TRIUMEQ

Dolutegravir-abacavir-lamivudine

QUALITATIVE AND QUANTITATIVE COMPOSITION

Purple, biconvex, oval, 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 sulfate and 300 mg of lamivudine.

CLINICAL INFORMATION

Indications

TRIUMEQ is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents from 12 years of age and weighing at least 40 kg, who are antiretroviral treatment-naïve or are infected with HIV without documented or clinically suspected resistance to any of the three antiretroviral agents in *TRIUMEQ*.

Dosage and Administration

Pharmaceutical form: Film-coated tablets

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

TRIUMEQ should not be administered to adults or adolescents who weigh less than 40 kg.

TRIUMEQ can be taken with or without food.

TRIUMEQ is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments, such as those with creatinine clearance less than 30 mL/min or with mild hepatic impairment. Separate preparations of *TIVICAY*, *ZIAGEN* or *EPIVIR* 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 *TIVICAY* is available where a dose adjustment is required due to drug-drug interactions (see *Interactions*).

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

Populations

- **Adults and adolescents**

The recommended dose of *TRIUMEQ* in adults and adolescents weighing at least 40 kg is one tablet once daily.

- **Children**

TRIUMEQ is not currently recommended for treatment of children less than 12 years of age or weighing less than 40 kg.

- **Elderly**

There are limited data available on the use of *TIVICAY, ZIAGEN* and *EPIVIR* in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (*see Pharmacokinetics – Special Patient Populations*). When treating elderly patients, consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, concomitant medicinal products or disease.

- **Renal impairment**

Whilst no dosage adjustment of dolutegravir or abacavir is necessary in patients with renal impairment, a dose reduction of *EPIVIR* is required due to decreased clearance. Therefore, *TRIUMEQ* is not recommended for use in patients with a creatinine clearance less than 30 mL/min (*see Pharmacokinetics – Special Patient Populations*).

- **Hepatic impairment**

A dose reduction of *ZIAGEN* 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 *TIVICAY, ZIAGEN* and *EPIVIR* should be used when this is judged necessary. Abacavir is contraindicated in patients with moderate and severe hepatic impairment. *TRIUMEQ* is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (*see Pharmacokinetics – Special Patient Populations*).

Contraindications

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

TRIUMEQ must not be administered concurrently with medicinal products with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to dofetilide, pilsicainide or fampridine (also known as dalfampridine; see Interactions).

TRIUMEQ is contraindicated in patients with moderate and severe hepatic impairment.

Warnings and Precautions

The special warnings and precautions relevant to *TIVICAY, ZIAGEN* and *EPIVIR* are included in this section. There are no additional precautions and warnings relevant to *TRIUMEQ*.

Hypersensitivity reactions (*see also Adverse Reactions*):

Both abacavir and dolutegravir are associated with a risk for hypersensitivity reactions (HSR) (*see Clinical Description of HSR below, and Adverse Reactions*), and share some common features such as fever and/or rash with other symptoms indicating multi-organ involvement. Clinically, it is not possible to determine whether a HSR with *TRIUMEQ* is caused by abacavir or dolutegravir. Hypersensitivity reactions have been observed more commonly with abacavir, some of which have been life-threatening, and in rare cases fatal. The risk for abacavir HSR to occur is significantly increased for patients who test positive for the *HLA-B*5701* allele. However, abacavir HSRs have been reported in patients who do not carry this allele.

The following should be adhered to:

- Testing for *HLA-B*5701* status should be considered before initiating abacavir treatment and also before re-starting abacavir treatment in patients of unknown *HLA-B*5701* status who have previously tolerated abacavir.

- *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 other medicinal product containing abacavir (e.g. *ZIAGEN*, *KIVEXA*, *TRIZIVIR*) regardless of *HLA-B*5701* status.

- Each patient should be reminded to read the Patient Alert Card included in the *TRIUMEQ* pack. They should be reminded of the importance of removing the Alert Card, included in the pack, and keeping it with them at all times.

- In any patient treated with *TRIUMEQ*, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision making.

- ***TRIUMEQ* must be stopped without delay, even in the absence of the *HLA-B*5701* allele, if a HSR is suspected. Delay in stopping treatment with *TRIUMEQ* after the onset of hypersensitivity may result in a life-threatening reaction**. Clinical status including liver aminotransferases and bilirubin should be monitored.

- Patients who have experienced a hypersensitivity reaction should be instructed to dispose of their remaining *TRIUMEQ* tablets, in order to avoid restarting abacavir.

- **After stopping treatment with *TRIUMEQ* for reasons of a suspected**

HSR, *TRIUMEQ* or any other medicinal product containing abacavir or dolutegravir must never be re-initiated.

- **Restarting abacavir-containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours and may include life-threatening hypotension and death.**

- If a hypersensitivity reaction is ruled out, patients may restart *TRIUMEQ*. Rarely, patients who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re-initiating abacavir therapy (*see Adverse Reactions, Description of selected adverse reactions*). Patients must be made aware that HSR can occur with reintroduction of *TRIUMEQ* or any other medicinal product containing abacavir (e.g. *ZIAGEN*, *KIVEXA*, *TRIZIVIR*) and that reintroduction of *TRIUMEQ* or any other medicinal product containing abacavir (e.g. *ZIAGEN*, *KIVEXA*, *TRIZIVIR*) should be undertaken only if medical care can be readily accessed.

• *Clinical Description of HSR with dolutegravir:*

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterized 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 raised liver enzymes, 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.

