TRIUMEQ

Dolutegravir-abacavir-lamivudine

QUALITATIVE AND QUANTITATIVE COMPOSITION

Purple, biconvex, oval, tablets, debossed with "572 fix" 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.

PHARMACEUTICAL FORM

Film-coated tablets.

CLINICAL PARTICULARS

Indications

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

Dosage and Administration

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 because it is a fixed-dose tablet that cannot be dose reduced. *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 50 ml/min. 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.

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 children less than 12 years of age as the necessary dose adjustment cannot be made. Clinical data is currently not available for this combination. Physicians should refer to the individual product information for *TIVICAY*, *ZIAGEN* and *EPIVIR*.

- **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 haematologic 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* not recommended for use in patients with a creatinine clearance less than 50 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). No dose reduction is not possible with *TRIUMEQ*, the separate preparations of *TIVICAY*, *ZIAGEN* and *EPIVIR* should be used when this is judged necessary. *TRIUMEQ* is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (*see 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 is contraindicated in combination with dofetilide or pilsicainide.

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 *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 Leaflet 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 retarting 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 reinitiation of *TRIUMEQ* or any other medicinal product containing abacavir (e.g. *ZIAGEN*, *KIVEXA*, *TRIZIVIR*) and that reinitiation 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 abacavir:*

Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury.

- *Clinical Description of HSR with abacavir:*

Abacavir HSR has been well characterized 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 and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including abacavir and lamivudine. A majority of these cases have been in women.

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

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

Serum lipids and blood glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurements of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reconstitution Syndrome:

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by Pneumocystis jirovecii (formerly known 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 Co-infection (*see Patients co-infected with hepatitis B virus (HBV) later in this section and Adverse Reactions*).

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

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

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

Opportunistic infections:

Patients receiving *TRIUMEQ* or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission of infection:

Patients should be advised that current antiretroviral therapy, including *TRIUMEQ* has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Mycoplasal Infections:

Several observational, epidemiological studies have reported an association with abacavir use and risk of mycoplasal infection. Meta-analyses of randomised controlled trials have observed no excess risk of mycoplasal infection 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 mycoplasal infection is inconclusive. As a precaution the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimise all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Drug Interactions:

Caution should be given to co-administering medications (prescription and non-prescription) that may change the exposure of dolutegravir, abacavir, lamivudine or medicines 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).

Since the recommended dose of *TIVICAY* is 50 mg twice daily for patients treatment (without boosted protease inhibitors), efavirenz, nevirapine, rifampicin, tipranavir/ritonavir, carbamazepine, phenytoin, phenobarbital and St. John's wort, the use of *TRIUMEQ* is not recommended for patients taking these medicines (*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 coadministration of dolutegravir with metformin, to maintain glycaemic control (*see Interactions*).

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 anion 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. 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, ethinylestradiol, levonorgestrel, metformin, acyclovir, famciclovir, fluconazole, rifampicin, ribavirin, boceprevir, telaprevir, daclatasvir and oral contraceptives containing norgestimate and ethinyl estradiol.

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) (IC50 = 1.95 μM), multidrug and toxin extrusion transporter (MATE) 1 (IC50 = 0.34 μM) and MATE2-K (IC50 = 2.8 μM). Given dolutegravir's *in vivo* exposure, it has a low potential to affect the transport of MATE2-K substrates *in vivo*. *In vivo*, dolutegravir may increase plasma concentrations of drugs in which excretion is dependent upon OCT2 or MATE1 (tenofovir, pilsicainide or metformin) (*see Table 1*).

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.

Abacavir and lamivudine do not inhibit or induce CYP enzymes (such as CYP1A, CYP2C and CYP 2D6) and demonstrate no or weak inhibition of the OATP1B1, 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 transporter 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 efavirenz-mediated effect 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, peginterferon, ribavirin, daclatasvir and methadone 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 excretion of lamivudine. In vitro, abacavir is not a substrate of OAP1B1, 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 to date clinically significant changes in abacavir pharmacokinetics when co-administered with topiravir/ritonavir (Pgp and BCRP inhibitor) 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. Nevertheless (in solution 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.

