Triumeq

1. NAME OF THE MEDICINAL PRODUCT

Triumeq film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Purple, biconvex, film-coated oval tablets, approximately 22 x 11 mm, debossed with “572 Trı” on one side.

Patient Alert Card

The marketing of Triumeq is subject to risk management plan (RMP) including a "Patient Alert card". The "Patient Alert card", emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Triumeq is indicated for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age weighing at least 40 kg (see sections 4.4 and 5.1).

Before initiating treatment with abacavir-containing products, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin (see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

4.2 Posology and method of administration

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

Posology

Adults and adolescents (weighing at least 40kg)
The recommended dose of Triumeq in adults and adolescents is one tablet once daily.

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.

Separate preparations of dolutegravir, abacavir or lamivudine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. In these cases the physician should refer to the individual product information for these medicinal products.
A separate preparation of dolutegravir is applicable where a dose adjustment is indicated due to drug-drug interactions (e.g. rifampicin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St. John's wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir (see sections 4.4 and 4.5).

Missed doses
If the patient misses a dose of Triumeq, the patient should take it as soon as possible, providing the next dose is not due within 4 hours. If the next dose is due within 4 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Elderly
There are limited data available on the use of dolutegravir, abacavir and lamivudine in patients aged 65 years and over. There is no evidence that elderly patients require a different dose than younger adult patients (see section 5.2). Special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

Renal impairment
Triumeq is not recommended for use in patients with a creatinine clearance < 50 ml/min (see section 5.2).

Hepatic impairment
Abacavir is primarily metabolised by the liver. No clinical data are available in patients with moderate or severe hepatic impairment, therefore the use of Triumeq is not recommended unless judged necessary. In patients with mild hepatic impairment (Child-Pugh score 5-6) close monitoring is required, including monitoring of abacavir plasma levels if feasible (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Triumeq in children less than 12 years of age has not yet been established. No data are available.

Method of administration

Oral use
Triumeq can be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Co-administration with medicinal products with narrow therapeutic windows, that are substrates of organic cation transporter (OCT) 2, including but not limited to fampridine (also known as dalfampridine; see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity reactions (see section 4.8)

Both abacavir and dolutegravir are associated with a risk for hypersensitivity reactions (HSR) (see section 4.8), 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 would be 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,

when not managed appropriately. The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a low frequency in patients who do not carry this allele.

Therefore, the following should always be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.

- Triumeq should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen.

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

- 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. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.

- In order to avoid restarting abacavir and dolutegravir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining Triumeq tablets.

Clinical description of HSRs

Hypersensitivity reactions have been reported in <1% of patients treated with dolutegravir in clinical studies, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions.

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 will include fever and/or rash. Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in section 4.8 (Description of selected adverse reactions), including respiratory and gastrointestinal symptoms. Importantly, such symptoms **may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.** The symptoms related to this HSR worsen with continued therapy and **can be life-threatening**. These symptoms usually resolve upon discontinuation of abacavir.

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 Section 4.8 Description of selected adverse reactions). Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

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 and weight, there is in some cases evidence for a treatment effect. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Liver disease

The safety and efficacy of Triumeq has not been established in patients with significant underlying liver disorders. Triumeq is not recommended in patients with moderate to severe hepatic impairment (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction, including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients with chronic hepatitis B or C

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Triumeq includes lamivudine, which is active against hepatitis B. Abacavir and dolutegravir lack such activity. Lamivudine monotherapy is generally not considered an adequate treatment for hepatitis B, since the risk for hepatitis B resistance development is high. If Triumeq is used in patients co-infected with hepatitis B an additional antiviral is, therefore, generally needed. Reference should be made to treatment guidelines.

If Triumeq is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia (often referred to as PCP). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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 with chronic hepatitis B or C' earlier in this section and also see section 4.8).

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues, these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), and metabolic disorders (hyperlactatemia, hyperlipasemia). These reactions have often been transitory. Some late-onset

neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown aetiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Myocardial infarction

Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical studies showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing Triumeq, action should be taken to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Osteonecrosis

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

Opportunistic infections

Patients should be advised that Triumeq or any other antiretroviral therapy does not cure HIV infection and that they 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.

Drug resistance

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.

Drug interactions

The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St. John’s wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir (see section 4.5).

Triumeq should not be co-administered with polyvalent cation-containing antacids. Triumeq is recommended to be administered 2 hours before or 6 hours after these medicinal products (see section 4.5).