• *Clinical Description of HSR with abacavir:*

Abacavir HSR has been well characterised through clinical studies and during post marketing follow-up. Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, **although these reactions may occur at any time during therapy.**

Almost all HSR to abacavir include fever and/or rash as part of the syndrome.

Other signs and symptoms that have been observed as part of abacavir HSR include respiratory and gastrointestinal symptoms, **which may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis** (*see Adverse Reactions, Description of Selected Adverse Reactions*). The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Lactic acidosis/severe hepatomegaly with steatosis:

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure. Lactic acidosis generally occurred after a few or several months of treatment. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

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 in obese women, or in patients with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin constitute a risk. 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).

Weight and metabolic parameters:

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is in some cases, evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose, reference is made to established HIV treatment guidelines. 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 jirovecii* 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*).

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.

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 minimize all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Drug 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* (*see Contraindications and Interactions*).

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 *TIVICAY* 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 (*see Interactions*).

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 (*see Interactions*).

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

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycaemic control (*see Interactions*).

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, biphosphonates, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported in patients with advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Interactions

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 *KIVEXA* alone.

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

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50>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. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe, however a weak inhibition can presently not be excluded. 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, rilpivirine, boceprevir, telaprevir, daclatasvir and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) (IC50 = 1.93 μM), multidrug and toxin extrusion transporter (MATE) 1 (IC50 = 6.34 μM) and MATE2-K (IC50 = 24.8 μM). Based on the *in vitro* data, dolutegravir has a low potential to affect the transport of MATE2-K substrates *in vivo*. *In vivo*, a 10-14% increase of mean serum creatinine (secretory fraction is dependent on OCT2 and MATE-1 transport) was observed in patients but did not progress over time and is not associated with a change in renal glomerular filtration rate. *In vivo*, dolutegravir may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 or MATE-1 (for example dofetilide, pilsicainide, fampridine [also known as dalfampridine] or metformin).

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC50 = 2.12 μM) and OAT3 (IC50 = 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 studies have shown that abacavir has potential to inhibit CYP1A1 and limited potential to inhibit metabolism mediated by CYP3A4. Lamivudine does not inhibit or induce CYP3A4. Abacavir and lamivudine do not inhibit or induce other CYP enzymes (such as CYP2C9 or CYP2D6) and 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 MATE1or 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 Dolutegravir, Abacavir and Lamivudine

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore, drugs that induce these enzymes or transporters may theoretically decrease dolutegravir plasma concentration and reduce the therapeutic effect of *TRIUMEQ*. 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, darunavir/ritonavir, rilpivirine, boceprevir, telaprevir, prednisone, rifabutin, daclatasvir and omeprazole 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 human are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. These metabolites are excreted in the urine. The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. *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*.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
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:	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39%	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-

Efavirenz (EFV)	Cτ ↓ 75% EFV ↔	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 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%	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with

	TPV ↔ RTV ↔	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.*
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.
Protease Inhibitor: Darunavir/ritonavir (DRV+RTV)	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% Cτ ↓ 38% DRV ↔ RTV ↔	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%	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

	Cτ ↑ 19%	
Other Antiviral Agents		
Protease Inhibitor: Telaprevir	Dolutegravir ↑ AUC ↑ 25% C_{max} ↑ 19% Cτ ↑ 37% Telaprevir ↔ (historical controls) (inhibition of CYP3A enzyme)	No dose adjustment is necessary.
Protease Inhibitor: Boceprevir	Dolutegravir ↔ AUC ↑ 7% C_{max} ↑ 5% Cτ ↑ 8% Boceprevir ↔ (historical controls)	No dose adjustment is necessary.
Other Agents		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with dolutegravir is contraindicated due to potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration.
Fampridine (also known as dalfampridine)	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co-administration with dolutegravir is contraindicated.
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% Cτ ↓ 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.*
Oxcarbazepine 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.*
Antacids containing polyvalent cations (e.g., Mg, Al)	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% C_{24} ↓ 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% C_{24} ↓ 39%	*TRIUMEQ* is recommended to be administered 2 hours before or 6 hours after taking products containing calcium.
Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56%	*TRIUMEQ* is recommended to be administered 2 hours before or 6 hours after taking products containing iron.

Multivitamin	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32%	*TRIUMEQ* is recommended to be administered 2 hours before or 6 hours after taking products containing multivitamins.
Metformin	Metformin ↑ When co-administered with dolutegravir 50mg QD: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50mg 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% Cτ ↓ 72%	Rifampicin decreased dolutegravir plasma concentration. The 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 physician should refer to the individual product information for *TIVICAY*.
Oral contraceptives (Ethinyl estradiol (EE) and Norelgestromin (NGMN))	Effect of dolutegravir: EE ↔ AUC ↑ 3% C_{max} ↓ 1% Cτ ↑ 2% Effect of dolutegravir: NGMN ↔ AUC ↓ 2% C_{max} ↓ 11%	Dolutegravir did not change ethinyl estradiol and norelgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with dolutegravir.