TRIUMEQ is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments due to interacting concomitant medications. Separate preparations of *TIVICAY*, *ZIAGEN* or *EPIVIR* should be administered in cases where dose adjustment is required. In these cases the physician should refer to the individual product information for these medicinal products.

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_{12} ↓ 71% C_{max} ↓ 52% C_{12} ↓ 88% ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. Since the recommended dose of dolutegravir is 50 mg twice daily for patients taking etravirine without boosted protease inhibitors, *TRIUMEQ* is not recommended for patients taking etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Protease Inhibitor: Lopinavir/ritonavir (LPV/RTV) + Etravirine (LPV/RTV + ETR)	Dolutegravir ↔ AUC_{τ} ↑ 11% C_{max} ↑ 7% C_{12} ↑ 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 (DRV/RTV) + Etravirine (DRV/RTV + ETR)	Dolutegravir ↓ AUC_{τ} ↓ 22% C_{max} ↓ 12% C_{12} ↓ 36% DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC_{τ} ↓ 57% C_{max} ↓ 39% C_{12} ↓ 75% EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. Since the dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz the co-administration of efavirenz with *TRIUMEQ* is not recommended.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Because of nevirapine's long half-life, co-administration of *TRIUMEQ* is less likely than that of efavirenz. Since the dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine, the co-administration of nevirapine with *TRIUMEQ* is not recommended.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC_{τ} ↑ 91% C_{max} ↑ 34% C_{12} ↑ 121% ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV+RTV)	Dolutegravir ↑ AUC_{τ} ↑ 62% C_{max} ↑ 24% C_{12} ↑ 121% ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC_{τ} ↓ 59% C_{max} ↓ 47% C_{12} ↓ 76% TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. Since the dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir, the co-administration of tipranavir/ritonavir with *TRIUMEQ* is not recommended.
Protease Inhibitor: Fosamprenavir/ritonavir (FPV+RTV)	Dolutegravir ↓ AUC_{τ} ↓ 35% C_{max} ↓ 24% C_{12} ↓ 49% FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients.
Protease Inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV+RTV)	DTG ↔ AUC_{τ} ↓ 4% C_{max} ↔ C_{12} ↓ 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_{τ} ↓ 22% C_{max} ↓ 11% C_{12} ↓ 38% DRV ↔ RTV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

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

Table 2 Drug Interactions studied with lamivudine

Concomitant Drug Class: Drug Name	Effect on Concentration of abacavir or Concomitant Drug	Clinical Comment
Nucleoside Reverse Transcriptase Inhibitor: Zidovudine (AZT)	Abacavir AUC ↔ C_{max} ↓ 35% Methadone CL/F ↑22%	The changes in abacavir pharmacokinetics are not considered clinically relevant. The changes in methadone pharmacokinetics are not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.
Ethanol	Abacavir AUC ↑ 41% Ethanol AUC ↔	Given the safety profile of abacavir, these findings are not considered clinically significant.

Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration, CL/F = apparent clearance

Table 3 Drug Interactions studied with lamivudine

Concomitant Drug Class: Drug Name	Effect on Concentration of lamivudine or Concomitant Drug	Clinical Comment
Trimethoprim/sulfamethoxazole (Co-trimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary when co-administered. 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 jirovecci pneumonia and toxoplasmosis has not been studied. *TRIUMEQ* is not recommended for use in patients taking trimethoprim/ co-trimoxazole.
Emtricitabine	Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the pharmacokinetics of lamivudine and emtricitabine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs is expected to be affected when used in combination. It is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.	
Other Agents		
Sorbitol solution (3.2, 10.2 g, 13.4 g)	Single dose lamivudine oral solution 300 mg Lamivudine: AUC_{τ} ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%, 55%.	When possible, avoid chronic coadministration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration

Pregnancy and Lactation

Fertility

There are no data on the effects of dolutegravir, abacavir or lamivudine on human male or female fertility. Animal studies indicate no effects of dolutegravir, abacavir or lamivudine on male or female fertility (*see Pre-clinical Safety Data*).