When taken with food, Triumeq and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. If Triumeq is administered under fasting conditions, supplements or multivitamins containing calcium, iron or magnesium are recommended to be taken 2 hours after or 6 hours before Triumeq (see section 4.5).

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 section 4.5). Metformin is eliminated renally and therefore it is of importance to monitor renal function when co-treated with dolutegravir. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance [CrCl] 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered.

The combination of lamivudine with cladribine is not recommended (see section 4.5).

Triumeq should not be taken with any other medicinal products containing dolutegravir, abacavir, lamivudine or emtricitabine, except where a dose adjustment of dolutegravir is indicated due to drug-drug interactions (see section 4.5).

Excipients

Triumeq contains less than 1 mmol sodium (23 mg) per tablet, that is to say is essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Triumeq contains dolutegravir, abacavir and lamivudine, therefore any interactions identified for these individually are relevant to Triumeq. No clinically significant drug interactions are expected between dolutegravir, abacavir and lamivudine.

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

Dolutegravir is eliminated mainly through metabolism by uridine diphosphate glucuronosyl transferase (UGT) 1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). Co-administration of Triumeq and other medicinal products that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or P-gp may therefore increase dolutegravir plasma concentration. Medicinal products that induce those enzymes or transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir (see Table 1).

The absorption of dolutegravir is reduced by certain anti-acid medicinal products (see Table 1).

Abacavir is metabolised by UGT (UGT2B7) and alcohol dehydrogenase; co-administration of inducers (e.g. rifampicin, carbamazepine and phenytoin) or inhibitors (e.g. valproic acid) of UGT enzymes or with compounds eliminated through alcohol dehydrogenase could alter abacavir exposure.

Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through the OCT2 and multidrug and toxin extrusion transporters (MATE1 and MATE2-K). Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations, however the resulting increase was not clinically significant (see Table 1). Dolutegravir is an OCT2 and MATE1 inhibitor; however, lamivudine concentrations were similar with or without co-administration of dolutegravir based on a cross study analysis, indicating that dolutegravir has no effect on lamivudine exposure *in vivo*. Lamivudine is also 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.

Although abacavir and lamivudine are substrates of BCRP and P-gp *in vitro*, given the high absolute bioavailability of abacavir and lamivudine, (see section 5.2), inhibitors of these efflux transporters are unlikely to result in a clinically relevant impact on abacavir or lamivudine concentrations.

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

In vivo, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on *in vivo* and/or *in vitro* data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of any major enzyme or transporter such as CYP3A4, CYP2C9 and P-gp (for more information see section 5.2).

In vitro, dolutegravir inhibited the renal transporters OCT2 and MATE1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 and/or MATE1 (e.g. fampridine [also known as dalfampridine], metformin) (see Table 1).

In vitro, dolutegravir inhibited the renal uptake organic anion transporters (OAT)1 and OAT3. Based on the lack of effect on the *in vivo* pharmacokinetics of the OAT substrate tenofovir, *in vivo* inhibition of OAT1 is unlikely. Inhibition of OAT3 has not been studied *in vivo*. Dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OAT3.

In vitro, abacavir demonstrated the potential to inhibit CYP1A1 and limited potential to inhibit metabolism mediated by CYP3A4. Abacavir was an inhibitor of MATE1; the clinical consequences are not known.

In vitro, lamivudine was an inhibitor of OCT1 and OCT2; the clinical consequences are not known.

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in Table 1.

Interaction table

Interactions between dolutegravir, abacavir, lamivudine and co-administered medical products are listed in Table 1 (increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}", concentration at end of dosing interval as "Cτ"). The table should not be considered exhaustive but is representative of the classes studied.

Table 1: Drug interactions

Medicinal products by therapeutic areas	**Interaction geometric mean change (%)**	**Recommendations concerning co-administration**
Antiretroviral medicinal products		
Non-nucleoside reverse transcriptase inhibitors		
Etravirine without boosted protease inhibitors / Dolutegravir	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	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 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Triumeq for the duration of the etravirine without boosted protease inhibitor co-administration (a separate preparation of dolutegravir is available for this dose adjustment, see section 4.2).