	Cτ ↓ 7%	
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 $AUC_{(0-\infty)}$ when compared to historical riociguat $AUC_{(0-\infty)}$ reported in healthy subjects. Riociguat dose may need to be reduced, consult the riociguat product labeling for dosing recommendations.
Methadone (40 to 90mg once daily for 14 days/600mg single dose, then 600mg 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%	Given the safety profile of abacavir, these findings are not considered

	Ethanol AUC ↔	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) (160mg/800mg once daily for 5 days/300mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (*see Dosage and 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 jirovecii* pneumonia and toxoplasmosis has not been studied. *TRIUMEQ* is not recommended for subjects 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,	Single dose lamivudine oral solution 300 mg	When possible, avoid chronic co-administration of sorbitol-containing medicines with lamivudine. Consider

13.4 g)	Lamivudine: AUC ↓ 14%; 32%; 36% Cmax ↓ 28%; 52%, 55%.	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

Pregnancy and Lactation

Pregnancy

TRIUMEQ should be used during pregnancy only if the benefit to the mother outweighs the possible risk to the foetus. Women of childbearing potential (WOCBP) should be informed about the potential risk of neural tube defects with dolutegravir and counselled about the use of effective contraception. It is recommended that pregnancy testing is conducted prior to initiation of *TRIUMEQ*. If there are plans to become pregnant, or if pregnancy is confirmed within the first trimester while on *TRIUMEQ*, the risks and benefits of continuing *TRIUMEQ* versus switching to another antiretroviral regimen should be discussed with patient. Factors to consider should include feasibility of switching, tolerability, ability to maintain viral suppression, actual gestational age, risk of transmission to the infant and the available data around the potential risk of neural tube defects and other pregnancy outcomes for dolutegravir and alternative antiretroviral drugs.

In a birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was identified with exposure to dolutegravir compared to non-dolutegravir-containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking dolutegravir-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-dolutegravir-containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI -0.03, 0.30).

In the same study, an increased risk of neural tube defects was not identified in women who started dolutegravir during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with five out of 6,748 deliveries (0.07%) to mothers who started non-dolutegravir-containing regimens during pregnancy.

A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As most neural tube defects occur within the first 4 weeks of foetal development (approximately 6 weeks after the last menstrual period), this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

Data analysed to date from other sources including the Antiretroviral Pregnancy Registry, clinical trials, and post-marketing data are insufficient to address the risk of neural tube defects with dolutegravir.

More than 1,000 outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

In animal reproductive toxicity studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified (*see Non-Clinical Information*).

Dolutegravir, abacavir and lamivudine use during pregnancy have been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 600, 2,500 and 12,500 women, respectively (as of July 2019). Available human data from the APR do not show an increased risk of major birth defects for dolutegravir, abacavir or lamivudine compared to the background rate.

Dolutegravir readily crosses the placenta in humans. In HIV-infected pregnant women, 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 neonates.

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 (*see Non-Clinical Information*).

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 breast-feeding 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).

Lamivudine is excreted in human milk at similar concentrations to those found in serum. Abacavir is excreted in human milk at similar concentrations to those found in serum.

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. However, patients should be informed that dizziness has been reported during treatment with dolutegravir. 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

Adverse Reactions

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.

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 Warnings and Precautions*).

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 dolutegravir plus abacavir/lamivudine 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. However, the following common treatment-emergent adverse reactions were observed with the combination but were not listed in the prescriber information for any of the individual components:

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

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

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

Table 4 Adverse reactions associated with the individual components of *TRIUMEQ* based on clinical study experience.

System organ class	**Dolutegravir**	**Abacavir**	**Lamivudine**
Blood and lymphatic systems disorders			Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia *Very rare:* Pure red cell aplasia
Immune system disorders	Uncommon: hypersensitivity (*see Warnings and Precautions*), Immune Reconstitution Syndrome (*see Warnings and Precautions*)	Common: hypersensitivity (*see Warnings and Precautions*)	
Metabolism and nutrition disorders		Common: anorexia	
Psychiatric disorders	Common: Insomnia, abnormal dreams, depression, anxiety Uncommon: Suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)		

System organ class	Dolutegravir	Abacavir	Lamivudine
Nervous system disorders	Very common: headache Common: dizziness	Common: headache	Common: headache, insomnia Very rare: Cases of peripheral neuropathy (or paraesthesia) have been reported
Respiratory, thoracic and mediastinal disorders			Common: Cough, nasal symptoms
Gastrointestinal disorders	Very common: nausea, diarrhoea Common: vomiting, flatulence, abdominal pain, upper abdominal pain, abdominal discomfort	Common: nausea, vomiting, diarrhoea Rare: pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain	Common: nausea, vomiting, abdominal pain or cramps, diarrhoea Rare: Rises in serum amylase. Cases of pancreatitis have been reported
Hepatobiliary disorders	Uncommon: hepatitis		Uncommon: transient rises in liver enzymes (AST, ALT) Rare: Hepatitis
Skin and subcutaneous tissue disorders	Common: rash, pruritus	Common: rash (without systemic symptoms) Very rare*:* erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	Common: rash, alopecia
General disorders and administration site conditions	Common: fatigue	Common: fever, lethargy, fatigue	Common: fatigue, malaise, fever

System organ class	Dolutegravir	Abacavir	Lamivudine
Musculoskeletal and connective tissue disorders			Common: Arthralgia, muscle disorders Rare: Rhabdomyolysis

Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 96 weeks. In ING114467, 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 Pharmacodynamics – Effects on Renal Function*).

Small increases in total bilirubin (without clinical jaundice) were observed on dolutegravir and raltegravir (but not efavirenz) arms in the programme. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) (*see Pharmacokinetics – Metabolism*).

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

Co-infection with Hepatitis B or C

In dolutegravir Phase III studies, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (*see Warnings and Precautions*).

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.

Post-marketing data

In addition to the adverse reactions included from clinical trial data, the adverse reactions listed in Table 5 below have been identified during post-approval use of dolutegravir, abacavir, lamivudine or DTG/ABC/3TC FDC. These events have been chosen for inclusion due to a potential causal connection to dolutegravir, abacavir and/or lamivudine.

