than the IC50 of abacavir of 0.08 microgram/mL or 0.26 micromolar when abacavir is given at 600 mg twice daily.

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

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue, and vaginal tissue were 6 to 10% of that in corresponding plasma at steady-state. AUC was 7% in semen and 17% in rectal tissue, of those in corresponding plasma at steady-state.

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 drug 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 drug 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%).

Excretion

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 from 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

In a paediatric study including 23 antiretroviral treatment-experienced HIV-1 infected adolescents aged 12 to 18 years of age, the pharmacokinetics of dolutegravir was evaluated in 10 adolescents and showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure in paediatric patients comparable to that observed in adults who received dolutegravir 50 mg once daily (see Table 9).

Table 9: Paediatric 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 patient 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

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

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

Hepatically impaired

Pharmacokinetic data has been obtained for dolutegravir, abacavir and lamivudine alone. Based on data obtained for abacavir, TRIUMEQ 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. TRIUMEQ 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 patients 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.

Renally impaired

Pharmacokinetic data have been obtained for dolutegravir, abacavir and lamivudine alone.

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr <3 0 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.

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.

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

Based on the lamivudine data, TRIUMEQ is not recommended for patients with creatinine clearance of < 30 mL/min.

Polymorphisms in drug metabolising enzymes

There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy patients, patients with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with patients with genotypes associated with normal metabolism via UGT1A1 (n = 41). Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics of dolutegravir.

Gender

The dolutegravir exposure in healthy patients appear to be slightly higher (~ 20%) in women than men based on data obtained in a healthy patient study (males n = 17, females n = 24). Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of gender on the exposure of dolutegravir.

There is no evidence that a dose adjustment of dolutegravir, abacavir or lamivudine would be required based on the effects of gender on PK parameters.

Race

Population PK analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials revealed no clinically relevant effect of race on the exposure of dolutegravir. The pharmacokinetics of dolutegravir following single dose oral administration to Japanese patients appear similar to observed parameters in Western (US) patients.

There is no evidence that a dose adjustment of dolutegravir, abacavir or lamivudine would be required based on the effects of race on PK parameters.

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 patients with hepatitis B co-infection (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with the combination of dolutegravir, abacavir and lamivudine.

Dolutegravir was not mutagenic or clastogenic using in vitro tests in bacteria and cultured mammalian cells, and an in vivo rodent micronucleus assay.

Neither abacavir nor lamivudine were mutagenic in bacterial tests, but both induced mutations in a mouse lymphoma assay and were clastogenic in human peripheral lymphocytes in vitro. In rats, lamivudine did not cause chromosomal damage in bone marrow cells in vivo or cause DNA damage in primary hepatocytes. Abacavir was clastogenic in an in vivo micronucleus assay in mice, but not in rats when tested in combination with lamivudine at systemic exposures corresponding to 86 and 31 times the clinical exposure level for ABC and 3TC, respectively.

Carcinogenicity

No carcinogenicity studies have been conducted with the combination of dolutegravir, abacavir and lamivudine.

Dolutegravir was not carcinogenic in long term studies in the mouse and rat (respectively, 27 and 23 times the 50 mg human clinical exposure when dolutegravir is administered in combination with abacavir and lamivudine, based on AUC).

Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver, urinary bladder, lymph nodes and the subcutis of female rats. Nonmalignant tumours occurred in the liver of mice and rats, Harderian gland of female mice, and thyroid gland of rats. In rats, there were also increased incidences of urothelial hyperplasia and urinary bladder tumours, associated with increased urinary calculi.

The majority of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. These dose levels were equivalent to 21 to 30 times the expected systemic exposure in humans when abacavir is administered in combination with dolutegravir and lamivudine. The exception was preputial gland tumours in mice which occurred at a dose of 110 mg/kg. Exposure at this dose is approximately 5 times the expected human systemic exposure. The carcinogenic potential in humans is unknown.

When lamivudine was administered orally to separate groups of rodents at doses up to 2000 times (mice and male rats) and 3000 (female rats) mg/kg/day, there was no evidence of a carcinogenic effect due to lamivudine in the mouse study. In the rat study there was an increased incidence of endometrial tumours at the highest dose (approximately 70 times the estimated human exposure at the recommended therapeutic dose of one tablet twice daily, based on AUC). However, the relationship of this increase to treatment is uncertain.

Animal toxicology

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 38 and 1.5 times the 50 mg human clinical exposure when dolutegravir is administered in combination with abacavir and lamivudine, based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local drug administration, mg/kg or mg/m2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 30 times the human mg/kg equivalent dose (based on 50 kg human), and 11 times the human mg/m2 equivalent dose for a total daily clinical dose of 50 mg.

Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for two years. The systemic exposures were equivalent to 7 to 19 times human exposure at 600 mg when abacavir is administered in combination with dolutegravir and lamivudine. The clinical relevance of this finding has not been determined.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TRIUMEQ tablets also contain: mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, iron oxide black, and iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Do not remove the desiccant.

6.5 NATURE AND CONTENTS OF CONTAINER

TRIUMEQ tablets are supplied in white high density polyethylene (HDPE) bottles with child resistant closure packs containing 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

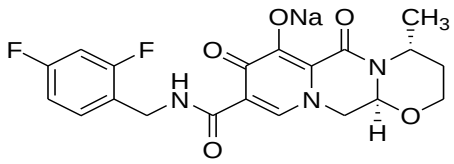
The chemical (IUPAC) name for dolutegravir sodium is Sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino [2,1-b][1,3]oxazin-7-olate. It has a molecular formula of C20H18F2N3NaO5 and a molecular weight of 441.36 g/mol. The partition coefficient (log P) for dolutegravir sodium is 2.2 and the pKa is 8.2.

The chemical name of abacavir sulfate is (1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with 1S, 4R absolute configuration on the cyclopentene ring. It has a molecular formula of (C14H18N6O)2.H2SO4 and a molecular weight of 670.76 g/mol.

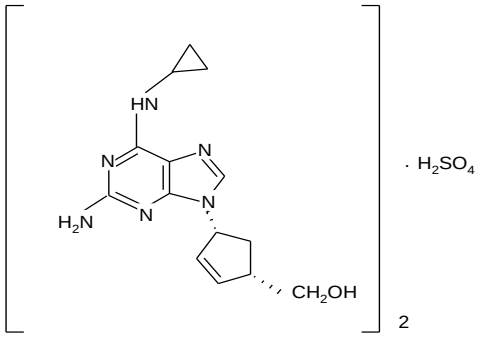
The chemical name of lamivudine is (2R,cis)-4-amino-1-[2- (hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of C8H11N3O3S and a molecular weight of 229.3 g/mol.

Chemical structure

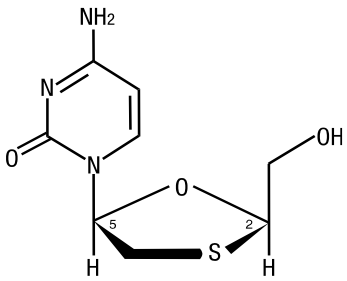
Dolutegravir sodium



Abacavir sulfate



Lamivudine



CAS number

1051375-19-9 (dolutegravir sodium)

188062-50-2 (abacavir sulfate)

134678-17-4 (lamivudine)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

14 January 2015

10 DATE OF REVISION

7 January 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Update to section Women of childbearing potential and pregnancy
4.6	Updated information from Botswana (Tsepamo) and Eswatini studies on neural tube defect and antiretroviral pregnancy register data
5.1	Updated data on the Antiretroviral Pregnancy Registry

Version 16