Lopinavir+ritonavir+etravirine/ Dolutegravir	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% Lopinavir ↔ Ritonavir ↔ Etravirine ↔	No dose adjustment is necessary.
Darunavir+ritonavir+etravirine/ Dolutegravir	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% Cτ ↓ 36% Darunavir ↔ Ritonavir ↔ Etravirine ↔	No dose adjustment is necessary.
Efavirenz/Dolutegravir	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. As Triumeq is a fixed dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Triumeq for the duration of the efavirenz co-administration (a separate preparation of dolutegravir is available for this dose adjustment, see section 4.2).
Nevirapine/Dolutegravir	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	Co-administration with nevirapine may 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 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Triumeq for the duration of the nevirapine co-administration (a separate preparation of dolutegravir is available for this dose adjustment, see section 4.2).
Rilpivirine	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Tenofovir	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% Cτ ↓ 8% Tenofovir ↔	No dose adjustment is necessary when Triumeq is combined with nucleoside reverse transcript inhibitors.

Emtricitabine, didanosine, stavudine, zidovudine.	Interaction not studied	Triumeq is not recommended for use in combination with emtricitabine containing products, since both lamivudine (in Triumeq) and emtricitabine are cytidine analogues (i.e. risk for intracellular interactions, (see section 4.4))
Protease inhibitors		
Atazanavir/Dolutegravir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% Cτ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Atazanavir+ ritonavir/ Dolutegravir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121% Atazanavir ↔ Ritonavir ↔	No dose adjustment is necessary.
Tipranavir+ritonavir/ Dolutegravir	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% Cτ ↓ 76% Tipranavir ↔ Ritonavir ↔ (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of-dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir. As Triumeq is a fixed dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Triumeq for the duration of the tipranavir/ritonavir co-administration (a separate preparation of dolutegravir is available for this dose adjustment, see section 4.2).
Fosamprenavir+ritonavir/ Dolutegravir	Dolutegravir↓ AUC ↓ 35% C_{max} ↓ 24% Cτ ↓ 49% Fosamprenavir↔ Ritonavir ↔ (induction of UGT1A1 and CYP3A enzymes)	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.
Lopinavir+ritonavir/ Dolutegravir Lopinavir+ritonavir/ Abacavir	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔ 0% C_{24} ↓ 6% Lopinavir ↔ Ritonavir ↔	No dose adjustment is necessary.

	Abacavir AUC ↓ 32%	
Darunavir+ritonavir/ Dolutegravir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% Cτ ↓ 38% Darunavir ↔ Ritonavir ↔ (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Other antiviral agents		
Daclatasvir/Dolutegravir	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.
Anti-infective products		
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Abacavir Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Lamivudine (160mg/800mg once daily for 5 days/300mg single dose)	Interaction not studied Lamivudine: AUC ↑43% C_{max} ↑7% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	No Triumeq dose adjustment necessary, unless patient has renal impairment (See Section 4.2).
Antimycobacterials		
Rifampicin/Dolutegravir	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓ 72% (induction of UGT1A1 and CYP3A enzymes)	The dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin. As Triumeq is a fixed dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Triumeq for the duration of the rifampicin co-administration (a separate preparation of dolutegravir is available for this dose adjustment, see section 4.2).
Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% Cτ ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Anticonvulsants		
Carbamazepine/Dolutegravir	Dolutegravir ↓ AUC ↓ 49%	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine. As

	C_{max} ↓ 33% Cτ ↓ 73%	Triumeq is a fixed dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Triumeq for the duration of the carbamazepine co-administration (a separate preparation of dolutegravir is available for this dose adjustment, see section 4.2).
Phenobarbital/Dolutegravir Phenytoin/Dolutegravir Oxcarbazepine/Dolutegravir	Dolutegravir↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	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 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Triumeq for the duration of the co-administration with these metabolic inducers (a separate preparation of dolutegravir is available for this dose adjustment, see section 4.2).
Antihistamines (histamine H2 receptor antagonists)		
Ranitidine	Interaction not studied. Clinically significant interaction unlikely.	No dose adjustment necessary.
Cimetidine	Interaction not studied. Clinically significant interaction unlikely.	No dose adjustment necessary.
Cytotoxics		
Cladribine/Lamivudine	Interaction not studied. *In vitro* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine	Concomitant use of Triumeq with cladribine is not recommended (see section 4.4).
Opioids		
Methadone/Abacavir (40 to 90mg once daily for 14 days/600mg single dose, then 600mg twice daily for 14 days)	Abacavir: AUC ↔ Cmax ↓35% Methadone: CL/F ↑22%	Methadone dose adjustment likely not needed in majority of patients; occasionally methadone re-titration may be required.
Retinoids		