Pregnancy

The safe use of *TRIUMEQ* in human pregnancy has not been established. Dolutegravir was shown to cross the placenta in reproductive toxicity studies in animals. Lamivudine and abacavir have shown placental transfer in animal reproductive toxicity studies (*see Pre-clinical Safety Data*). Therefore administration of *TRIUMEQ* in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the foetus.

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.

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.

It is expected that dolutegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans. In a study following repeat oral dose of either 150 mg lamivudine twice daily (given in combination with 300 mg zidovudine twice daily) or 300 mg lamivudine twice daily, lamivudine was secreted in breast milk (0.15 to 6.2 mcrograms/ml) at similar concentrations to those found in serum. In other studies following repeat oral dose of 150 mg lamivudine twice daily (given either in combination with 300 mg zidovudine or as 300mg/ml of TRIZIVIR) the breast milk maternal plasma ratio ranged between 0.6 and 3.3. In a study after repeat oral administration of 300 mg abacavir twice daily (given as ZIAGEN), the breast milk/maternal plasma ratio was 0.9. No pharmacokinetic studies were conducted with abacavir once daily oral administration. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/ml, and were not detectable in one of the studies (assay sensitivity 7 ng/ml). Most infants (8 out of 9) had non-detectable levels of abacavir (assay sensitivity 16 ng/ml). Intracellular carbovir and lamivudine triphosphate (active metabolites of abacavir and lamivudine) levels in breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compounds measured is unknown.

Effects on Ability to Drive and Use Machines

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

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 mode-orange 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 in a clinical environment with immediate medical support (*see Special considerations following an interruption of TRIUMEQ therapy in Warnings and Precautions*).

Adverse drug reactions from 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 frequency of some of the observed adverse reactions were observed with the combination but were not listed in the product information for any of the individual components:

Gastrointestinal disorders: abdominal distension, gastro-oesophageal reflux disease, dyspepsia

Nervous system disorders: insomnia

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 of 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 rate of HSR for the individual components in severity for any drug-related adverse events.

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, anaemia, thrombocytopenia
Immune system disorders	Uncommon: hypersensitivity (*see Warnings and Precautions*), Immune Reconstitution Syndrome (*see Warnings and Precautions*)	Common: drug hypersensitivity (*see Warnings and Precautions*)	
Metabolism and nutrition disorders		Common: anorexia	
Psychiatric disorders	Common: Insomnia, abnormal dreams, depression Uncommon: Suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)		
Nervous system disorders	Very common: headache Common: dizziness	Common: headache	Common: headache
Gastrointestinal disorders	Very common: nausea, diarrhoea Common: vomiting, flatulence, abdominal pain, upper abdominal pain, abdominal discomfort	Common: nausea, vomiting, diarrhoea	Common: nausea, vomiting, upper abdominal pain, diarrhoea
Hepatobiliary disorders	Uncommon: hepatitis		Uncommon: transient rises in liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	Common: rash, pruritus		Common: rash
General disorders and administration site conditions	Common: fatigue	Common: fever, lethargy, fatigue	Common: fatigue, malaise, fever

Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 96 weeks. In INGI114467, 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 and clinical jaundice were observed in clinical trials of dolutegravir, but not in the Phase III clinical studies in the programme. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconiugated 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.

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 *ZIAGEN* and *EPIVIR* have been investigated separately, and as a dual nucleoside backbone in combination with antiretroviral therapy to treat ART-naive 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 and lamivudine. 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: hyperlactatemia Rare: lactic acidosis	Common: hyperlactatemia Rare: lactic acidosis
Nervous system disorders			Very rare: paresthesiae, peripheral neuropathy has been reported although 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
Skin and subcutaneous tissue disorders		Common: rash (without systemic symptoms) Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	Common: alopecia
Musculoskeletal and connective tissue disorders		Uncommon: arthralgia Uncommon: myalgia	Common: arthralgia, muscle disorders Rare: rhabdomyolysis

Lactic acidosis (*see Warnings and Precautions*)

Description of Selected Adverse Reactions

*Hypersensitivity (