AUSTRALIAN PRODUCT INFORMATION

DOVATO (dolutegravir/lamivudine fixed-dose combination) film-coated tablets

1 NAME OF THE MEDICINE

Dolutegravir (as dolutegravir sodium) and lamivudine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DOVATO film-coated tablets contain 50 mg of dolutegravir (as dolutegravir sodium) and 300 mg of lamivudine. Product information for dolutegravir and lamivudine contain additional information.

Dolutegravir sodium is a white to light yellow powder.

Lamivudine is a white to off-white crystalline solid.

DOVATO tablets also contain mannitol.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Oval, biconvex, white, film-coated tablet, debossed with “SV 137” on one face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DOVATO (a fixed dose combination of dolutegravir and lamivudine) is indicated for the treatment of Human Immunodeficiency Virus-1 (HIV-1) infection in adults and adolescents (from 12 years of age weighing at least 40 kg):

- in antiretroviral treatment-naïve patients with no antiretroviral treatment history who have no known or suspected resistance to either antiretroviral component; or
- to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to the integrase inhibitor class or lamivudine (see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

DOVATO can be taken with or without food.

DOVATO is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments.

Separate preparations of dolutegravir or lamivudine should be administered in cases where discontinuation or dose adjustments are required. In these cases, the physician should refer to the individual product information for these medicinal products.

Adults and Adolescents
The recommended dose of DOVATO in adults and adolescents weighing at least 40 kg is one tablet (containing 50 mg of dolutegravir and 300 mg of lamivudine) once daily.

Children
The safety and efficacy of DOVATO in children aged less than 12 years or weighing less than 40 kg have not been established. No data are available.

Elderly
There are limited data available on the use of dolutegravir and lamivudine in patients aged 65 years and over. However, there is no evidence that elderly patients require a different dose than younger adult patients (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations). When treating elderly patients, consideration needs to be given to the greater frequency of decreased hepatic and renal function, haematological abnormalities, and concomitant medicinal products or disease.

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

Lamivudine exposure is significantly increased in patients with a creatinine clearance < 50 mL/min. Whilst no dosage adjustment of dolutegravir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to decreased clearance (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES – Special patient populations – Renal impairment). Therefore, DOVATO is not recommended for use in patients with a creatinine clearance less than 30 mL/min.. If lamivudine dose adjustment is indicated, DOVATO should be discontinued and the individual components should be used to construct the treatment regimen.**Hepatic impairment**
DOVATO has not been evaluated in subjects with hepatic impairment. No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). No data are available for dolutegravir in patients with severe hepatic impairment (Child-Pugh score C) (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations). DOVATO is not recommended for patients with severe hepatic impairment.

Women of child bearing potential and pregnancy

A benefit-risk assessment should be considered at the time of conception through the first trimester due to the potential risk of neural tube defects (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in pregnancy).

4.3 CONTRAINDICATIONS

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Hypersensitivity reactions
Hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Discontinue DOVATO and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with DOVATO or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Lactic acidosis/severe hepatomegaly with steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including lamivudine. A majority of these cases have been in women.

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

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

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

In the GEMINI clinical trials (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials), for both pooled treatment groups, the overall lipid profiles were generally improved from baseline, and the proportions of subjects showing favourable improvements in total cholesterol/HDL cholesterol ratio were similar between the 2 treatment groups (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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

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

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection (see Patients co-infected with Hepatitis B Virus (HBV) later in this section.

Patients co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV)
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.

Particular diligence should be applied in initiating or maintaining effective hepatitis B therapy when starting therapy with DOVATO in hepatitis B co-infected patients. DOVATO includes lamivudine, which is active against hepatitis B. Dolutegravir lacks 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 DOVATO is used in patients co-infected with hepatitis B, an additional antiviral is therefore generally needed. Reference should be made to treatment guidelines.

Data from clinical trials and marketed use of lamivudine, have shown that some patients co-infected with chronic HBV disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If DOVATO is discontinued in patients co-infected with HBV, periodic monitoring of both liver function tests and markers of HBV replication is strongly recommended.