Retinoid compounds (e.g. Isotretinoin)	Interaction not studied Possible interaction given common pathway of elimination via alcohol dehydrogenase (abacavir-component).	Insufficient data to recommend dose adjustment.
Miscellaneous		
Alcohol		
Ethanol/Dolutegravir Ethanol/Lamivudine Ethanol/Abacavir (0.7 g/kg single dose/600mg single dose)	Interaction not studied (Inhibition of alcohol dehydrogenase) Abacavir: AUC ↑ 41% Ethanol: AUC ↔	No dose adjustment necessary.
Sorbitol		
Sorbitol solution (3.2 g, 10.2 g, 13.4 g)/Lamivudine	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%, 55%.	When possible, avoid chronic coadministration of Triumeq with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (eg: xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.
Potassium channel blockers		
Fampridine (also known as dalfampridine)/Dolutegravir	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 Triumeq is contraindicated (see section 4.3).
Antacids and supplements		
Magnesium/ aluminium-containing antacids/Dolutegravir	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacids should be taken well separated in time from the administration of Triumeq (minimum 2 hours after or 6 hours before the intake of Triumeq).
Calcium supplements/Dolutegravir	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39% (Complex binding to polyvalent ions)	- When taken with food, Triumeq and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. - If Triumeq is taken in a fasted state, such supplements should be taken a minimum 2 hours after or 6 hours before the intake of Triumeq.
Iron supplements/Dolutegravir	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56%	

	(Complex binding to polyvalent ions)	The stated reductions in dolutegravir exposure were observed with the intake of dolutegravir and these supplements during fasted conditions. In fed state, the changes in exposure following intake together with calcium or iron supplements were modified by the food effect, resulting in an exposure similar to that obtained with dolutegravir administered in the fasted state.
Multivitamins (containing calcium, iron and magnesium) /Dolutegravir	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32%	
Corticosteroids		
Prednisone	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% Cτ ↑ 17%	No dose adjustment is necessary.
Antidiabetics		
Metformin/Dolutegravir	Metformin ↑ Dolutegravir ↔ 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%	A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when coadministered with dolutegravir, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (section 4.4).
Herbal products		
St. John's wort/Dolutegravir	Dolutegravir↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. As Triumeq is a fixed dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Triumeq for the duration of the St John's wort co-administration (a separate preparation of dolutegravir is available for this dose adjustment, see section 4.2).
Oral contraceptives		
Ethinyl estradiol (EE) and Norgestromin (NGMN)/Dolutegravir	Effect of dolutegravir: EE ↔ AUC ↑ 3% C_{max} ↓ 1% Effect of dolutegravir: NGMN ↔ AUC ↓ 2% C_{max} ↓ 11%	Dolutegravir had no Pharmacodynamic effect on Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and progesterone. No dose adjustment of oral contraceptives is necessary when co-administered with Triumeq.
Antihypertensive		

Riociguat/Abacavir	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 prescribing information for dosing recommendations.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be counselled about the potential risk of neural tube defects with dolutegravir (a component of Triumeq, see below), including consideration of effective contraceptive measures.

If a woman plans pregnancy, the benefits and the risks of continuing treatment with Triumeq should be discussed with the patient.

Pregnancy

Human experience from a birth outcome surveillance study in Botswana shows a small increase of neural tube defects; 7 cases in 3,591 deliveries (0.19%; 95% CI 0.09%, 0.40%) to mothers taking dolutegravir-containing regimens at the time of conception compared to 21 cases in 19,361 deliveries (0.11%: 95% CI 0.07%, 0.17%) to women exposed to non-dolutegravir regimens at the time of conception.

The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births (0.05-0.1%). Most neural tube defects occur within the first 4 weeks of embryonic development after conception (approximately 6 weeks after the last menstrual period). If a pregnancy is confirmed in the first trimester while on Triumeq, the benefits and risks of continuing Triumeq versus switching to another antiretroviral regimen should be discussed with the patient taking the gestational age and the critical time period of neural tube defect development into account.

Data analysed from the Antiretroviral Pregnancy Registry do not indicate an increased risk of major birth defects in over 600 women exposed to dolutegravir during pregnancy but are currently insufficient to address the risk of neural tube defects.

In animal reproductive toxicology studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified (see section 5.3).

More than 1000 outcomes from exposure to dolutegravir during second and third trimester pregnancy indicate no evidence of increased risk of foetal/neonatal toxicity. Triumeq may be used during the second and third trimester of pregnancy when the expected benefit justifies the potential risk to the foetus.

Dolutegravir crosses the placenta in humans. In pregnant women living with HIV, the median foetal umbilical cord concentration of dolutegravir was approximately 1.3-fold greater compared with the maternal peripheral plasma concentration.