Table 5 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: [1]lactic acidosis	Common: hyperlactataemia Rare: [1]lactic acidosis
Nervous system disorders			Very rare: paraesthesia, 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

System organ class	Dolutegravir	Abacavir	Lamivudine
Skin and subcutaneous tissue disorders		Common: rash (without systemic symptoms) Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	Common: Rash, alopecia
Musculoskeletal and connective tissue disorders	Uncommon: arthralgia Uncommon: myalgia		Common: arthralgia, muscle disorders Rare: rhabdomyolysis
Investigations	Common: weight increased		
Post marketing events observed with DTG/ABC/3TC FDC			
Hepatobiliary disorders	Rare: acute hepatic failure		

[1]Lactic acidosis (*see Warnings and Precautions*)

Description of Selected Adverse Reactions

Hypersensitivity (see also Warnings and Precautions):

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. Treatment with *TRIUMEQ* must be stopped without delay if HSR cannot be ruled out on clinical grounds, and therapy with *TRIUMEQ* or other abacavir or dolutegravir containing products must never be re-initiated *(see Warnings and Precautions)*.

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**, hepatitis, 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 Warnings and Precautions.*

Symptoms related to this HSR worsen with continued therapy and can be life-threatening and in rare instance, have been fatal.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy *(see Warnings and Precautions)*.

Osteonecrosis

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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment *(see Warnings and Precautions)*.

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 subjects) 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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

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.

Abacavir and lamivudine are potent, selective inhibitors of HIV-1 and HIV-2. Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective 5'-triphosphate (TP) which are the active moieties with extended intracellular half-lives supporting once daily dosing (*see Pharmacokinetics, Elimination*). Lamivudine-TP (an analogue for cytidine) and carbovir-TP (the active triphosphate form of abacavir, an analogue for guanosine) 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

Antiviral activity in vitro

Dolutegravir, abacavir and lamivudine have been shown to inhibit replication of lab-strains and clinical isolates of HIV in a number of cell types, including transformed T cell lines, monocyte/macrophage derived lines and primary cultures of activated peripheral blood mononuclear cells (PBMCs) and monocyte/macrophages. The concentration of drug necessary to affect viral replication by 50% (IC50 - half maximal inhibitory concentration) varied according to virus and host cell type.

The IC50 for dolutegravir in various lab-strains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC50s were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC50 value was 0.2 nM (range 0.02-2.14). The mean IC50 for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).

The mean IC50 for abacavir against lab-strains of HIV-1IIIB and HIV-1HXB2 ranged from 1.4 to 5.8 μM. The median or mean IC50 values for lamivudine against lab-strains of HIV-1 ranged from 0.007 to 2.3 μM. The mean IC50 against lab-strains of HIV-2 (LAV2 and EHO) ranged from 1.57 to 7.5 μM for abacavir and from 0.16 to 0.51 μM for lamivudine.

The IC50 values of abacavir against HIV-1 Group M subtypes (A-G) ranged from 0.002 to 1.179 μM, against Group O from 0.022 to 1.21 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. For lamivudine, the IC50 values against HIV-1 subtypes (A-G) ranged from 0.001 to 0.170 μM, against Group O from 0.030 to 0.160 μM and against HIV-2 isolates from 0.002 to 0.120 μM in peripheral blood mononuclear cells.

HIV-1 isolates (CRF01_AE, n=12; CRF02_AG, n=12; and Subtype C or CRF_AC, n=13) from 37 untreated patients in Africa and Asia were susceptible to abacavir (IC50 fold changes < 2.5), and lamivudine (IC50 fold changes < 3.0), except for two CRF02_AG isolates with fold changes of 2.9 and 3.4 for abacavir. Group O isolates from antiviral naïve patients tested for lamivudine activity were highly sensitive.

The combination of abacavir and lamivudine has demonstrated antiviral activity in cell culture against non-subtype B isolates and HIV-2 isolates with equivalent antiviral activity as for subtype B isolates.

Antiviral activity in combination with other antiviral agents

No antagonistic effects *in vitro* were seen with dolutegravir and other antiretrovirals (tested agents: stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc, adefovir and raltegravir). In addition, ribavirin had no apparent effect on dolutegravir activity.

The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine).

Effect of human serum

In 100% human serum, the mean fold shift for dolutegravir activity was 75-fold, resulting in protein adjusted IC90 of 0.064 ug/mL. 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

Resistance in vitro*: *(dolutegravir)

Serial passage is used to study resistance evolution *in vitro*. When using the lab-strain HIVIII during passage over 112 days, mutations selected appeared slowly, with substitutions at positions S153Y and S153F. These mutations were not selected in patients treated with dolutegravir in the clinical studies. Using strain NL432 mutations E92Q (fold change 3) and G193E (fold change 3) were selected. These mutations have been selected in patients with pre-existing raltegravir resistance and who were then

treated with dolutegravir (listed as secondary mutations for dolutegravir).

In further selection experiments using clinical isolates of subtype B, mutation R263K was seen in all five isolates (after 20 weeks and onwards). In subtype C (n=2) and A/G (n=2) isolates, the integrase substitution R263K was selected in one isolate, and G118R in two isolates. R263K was reported from two individual patients with subtype B and subtype C in the clinical program for ART experienced, INI naïve subjects, but without effects on dolutegravir susceptibility *in vitro*. G118R lowers the susceptibility to dolutegravir in site directed mutants (fold change 10), but was not detected in patients receiving dolutegravir in the Phase III program.