Hepatotoxicity
Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy. Cases of hepatic toxicity, including abnormal liver function tests, hepatitis, and acute liver failure, have also been reported in patients receiving a dolutegravir-containing regimen who

had no pre-existing hepatic disease or other identifiable risk factors. Monitoring for hepatotoxicity is recommended. If there is evidence of worsening liver disease, interruption or discontinuation of treatment must be considered.

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

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

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

Use in hepatic impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Use in renal impairment
Administration in subjects with moderate renal impairment

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

Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive DOVATO should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, per lamivudine prescribing information, is indicated, which cannot be achieved with DOVATO. DOVATO should be discontinued and the individual components should be used to construct the treatment regimen. (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Use in the elderly
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Paediatric use
DOVATO is not currently recommended for the treatment of children less than 12 years of age as the necessary dose adjustment cannot be made. Clinical data is currently not available for this combination. Physicians should refer to the individual product information for dolutegravir and lamivudine.

Effects on laboratory tests
Increases in serum creatinine occurred within the first 4 weeks of treatment with dolutegravir plus lamivudine and remained stable through 48 weeks. A mean change from baseline of 10.3 μmol/L (range: -36.3 μmol/L to 55.7 μmol/L) was observed after 48 weeks of treatment. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see Section 5.1 PHARMACODYNAMICS, Effects on renal function).

Small increases in total bilirubin (without clinical jaundice) were observed with dolutegravir plus lamivudine. These changes are not considered clinically relevant as they likely reflect competition between dolutegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see Section 5.2 PHARMACOKINETIC PROPERTIES, Metabolism).

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Caution should be given to co-administering medications (prescription and non-prescription) that may reduce the exposure of dolutegravir, lamivudine or medications that may have their exposure changed by DOVATO).

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

Since the recommended dose of dolutegravir is 50 mg twice daily for patients taking etravirine (without boosted protease inhibitors), efavirenz, nevirapine rifampicin, tipranavir/ritonavir, carbamazepine, phenytoin, phenobarbital and St. John’s wort, the use of DOVATO is not recommended for patients taking these medicines.

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

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

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of DOVATO with metformin, to maintain glycaemic control.

As DOVATO contains dolutegravir and lamivudine, any interactions that have been identified with these agents individually may occur with DOVATO. Due to the different routes of metabolism and elimination, no clinically significant drug interactions are expected between dolutegravir and lamivudine.

Effect of DOVATO on the pharmacokinetics of other agents

Effect of dolutegravir on the pharmacokinetics of other agents
Dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of cytochrome P450 enzymes, uridine diphosphate glucuronosyl transferase (UGT), or the transporters P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, multidrug resistance-associated protein (MRP) 2 or MRP4.

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50} > 50 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, uridine diphosphate glucuronosyl transferase (UGT)1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, MRP2 or MRP4. *In vitro,* dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. *In vivo*, dolutegravir did not have an effect on midazolam, a CYP3A4 probe. Based on these data, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

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

In vitro, dolutegravir inhibited the renal organic cation transporter 2 (OCT2) (IC_{50} = 1.93 μM), multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 μM) and MATE2-K (IC_{50} = 24.8 μM). Given the *in vivo* exposure, dolutegravir has a low potential to affect the transport of MATE2-K substrates *in vivo. In vivo* dolutegravir increases plasma concentrations of drugs in which excretion is dependent upon OCT2 or MATE1 (for example dofetilide, pilsicainide, fampridine or metformin) (see Table 1).

In vitro, dolutegravir inhibited the basolateral renal transporters: organic anion transporter (OAT) 1 (IC_{50} = 2.12 μM) and OAT3 (IC_{50} = 1.97 μM). However, dolutegravir had no notable effect on the *in vivo* pharmacokinetics of the OAT substrates tenofovir and para aminohippurate, and therefore has low propensity to cause drug interactions via inhibition of OAT transporters.