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

Concerning lamivudine, a large amount of data (more than 5200 outcomes from first trimester) indicates no malformative toxicity. A moderate amount of data (more than 1200 outcomes from first trimester) indicates no malformative toxicity for abacavir.

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

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues (see section 4.4).

Breast-feeding

Dolutegravir is excreted in human milk in small amounts (a median dolutegravir breast milk to maternal plasma ratio of 0.033 has been shown). There is insufficient information on the effects of dolutegravir in neonates/infants.

Abacavir and its metabolites are excreted into the milk of lactating rats. Abacavir is also excreted into human milk.

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

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

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 section 5.3).

4.7 Effects on ability to drive and use machines

Triumeq has no or negligible influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of Triumeq should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions related to dolutegravir and abacavir/lamivudine were nausea (12%), insomnia (7%), dizziness (6%) and headache (6%).

Many of the adverse reactions listed in the table below 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 (see section 4.4). Very rarely cases of erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported where abacavir hypersensitivity could not be ruled out. In such cases medicinal products containing abacavir should be permanently discontinued.

The most severe adverse reaction related to the treatment with dolutegravir and abacavir/lamivudine, seen in individual patients, was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4 and Description of selected adverse reactions in this section).

Tabulated list of adverse reactions

The adverse reactions with the components of Triumeq from clinical study and post-marketing experience are listed in Table 2 by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000).

Table 2: Tabulated list of adverse reactions associated with the combination of dolutegravir + abacavir/lamivudine in an analysis of pooled data from: Phase IIb to Phase IIIb clinical studies or post-marketing experience; and adverse reactions to treatment with dolutegravir, abacavir and lamivudine from clinical studies and post-marketing experience when used with other antiretrovirals

Frequency	**Adverse reaction**
Blood and lymphatic systems disorders:	
Uncommon:	Neutropenia[1], anaemia[1], thrombocytopenia[1]
Very rare:	pure red cell aplasia[1]
Immune system disorders:	
Common:	hypersensitivity (see section 4.4)
Uncommon:	immune reconstitution syndrome (see section 4.4)
Metabolism and nutrition disorders:	
Common:	anorexia[1]
Uncommon:	hypertriglyceridaemia, hyperglycaemia
Very rare:	lactic acidosis[1]
Psychiatric disorders:	
Very common:	insomnia
Common:	abnormal dreams, depression, anxiety[1], nightmare, sleep disorder
Uncommon:	suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness), panic attack
Rare:	completed suicide (particularly in patients with a pre-existing history of depression or psychiatric illness)
Nervous system disorders:	
Very common:	headache

Common:	dizziness, somnolence, lethargy[1]
Very rare:	peripheral neuropathy[1], paraesthesia[1]
Respiratory, thoracic and mediastinal disorders:	
Common:	cough[1], nasal symptoms[1]
Gastrointestinal disorders:	
Very common:	nausea, diarrhoea
Common:	vomiting, flatulence, abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, gastro-oesophageal reflux disease, dyspepsia
Rare:	pancreatitis[1]
Hepatobiliary disorders:	
Common:	alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations
Uncommon:	hepatitis
Rare:	acute hepatic failure[1], increased bilirubin[2]
Skin and subcutaneous tissue disorders:	
Common:	rash, pruritus, alopecia[1]
Very rare:	erythema multiform[1], Stevens-Johnson syndrome[1], toxic epidermal necrolysis[1]
Musculoskeletal and connective tissue disorders:	
Common:	Arthralgia[1], muscle disorders[1](including myalgia[1])
Rare:	rhabdomyolysis[1]
General disorders and administration site conditions:	
Very common:	fatigue
Common:	asthenia, fever[1], malaise[1]
Investigations:	
Common:	CPK elevations, weight increased
Rare:	amylase elevations[1]
[1]This adverse reaction was identified from clinical studies or post-marketing experience for dolutegravir, abacavir or lamivudine when used with other antiretrovirals or post-marketing experience with Triumeq. [2]In combination with increased transaminases.	

Description of selected adverse reactions

Hypersensitivity reactions
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. Please refer to section 4.4 for further details on patient management in the event of a suspected HSR to Triumeq.

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

Abacavir hypersensitivity
The signs and symptoms of this 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, lethargy, 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

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

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. Similar 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).

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

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 section 4.4).

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 and autoimmune hepatitis) 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 section 4.4).

Changes in laboratory chemistries

Increases in serum creatinine occurred within the first week of treatment with dolutegravir and remained stable through 96 weeks. In the SINGLE study 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.

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.