Primary mutations for raltegravir/elvitegravir (Q148H/R/K, N155H, Y143R/H/C, E92Q, T66I) do not affect the *in vitro* susceptibility of dolutegravir as single mutations. When mutations listed as secondary integrase inhibitor associated mutations (for raltegravir/elvitegravir) are added to primary mutations (excluding at Q148) in experiments with site directed mutants, dolutegravir susceptibility remains at or near wildtype level. In the case of the Q148-mutation viruses, increasing dolutegravir fold change is seen as the number of secondary mutations increase. The effect of the Q148-based mutations (H/R/K) was also consistent with *in vitro* passage experiments with site directed mutants. In serial passage with strain NL432-based site directed mutants at N155H or E92Q, no further selection of resistance was seen (fold change unchanged around 1). In contrast, starting passage with mutants with mutation Q148H (fold change 1), a variety of raltegravir associated secondary mutations accumulated with a consequent increase of fold change to values >10.

A clinically relevant phenotypic cut-off value (fold change vs wild type virus) has not been determined; genotypic resistance was a better predictor for outcome.

Seven hundred and five raltegravir resistant isolates from raltegravir experienced patients were analyzed for susceptibility to dolutegravir. Dolutegravir has a <10-fold change against 94% of the 705 clinical isolates.

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, SPRING-2, SINGLE**,** FLAMINGO and ARIA studies).

In patients with prior failed therapies, but naïve to the integrase class (SAILING study), integrase inhibitor substitutions were observed in 4/354 patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen (BR). Of these four, two subjects had a unique R263K integrase substitution, with a maximum fold change of 1.93, one subject had a polymorphic V151V/I integrase substitution, with maximum fold change of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. The R263K mutation was also selected *in vitro* (see above).

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

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and *in vivo* and are associated with specific genotypic changes in the RT codon region (codons M184V, K65R, L74V and Y115F). During *in vitro* abacavir selection, the M184V mutation occurred first and resulted in about a 2-fold increase in IC50, below the abacavir clinical cut-off of 4.5-fold change. Continued passage in increasing concentrations of drug resulted in selection for double RT mutants 65R/184V and 74V/184V or triple RT mutant 74V/115Y/184V. Two mutations conferred a 7 to 8-fold change in abacavir susceptibility and combinations of three mutations were required to confer more than an 8-fold change in susceptibility.

HIV-1 resistance to lamivudine involves the development of a M184I or M184V amino acid change close to the active site of the viral RT. This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. M184V is associated with about a 2-fold increase in abacavir resistance but does not confer clinical resistance for abacavir.

Isolates resistant to abacavir may also show reduced sensitivity to lamivudine. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, and to viruses with L74V plus the M184V/I substitution.

Cross-resistance between dolutegravir or abacavir or lamivudine and antiretrovirals from other classes e.g. PIs or NNRTIs is unlikely.

Effects on Electrocardiogram

No relevant effects were seen on the QTc interval, with doses of dolutegravir exceeding the clinical dose by approximately 3-fold. Similar studies were not conducted with either abacavir or lamivudine.

Clinical efficacy and safety

The efficacy of *TRIUMEQ* in HIV-infected, therapy naïve subjects is based on the analyses of data from two randomized, international, double-blind, active-controlled trials, SINGLE (ING114467) and SPRING-2 (ING113086) and the international, open-label, active-controlled trial FLAMINGO (ING114915).

In SINGLE, 833 patients were treated with dolutegravir 50 mg once daily plus fixed-dose abacavir-lamivudine (DTG + ABC/3TC) 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. Week 48 outcomes (including outcomes by key baseline covariates) are shown in Table 6.

Table 6: Virologic Outcomes of Randomized Treatment of SINGLE at 48 Weeks (Snapshot algorithm)

	48 weeks	
	DTG 50 mg + ABC/3TC once daily N=414	**EFV/TDF/FTC once daily N=419**
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 subjects who discontinued prior to Week 48 for lack or loss of efficacy and subjects who are ≥50 copies in the 48 week window.
‡ Includes subjects 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 in the form of Kivexa/Epzicom fixed dose combination (FDC)
EFV/TDF/FTC = efavirenz 600 mg, tenofovir 300 mg, emtricitabine 200 mg in the form of Atripla FDC.

In the primary 48 weeks analysis, the proportion of patients with virologic suppression in the dolutegravir (DTG) + ABC/3TC arm was superior to the EFV/TDF/FTC arm, p=0.003, the same treatment difference was observed in subjects defined by baseline HIV RNA level (< or > 100,000 copies/mL). The median time to viral suppression was shorter with ABC/3TC + DTG (28 vs 84 days, p<0.0001). The adjusted mean change in CD4+ T cell count from baseline were 267 cells/mm^3 versus 208 cells/mm^3, respectively (p<0.001). Both the time to viral suppression and change from baseline analyses were pre-specified and adjusted for multiplicity. At 96 weeks, the response was 80% vs 72%, respectively. The difference in the endpoint remained statistically significant (p=0.006). The statistically higher responses on DTG+ABC/3TC were driven by a higher rate of withdrawals due to AEs in the EFV/TDF/FTC arm, irrespective of viral load strata. Overall treatment differences at Week 96 are applicable to patients with high and low baseline viral loads. At 144 weeks in the open-label phase of SINGLE, virologic suppression was maintained, the DTG +ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3% (2.0, 14.6).

In SPRING-2, 822 patients were treated with either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily (blinded), both with fixed-dose ABC/3TC (around 40%) or TDF/FTC (around 60%), given open label. Baseline demographics and outcomes are summarised in Table 7. Dolutegravir was non-inferior to raltegravir, including within the subset of patients with the abacavir/lamivudine background regimen.