Effect of lamivudine on the pharmacokinetics of other agents
Lamivudine does not inhibit or induce CYP enzymes (such as CYP3A4, CYP2C9 or CYP2D6) and demonstrates no or weak inhibition of the drug transporters OATP1B1, OATP1B3, BCRP and Pgp, OCT3, MATE1 or MATE2-K. Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these enzymes or transporters.

Although lamivudine is an inhibitor of OCT1 and OCT2 *in vitro*, it has low potential to affect the plasma concentrations of substrates of these transporters at the therapeutic dose (300mg)/exposure.

Effect of other agents on the pharmacokinetics of DOVATO

Effect of other agents on the pharmacokinetics of dolutegravir
Dolutegravir is eliminated mainly through metabolism by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, Pgp, and BCRP *in vitro;* therefore drugs that induce those enzymes or transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Co-administration of dolutegravir and other drugs that inhibit these enzymes or transporters may increase dolutegravir plasma concentration (see Table 1).

In vitro, dolutegravir is not a substrate of human OATP1B1, OATP1B3, or OCT1, therefore drugs that solely modulate these transporters are not expected to affect dolutegravir plasma concentration.

Rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir each reduced the plasma concentrations of dolutegravir significantly and require dolutegravir dose adjustment to 50 mg twice daily. A separate preparation of dolutegravir is available where a dose adjustment is required due to drug-drug interactions. An additional dose of 50 mg dolutegravir should be administered, approximately 12 hours after DOVATO. In these cases the physician should refer to the dolutegravir product information.

Effect of other agents on the pharmacokinetics of lamivudine
The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Lamivudine is not significantly metabolised by CYP enzymes. Although lamivudine is a substrate of BCRP and Pgp *in vitro*, inhibitors of these efflux transporters are unlikely to affect the disposition of lamivudine due to its high bioavailability. Lamivudine is an *in vitro* substrate of MATE1, MATE2-K and OCT2. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations however; the resulting increase was of such magnitude that a dose adjustment is not recommended as it is not expected to have clinical significance. Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Selected drug interactions are presented in Tables 1 and 2. Recommendations are based on either drug interaction studies performed in adults or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. DOVATO is not expected to be co-administered with other HIV-1 antiviral agents and information is provided for reference.

Table 1: Drug interactions studied with dolutegravir

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine, or Concomitant Drug*	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitor:	Dolutegravir ↓ AUC ↓ 71%	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. Since the recommended dose of dolutegravir is 50 mg twice daily for patients taking etravirine

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir, Lamivudine, or Concomitant Drug***	**Clinical Comment**
Etravirine (ETR) without boosted protease inhibitors	C_{max} ↓ 52% Cτ ↓ 88% ETR ↔	without boosted protease inhibitors., DOVATO is not recommended for patients taking etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV+ETR)	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% LPV ↔ RTV ↔	Lopinavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir + Etravirine (DRV/RTV+ETR)	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% Cτ ↓ 36% DRV ↔ RTV ↔	Darunavir/ritonavir and etravirine did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Efavirenz (EFV)	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75% EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz, the co-administration of efavirenz with DOVATO is not recommended
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine, the co-administration of nevirapine with DOVATO is not recommended.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% Cτ ↑ 180% ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV+RTV)	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121% ATV ↔ RTV ↔	Atazanavir/ritonavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Tipranavir/ritonavir (TPV+RTV)	Dolutegravir ↓ AUC ↓ 59%	Tipranavir/ritonavir decreases dolutegravir concentrations. Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with tipranavir/ritonavir, The co-