Paediatric population

There are no clinical study data on the effects of Triumeq in the paediatric population. Individual components have been investigated in adolescents (12 to 17 years).

Based on limited available data with the dolutegravir single entity used in combination with other antiretroviral agents to treat adolescents (12 to 17 years), there were no additional types of adverse reactions beyond those observed in the adult population.
The individual preparations of abacavir and lamivudine have been investigated separately, and as a dual nucleoside backbone, in combination antiretroviral therapy to treat ART- naive and ART- experienced HIV- infected paediatric patients (data available on the use of abacavir and lamivudine in infants less than three months are limited). No additional types of adverse reactions have been observed beyond those characterised for the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

Additionally, you should also report to GSK Israel (il.safety@gsk.com)

4.9 Overdose

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

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of Triumeq. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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'-triphosphates (TP) which are the active moieties with extended intracellular half-lives supporting once daily dosing (see section 5.2). 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 (PMBCs) and monocyte/macrophages. The concentration of active substance necessary to effect viral replication by 50% (IC_{50} - half maximal inhibitory concentration) varied according to virus and host cell type.

The IC_{50} 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 IC_{50}s 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 IC_{50} value was 0.2 nM (range 0.02-2.14). The mean IC_{50} for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).

The mean IC_{50} for abacavir against lab-strains of HIV-1IIIB and HIV-1HXB2 ranged from 1.4 to 5.8 μM. The median or mean IC_{50} values for lamivudine against lab-strains of HIV-1 ranged from 0.007 to 2.3 μM. The mean IC_{50} 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 IC_{50} 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 IC_{50} 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 (IC_{50} fold changes < 2.5), and lamivudine (IC_{50} 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 IC_{90} 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 F. 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 naive 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)
In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase class, or to the NRTI class was seen (n=876, follow-up of 48-96 weeks).

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 IC_{50}, 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 naive subjects is based on the analyses of data from a number of trials. The analyses included two randomised, international, double-blind, active-controlled

trials, SINGLE (ING114467) and SPRING-2 (ING113086), the international, open-label, active-controlled trial FLAMINGO (ING114915), and the randomised, open-label, active-controlled, multicentre, non-inferiority study ARIA (ING117172).

The STRIIVING study (201147), was a randomised, open-label, active-controlled, multicentre, non-inferiority switch study in virologically suppressed subjects with no documented history of resistance to any class.

In SINGLE, 833 patients were treated with dolutegravir 50 mg film-coated tablets 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 3.

Table 3: Virologic Outcomes of Randomised 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 medicinal product due to adverse event or death‡	2%	10%
Discontinued study/study medicinal product 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 disoproxil 245 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 + 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 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 film-coated tablets 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 4. Dolutegravir was non-inferior to raltegravir, including within the subset of patients with the abacavir/lamivudine background regimen.

Table 4: Demographics and virologic outcomes of randomised 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 medicinal product due to adverse event or death‡	2%	1%
Discontinued study/study medicinal product 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 film-coated tablets 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 5.

Table 5: Demographics and Week 48 virologic outcomes of randomised 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 medicinal product due to adverse event or death‡	1%	4%
Discontinued study/study medicinal product for other reasons§	2%	5%
Missing data during window but on study	<1%	2%
HIV-1 RNA <50copies/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.

In ARIA (ING117172), a randomised, open-label, active-controlled, multicenter, parallel group, non-inferiority study; 499 HIV-1 infected ART naïve adult women were randomised 1:1 to receive either; DTG/ABC/3TC FDC film-coated tablets 50 mg/600 mg/300 mg; or atazanavir 300 mg plus ritonavir 100 mg plus tenofovir disproxil / emtricitabine 245 mg/200 mg (ATV+RTV+TDF/FTC FDC), all administered once daily.

Table 6: Demographics and Week 48 virologic outcomes of randomised treatment of ARIA (snapshot algorithm)

	DTG/ABC/3TC FDC N=248	**ATV+RTV+TDF/FTC FDC N=247**
Demographics		
Median Age (years)	37	37
Female	100 %	100 %
Non-white	54 %	57 %
Hepatitis B and/ or C	6 %	9%
CDC class C	4 %	4 %
Week 48 Efficacy Results		
HIV-1 RNA <50 copies/mL	82 %	71 %
Treatment difference	10.5 (3.1% to 17.8%) [p=0.005].	
Virologic Failure	6 %	14 %
Reasons Data in window not below 50 c/mL threshold Discontinued for lack of efficacy Discontinued for other reason while not below threshold	 2 % 2 % 3 %	 6 % <1 % 7 %
No Virologic Data	12 %	15 %
Discontinued due to AE or death Discontinued for other reasons Missing data during window but on study	4 % 6 % 2 %	7 % 6 % 2 %