Table 7: Demographics and virologic outcomes of randomized treatment of SPRING-2 (snapshot algorithm)

	DTG 50 mg once daily + 2 NRTI N=411	RAL 400mg twice daily + 2 NRTI N=411
Demographics		
Median Age (years)	37	35
Female	15%	14%
Non-white	16%	14%
Hepatitis B and/or C	13%	11%
CDC class C	2%	2%
ABC/3TC backbone	41%	40%
Week 48 efficacy results		
HIV-1 RNA <50 copies/mL	88%	85%
Treatment difference*	2.5% (95% CI: -2.2%, 7.1%)	
Virologic non response†	5%	8%
No virologic data at Weeks 48 window	7%	7%
Reasons		
Discontinued study/study drug due to adverse event or death‡	2%	1%
Discontinued study/study drug for other reasons§	5%	6%
HIV-1 RNA <50 copies/mL for those on ABC/3TC	86%	87%
Week 96 efficacy results		
HIV-1 RNA <50 copies/mL	81%	76%
Treatment difference*	4.5% (95% CI: -1.1%, 10.0%)	
HIV-1 RNA <50 copies/mL for those on ABC/3TC	74%	76%

* Adjusted for baseline stratification factors.
† Includes subjects who discontinued prior to Week 48 for lack or loss of efficacy and subjects who are ≥50 copies in the 48 week window.
‡ Includes subjects 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 protocol deviation, lost to follow up, and withdrew consent.
Notes: DTG = dolutegravir, RAL = raltegravir.

In FLAMINGO, 485 patients were treated with dolutegravir 50 mg once daily or darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily, both with ABC/3TC (around 33%) or TDF/FTC (around 67%). All treatments were given open-label. Main demographics and outcomes are summarised in Table 8.

Table 8: Demographics and Week 48 virologic outcomes of randomized treatment of FLAMINGO (snapshot algorithm)

	DTG 50 mg once daily + 2 NRTI N=242	DRV+RTV 800mg + 100mg once daily +2 NRTI N=242
Demographics		
Median Age (years)	34	34
Female	13%	17%
Non-white	28%	27%
Hepatitis B and/or C	11%	8%
CDC class C	4%	2%
ABC/3TC backbone	33%	33%
Week 48 Efficacy Results		
HIV-1 RNA <50 copies/mL	90%	83%
Treatment Difference*	7.1% (95% CI: 0.9%, 13.2%)	
Virologic non response†	6%	7%
No virologic data at Weeks 48 window	4%	10%
Reasons		
Discontinued study/study drug due to adverse event or death‡	1%	4%
Discontinued study/study drug for other reasons§	2%	5%
Missing data during window but on study	<1%	2%
HIV-1 RNA <50 copies/mL for those on ABC/3TC	90%	85%
Median time to viral suppression**	28 days	85 days

* Adjusted for baseline stratification factors, p=0.025.
† Includes subjects who discontinued prior to Week 48 for lack or loss of efficacy and subjects who are ≥50 copies in the 48 week window.
‡ Includes subjects 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, protocol deviation.
** p<0.001.
Notes: DRV+RTV = darunavir + ritonavir, DTG = dolutegravir.

At 96 weeks, virologic suppression in the dolutegravir group (80%) was superior to the DRV/r group (68%), (adjusted treatment difference [DTG-(DRV+RTV)]: 12.4%; 95% CI: [4.7, 20.2]). Response rates at 96 weeks were 82% for DTG+ABC/3TC and 75% for DRV/r+ABC/3TC.

Antiretroviral naïve female subjects

In Aria (ING117172), a randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study; 499 HIV-1 infected ART naïve adult women were randomized 1:1 to receive either; DTG/ABC/3TC FDC 50 mg/600 mg/300 mg; or atazanavir 300 mg plus ritonavir 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% white and 42% African American/African Heritage, 93% tested negative for hepatitis C (HCV) infection and 84% of subjects 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 ATV+RTV+TDF/FTC FDC group (71%). The adjusted difference in proportion and 95% CI were between 10.5 (3.1% to 17.8%) [p=0.005].

Antiretroviral experienced subjects

The efficacy of the *TRIUMEQ* is also supported by data from a randomized, international, double-blind, active-controlled trial, SAILING (ING111762).

In the SAILING study, 719 HIV-1 infected, ART-experienced, integrase inhibitor naïve adults were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator selected background regimen (BR) consisting of 2 agents (including at least one fully active agent). At baseline, median patient age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C co-infection, and 46% were CDC Class C. All subjects had at least two class ART resistance, and 49% of subjects had at least 3-class ART resistance at baseline. Virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir arm (71%) was statistically superior to the raltegravir arm (64%), at Week 48 (p=0.030). Virologic suppression (HIV-1 RNA <50 copies/mL) treatment differences were comparable across the baseline characteristics of gender, race, and HIV subtype.

In STRIIVING (201147) a 48-week, randomized, open-label, active controlled, multicenter, 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 ABC/DTG/3TC FDC once daily (Early Switch).

The majority of subjects 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 subjects had CD4+ counts of <500 cell/mm^3. Overall, most subjects 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 ABC/DTG/3TC FDC group (85%) was statistically non-inferior to the current ART groups (88%) at 24 weeks. The adjusted difference in proportion and 95% CI [ABC/DTG/3TC vs current ART] were 3.4%; 95% CI: [-9.1, 2.4]. After 24 weeks, all remaining subjects switched to ABC/DTG/3TC FDC (Late Switch). Similar levels of virologic suppression were maintained in both the Early and Late Switch groups at 48 weeks.

In CAL30001 and ESS30008 ABC/3TC and ABC + 3TC were effectively used in combination therapy to maintain viral suppression in treatment experienced subjects with low rates of treatment emergent viral resistance mutations.

Antiretroviral Pregnancy Registry

The APR has received reports of over 600 exposures to dolutegravir during pregnancy resulting in live births, as of July 2019. These consist of over 370 exposures during the first trimester, over 230 exposures during the second/third trimester and included 12 and 9 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to dolutegravir in the first trimester was 3.2% (1.7%, 5.5%) and in the second/third trimester, 3.8% (1.7%, 7.0%).

The APR has received prospective reports of over 2,500 exposures to abacavir during pregnancy resulting in live births, as of July 2019. These consist of over 1,200 exposures during the first trimester, over 1,300 exposures during the second/third trimester and included 39 and 39 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to abacavir in the first trimester was 3.1% (2.2%, 4.2%) and in the second/third trimester, 3.0% (2.1%, 4.0%).

The APR has received reports of over 12,500 exposures to lamivudine during pregnancy resulting in live births, as of July 2019. These consist of over 5,200 exposures during the first trimester, over 7,400 exposures during the second/third trimester and included 161 and 216 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%).

The available data from the APR shows no significant increase in risk of major birth defects for dolutegravir, abacavir or lamivudine compared to the background rates in the two population based surveillance systems (Metropolitan Atlanta Congenital Defects Program with defects of 2.72 per 100 live births and the Texas Birth Defects Registry with 4.17 per 100 live births).

De novo resistance in patients failing therapy in SINGLE, SPRING-2 and FLAMINGO

De novo resistance was not detected to the integrase class or the NRTI class in any patients who were treated with dolutegravir + abacavir/lamivudine in the three studies mentioned.

For the comparators, typical resistance was detected with TDF/FTC/EFV (SINGLE; six with NNRTI associated resistance and one with major NRTI resistance) and with 2 NRTIs + raltegravir (SPRING-2; four with major NRTI resistance and one with raltegravir resistance), while no *de novo* resistance was detected in patients treated with 2 NRTIs + DRV/RTV (FLAMINGO).

Paediatric population

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 17 years of age) treated with dolutegravir once daily (35 mg n=4; 50 mg n=19) plus OBR achieved viral load less than 50 copies/mL.

Twenty out of 23 children and adolescents (87%) had >1 $\log_{10}$ c/mL decrease from baseline in HIV-1 RNA or HIV-1 RNA <400 c/mL at Week 24. Four subjects had virologic failure, none of which had INI resistance at the time of virologic failure.

Pharmacokinetics

The *TRIUMEQ* tablet has been shown to be bioequivalent to dolutegravir single entity tablet and abacavir/lamivudine fixed-dose combination tablet (ABC/3TC FDC) 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 600mg abacavir/300 mg lamivudine tablet (fasted) in healthy subjects (n=66).

The effect of a high fat meal on the *TRIUMEQ* tablet was evaluated in a subgroup of subjects in this study (n=12). Plasma C_{max} and AUC of dolutegravir following administration of *TRIUMEQ* with a high fat meal were 37% and 48% higher, respectively, than those following administration of *TRIUMEQ* in the fasted state. This is not considered clinically significant (*see Absorption*). The effect of food on plasma exposures of abacavir and lamivudine following administration of *TRIUMEQ* with a high fat meal were very similar to prior food effects observed with ABC/3TC FDC. 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, abacavir and lamivudine are rapidly absorbed following oral administration. The absolute bioavailability of dolutegravir has not been established. The absolute bioavailability of oral abacavir and lamivudine in adults is about 83% and 80 to 85% respectively. The mean time to maximal serum concentrations (t_{max}) is about 2 to 3 hours (post dose for tablet formulation), 1.5 hours and 1.0 hour for dolutegravir, abacavir and lamivudine, respectively.

Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects. In HIV-1–infected adult subjects following dolutegravir 50 mg once daily, the steady-state pharmacokinetic parameters (geometric mean [%CV]) based on population pharmacokinetic analyses were $AUC_{(0-24)}$ = 53.6 (27) µg.h/mL, C_{max} = 3.67 (20) µg/mL, and C_{min} = 1.11 (46) µg/mL. Following a single dose of 600 mg of abacavir, the mean (CV) C_{max} is 4.26 µg/mL (28%) and the mean (CV) AUC_{∞} is 11.95 µg.h/mL (21%). Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days, the mean (CV) steady-state C_{max} is 2.04 µg/mL (26%) and the mean (CV) AUC_{24} is 8.87 µg.h/mL (21%).

Plasma C_{max} and AUC of dolutegravir following administration of *TRIUMEQ* with a high fat meal were 37% and 48% higher, respectively, than those following administration of *TRIUMEQ* in the fasted state. For abacavir there was a decrease in C_{max} with 23% and AUC was unchanged. The exposure of lamivudine was similar with and without food. These results indicate that *TRIUMEQ* can be taken with or without food.

Distribution

The apparent volume of distribution of dolutegravir (following oral administration of suspension formulation, Vd/F) is estimated at 12.5 L. Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0.8 and 1.3 l/kg respectively.

Dolutegravir is highly bound (>99%) 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. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment. 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 *in vitro* (<36%).

Dolutegravir, abacavir and lamivudine are present in cerebrospinal fluid (CSF).

In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC50). 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 µg/mL or 0.26 µM when abacavir is given at 600 mg twice daily. The mean ratio of CSF/serum lamivudine concentrations 2-4 hours after oral administration was approximately 12%. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

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.

Biotransformation

Dolutegravir is primarily metabolized 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 active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two 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 (5-10%).