AE = Adverse event.
HIV-1 - human immunodeficiency virus type 1
DTG/ABC/3TC FDC - abacavir/dolutegravir/lamivudine fixed-dose combination
ATV+RTV+TDF/FTC FDC -atazanavir plus ritonavir plus tenofovir disproxil/emtricitabine fixed-dose combination

STRIIVING (201147) is a 48-week, randomised, open-label, active controlled, multicenter, non-inferiority study in patients without any prior treatment failure, and without any documented resistance to any class. 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 film-coated tablets once daily (Early Switch). Hepatitis B co-infection was one of the main exclusion criteria.

Patients were mainly white (66%) or black (28%) of male sex (87%). Main prior transmission routes were homosexual (73%) or heterosexual (29%) contact. The proportion with a positive HCV serology was 7%. The median time from first starting ART was around 4.5 years.

Table 7: Outcomes of randomised treatment of STRIIVING (snapshot algorithm)

Study Outcomes (Plasma HIV-1 RNA <50 c/mL) at Week 24 and Week 48 – Snapshot Analysis (ITT-E Population)				
	ABC/DTG/3TC FDC N=275 n (%)	**Current ART N=278 n (%)**	**Early Switch ABC/DTG/3TC FDC N=275 n (%)**	**Late Switch ABC/DTG/3TC FDC N=244 n (%)**
Outcome Time Point	**Day 1 to W 24**	**Day 1 to W 24**	**Day 1 to W48**	**W24 to W48**
Virologic Success	85 %	88 %	83 %	92 %
Virologic Failure	1 %	1 %	<1 %	1 %
Reasons				
Data in window not below threshold	1 %	1 %	<1 %	1 %
No Virologic Data	14 %	10 %	17 %	7 %
Discontinued due to AE or death	4 %	0 %	4 %	2 %
Discontinued for other reasons	9 %	10 %	12 %	3 %
Missing data during window but on study	1 %	<1 %	2 %	2 %
ABC/DTG/3TC FDC = abacavir/dolutegravir/lamivudine fixed-dose combination; AE = adverse event; ART = antiretroviral therapy; HIV-1 = human immunodeficiency virus type 1; ITT-E = intent-to-treat exposed; W = week.				

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.

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.

5.2 Pharmacokinetic properties

Triumeq film-coated tablet has been shown to be bioequivalent to dolutegravir single entity film-coated 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 80-85% 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 film-coated tablets 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%).

The effect of a high fat meal on Triumeq film-coated tablet was evaluated in a subgroup of subjects (n=12) of the single dose, 2-way crossover bioequivalence study. Plasma C_{max} and AUC of dolutegravir following administration of Triumeq film-coated tablets with a high fat meal were 37% and 48% higher, respectively, than those following administration of Triumeq film-coated tablets 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 film-coated tablets 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 is independent of dolutegravir 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 limited 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 IC_{50}). 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 IC_{50} 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 6-10% of those in corresponding plasma at steady state. AUC in semen was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

Biotransformation

Dolutegravir is primarily metabolised via UGT1A1 with a minor CYP3A component (9.7% of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance 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 approximately 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 by renal excretion of unchanged lamivudine. The likelihood of metabolic drug 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 (IC_{50}>50 µM) of the enzymes cytochrome P_{450} (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, OCT1, MATE2-K, multidrug resistance-associated protein 2 (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 4.5).

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

In vitro, abacavir did not inhibit or induce CYP enzymes (other than CY1A1 and CYP3A4 [limited potential], see section 4.5) and demonstrates no or weak inhibition of OATP1B1, OAT1B3, OCT1, OCT2, BCRP and P-gp or MATE2-K. Abacavir is therefore not expected to affect the plasma concentrations of medicinal products that are substrates of these enzymes or transporters.

Abacavir was not significantly metabolised by CYP enzymes. *In vitro*, abacavir was not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, MRP2 or MRP4 therefore medicinal products that modulate these transporters are not expected to affect abacavir plasma concentrations.

In vitro, lamivudine did not inhibit or induce CYP enzymes (such as CYP3A4, CYP2C9 or CYP2D6) and demonstrated no or weak inhibition of OATP1B1, OAT1B3, OCT3, BCRP, P-gp, MATE1 or MATE2-K. Lamivudine is therefore not expected to affect the plasma concentrations of medicinal products that are substrates of these enzymes or transporters.

Lamivudine was not significantly metabolised by CYP enzymes.

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 carbovirtriphosphate (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 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0.32 L/h/kg, predominantly by renal clearance (> 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 section 4.2).

Pharmacokinetic/pharmacodynamic relationship(s)

In a randomised, 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, supporting once daily dosing of ABC and 3TC.

Special populations

Hepatic impairment
Pharmacokinetic data has been obtained for dolutegravir, abacavir and lamivudine separately.

Dolutegravir is primarily metabolised and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5 to 2-fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls. No dose adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose. The results showed that there was a mean increase of 1.89-fold [1.32; 2.70] in the abacavir AUC, and 1.58 [1.22; 2.04] fold in the elimination half-life. No recommendation on dose reduction is possible in patients with mild hepatic impairment due to substantial variability of abacavir exposure.

Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

Based on data obtained for abacavir, Triumeq is not recommended in patients with moderate or severe hepatic impairment.

Renal impairment
Pharmacokinetic data have been obtained for dolutegravir, lamivudine and abacavir separately.

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

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

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

Based on the lamivudine data, Triumeq is not recommended for patients with creatinine clearance of < 50 ml/min.

Elderly
Population pharmacokinetic analysis of dolutegravir using data from 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 >65 years of age are limited.

Paediatric population
The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to 17 years) showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure comparable to that observed in adults who received dolutegravir 50 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.

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 pharmacokinetic 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 section 4.4).

5.3 Preclinical safety data

There are no data available on the effects of the combination of dolutegravir, abacavir and lamivudine in animals, except a negative *in vivo* rat micronucleus test which tested the effects of the combination of abacavir and lamivudine.

Mutagenicity and carcinogenicity

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

Neither abacavir nor lamivudine were mutagenic in bacterial tests, but consistent with other nucleoside analogues, inhibit cellular DNA replication in *in vitro* mammalian tests such as the mouse lymphoma assay. The results of an *in vivo* rat micronucleus test with abacavir and lamivudine in combination were negative.

Lamivudine has not shown any genotoxic activity in the *in vivo* studies. Abacavir has a weak potential to cause chromosomal damage both *in vitro* and *in vivo* at high tested concentrations.

The carcinogenic potential of a combination of dolutegravir, abacavir and lamivudine has not been tested. Dolutegravir was not carcinogenic in long term studies in the mouse and rat. In long-term oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. 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 rats in the thyroid gland of males and in the liver, urinary bladder, lymph nodes and the subcutis of females.

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. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy. While the clinical relevance of these findings is unknown, these data suggest that a potential carcinogenic risk to humans is outweighed by the clinical benefit.

Repeat-dose toxicity

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 based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local active substance 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.

In toxicology studies abacavir was shown to increase liver weights in rats and monkeys. The clinical relevance of this is unknown. There is no evidence from clinical studies that abacavir is hepatotoxic. Additionally, autoinduction of abacavir metabolism or induction of the metabolism of other medicinal products hepatically metabolised has not been observed in humans.

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 the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

Reproductive toxicology

In reproductive toxicity studies in animals, dolutegravir, lamivudine and abacavir 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 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 50mg human clinical exposure when 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 administered in combination with abacavir and lamivudine based on AUC).

Lamivudine was not teratogenic in animal studies but there were indications of an increase in early embryonic deaths in rabbits at relatively low systemic exposures, comparable to those achieved in humans. A similar effect was not seen in rats even at very high systemic exposure.

Abacavir demonstrated toxicity to the developing embryo and foetus in rats, but not in rabbits. These findings included decreased foetal body weight, foetal oedema, and an increase in skeletal variations/malformations, early intra-uterine deaths and still births. No conclusion can be drawn with regard to the teratogenic potential of abacavir because of this embryo-foetal toxicity.

Fertility studies in rats have shown that dolutegravir, abacavir and lamivudine have no effect on male or female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
D-Mannitol (E421)
Sodium starch glycolate
Magnesium stearate

Povidone K29/32
Tablet coating
Opadry II Purple 85F90057 containing:
Polyvinyl alcohol – part hydrolyzed (E1203)
titanium dioxide (E171)
macrogol/PEG
talc
iron oxide black (E172)
iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30°C.

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

6.5 Nature and contents of container

White HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closures, with a polyethylene faced induction heat seal liner. Each bottle contains 30 film-coated tablets and a desiccant.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

ViiV Healthcare UK Limited, Brentford, UK.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBER

153-49-34304

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*Triu DR v1*8