Drug interactions

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC50>50 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MATE2-K, MRP2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters *(see section Interactions).*

In vitro, dolutegravir was not a substrate of human OATP1B1, OATP1B3 or OCT1.

Elimination

Dolutegravir has a terminal half-life of ~14 hours. The apparent oral clearance (CL/F) is approximately 1 L/hr in HIV-infected patients based on a population pharmacokinetic analysis.

The mean half-life of abacavir is about 1.5 hours. The geometric mean terminal half-life of intracellular active moiety carbovir triphosphate (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 18 to 19 hours. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was prolonged to 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, predominantly by renal clearance (greater than 70%) via the organic cationic transport system. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance < 50 ml/min *(see Dosage and Administration section).*

Pharmacokinetic/pharmacodynamic relationship(s)

In a randomized, dose-ranging trial, HIV-1–infected subjects treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity with mean decline in HIV-1 RNA of 2.5 $\log_{10}$ at day 11 for 50 mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Intracellular pharmacokinetics

The geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6 hours, compared to the geometric mean abacavir plasma half-life of 2.6 hours. The terminal intracellular half-life of lamivudine-TP was prolonged to 16-19 hours, compared to the plasma lamivudine half-life of 5-7 hours, supporting once daily dosing of ABC and 3TC.

Special Patient Populations

Children

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents 12 to < 18 years of age showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure in paediatric subjects comparable to that observed in adults who received dolutegravir 50 mg once daily (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 subject weighing 37 kg received 35 mg once daily.

Limited data are available in adolescents receiving a daily dose of 600 mg of abacavir and 300 mg of lamivudine.

Pharmacokinetic parameters are comparable to those reported in adults.

Elderly

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 subjects 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 is likely to be required in patients with mild hepatic impairment. The separate preparation of *ZIAGEN* 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 contraindicated 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 metabolized and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Renally impaired

Pharmacokinetic data have been obtained for dolutegravir, abacavir and lamivudine alone. *TRIUMEQ* should not be used in patients with creatinine clearance of less than 30 mL/min because, whilst no dosage adjustment of dolutegravir or abacavir is necessary in patients with renal impairment, dose reduction is required for the lamivudine component. Therefore, the separate preparation of *EPIVIR* should be used to treat these patients (*see Dosage and Administration)*.

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

Abacavir is primarily metabolised by the liver, with approximately 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function.

Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr <30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr <30 mL/min) and matching healthy subjects were observed. There is limited information on dolutegravir in patients on dialysis, though differences in exposure are not expected.

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 subjects, subjects with

UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).

Gender

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 subjects appear similar to observed parameters in Western (US) subjects.

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 subjects with hepatitis B co-infection *(see Warnings and Precautions* for the use of *TRIUMEQ* in patients co-infected with hepatitis B*)*.

Non-Clinical Information

With the exception of a negative *in vivo* rat micronucleus test for the combination of abacavir and lamivudine, there are no data available on the effects of the combination of dolutegravir, abacavir and lamivudine in animals.

Carcinogenesis/mutagenesis

Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Dolutegravir was not carcinogenic in long term studies in the mouse and rat.

Neither abacavir nor lamivudine were mutagenic in bacterial tests, but like many nucleoside analogues they show activity in the *in vitro* mammalian tests such as the mouse lymphoma assay. This is consistent with the known activity of other nucleoside analogues. The results of an *in vivo* rat micronucleus test with abacavir and lamivudine in combination were negative.

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.

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 28 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. There is no structural counterpart for this gland in humans. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

Lamivudine has not shown any genotoxic activity in the *in vivo* studies at doses that gave plasma concentrations up to 30 to 40 times higher than clinical plasma levels. The results of long-term carcinogenicity studies in mice and rats did not show any carcinogenic potential at exposures approximately 12 to 72 times higher than clinical plasma levels.

Reproductive Toxicology

Pregnancy

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

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 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). In rabbits, maternal toxicity (decreased food consumption, scant/no faeces/urine, suppressed body weight gain) was observed at 1000 mg/kg (0.74 times the 50 mg human clinical exposure when dolutegravir is administered in combination with abacavir and lamivudine, based on AUC).

Abacavir demonstrated toxicity to the developing embryo and foetus only in rats at maternally toxic doses of 500 mg/kg/day and above. This dose is approximately 28 times human therapeutic exposure based on AUC, for a 600 mg dose in combination with dolutegravir and lamivudine. The findings included foetal oedema, variations and malformations, resorptions, decreased foetal body weight and an increase in still births. The dose at which there were no effects on pre or post-natal development was 160 mg/kg/day. This dose is equivalent to an exposure of about 9 times that in humans. Similar findings were not observed in rabbits.

Lamivudine was not teratogenic in animal studies, but there were indications of an increase in early embryonic deaths in rabbits at exposure levels comparable to 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}).

Animal toxicology and/or pharmacology

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/m^2 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/m^2 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 21 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.

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet core:

Mannitol
Microcrystalline cellulose
Povidone K29/32
Sodium starch glycolate
Magnesium stearate

Tablet coating:

Opadry II Purple 85F90057 containing:
Polyvinyl alcohol – partially hydrolyzed
Titanium dioxide
Macrogol/PEG
Talc
Iron Oxide Black
Iron Oxide Red

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

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

Nature and Contents of Container

TRIUMEQ film-coated tablets are available in white high density polyethylene (HDPE) bottles containing a desiccant.

Pack size: 30 tablets per bottle

Incompatibilities

No incompatibilities have been identified.

Use and Handling

There are no special requirements for use or handling of this product.

Not all presentations are available in every country.

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[ViiV Healthcare logo]

Product Registrant:

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