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine, or Concomitant Drug*	Clinical Comment
	C_{max} ↓ 47% Cτ ↓ 76% TPV ↔ RTV ↔	administration of tipranavir/ritonavir with DOVATO is not recommended
Protease Inhibitor: Fosamprenavir/ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35% C_{max} ↓ 24% Cτ ↓ 49% FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients.
Protease Inhibitor: Lopinavir/ritonavir (LPV+RTV)	DTG ↔ AUC ↓ 4% C_{max} ↔ Cτ ↓ 6% LPV ↔ RTV ↔	Lopinavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Protease Inhibitor: Darunavir/ritonavir (DRV+RTV)	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% Cτ ↓ 38% DRV ↔ RTV ↔	Darunavir/ritonavir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir (TDF)	Dolutegravir ↔ AUC ↔ C_{max} ↓3% Cτ ↓ 8% Tenofovir ↔ AUC ↑ 12% C_{max} ↑ 9% Cτ ↑ 19%	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.
Other Agents		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Dofetilide or pilsicainide co-administration with dolutegravir is contraindicated due to potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration.
Fampridine	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; coadministration has not

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine, or Concomitant Drug*	Clinical Comment
		been studied. Fampridine co-administration with dolutegravir is contraindicated.
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% $C\tau$ ↓ 73%	Carbamazepine decreased dolutegravir plasma concentration. Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with carbamazepine, DOVATO is not recommended for patients taking carbamazepine.
Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	Dolutegravir ↓	Co-administration with these metabolic inducers has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. The effect of these metabolic inducers on dolutegravir exposure is likely similar to carbamazepine. Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers, DOVATO is not recommended for patients taking these metabolic inducers.
Oxcarbazepine	Dolutegravir ↓	This interaction has not been studied. Although an inducer of CYP3A4, based on data from other inducers, a clinically significant decrease in dolutegravir is not expected. No dose adjustment is necessary.
Omeprazole	Dolutegravir ↔	Omeprazole did not change dolutegravir plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.
Antacids containing polyvalent cations (e.g., Mg, Al)	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% C24 ↓ 74%	Co-administration of antacids containing polyvalent cations decreased dolutegravir plasma concentration. DOVATO is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
Calcium supplements	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39%	DOVATO is recommended to be administered 2 hours before or 6 hours after taking products containing calcium, or alternatively, administer with food.
Iron supplements	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56%	DOVATO is recommended to be administered at least 2 hours before or 6 hours after taking products containing iron, or alternatively, administer with food.
Metformin	Metformin ↑ When co-administered with dolutegravir 50 mg QD: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50 mg BID: Metformin	Co-administration of DOVATO may increase metformin plasma concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of DOVATO with metformin, to maintain glycaemic control.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine, or Concomitant Drug*	Clinical Comment
	AUC ↑ 145% C_{max} ↑ 111%	
Rifampicin	Dolutegravir ↓ (by rifampicin) AUC ↓ 54% C_{max} ↓ 43% Cτ ↓ 72%	Rifampicin decreased dolutegravir plasma concentration. Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin the co-administration of DOVATO with rifampicin is not recommended
Rifabutin	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% Cτ ↓ 30%	No dose adjustment is necessary.
Oral contraceptives (Ethinyl oestradiol (EE) and Norelgestromin (NGMN))	Effect of dolutegravir: EE ↔ AUC ↑ 3% C_{max} ↓ 1% Cτ ↑ 2% Effect of dolutegravir: NGMN ↔ AUC ↓ 2% C_{max} ↓ 11% Cτ ↓ 7%	Dolutegravir did not change ethinyl estradiol and norelgestromin plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with DOVATO.
Methadone	Effect of dolutegravir: Methadone ↔ AUC ↓ 2% C_{max} ↔ 0% Cτ ↓ 1%	Dolutegravir did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when Co-administered with DOVATO.
Daclatasvir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.

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

Table 2: Drug Interactions studied with lamivudine

Concomitant Drug Class: Drug Name	Effect on Concentration of lamivudine or Concomitant Drug	Clinical Comment
Trimethoprim/sulfamethoxazole (Co-trimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see Section 4.2 DOSAGE AND METHOD OF ADMINISTRATION). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* pneumonia and toxoplasmosis has not been studied. DOVATO is not recommended for subjects with CrCl of <30 mL/min.
Emtricitabine		This interaction has not been studied. Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.
Other Agents		
Sorbitol solution (3.2 g, 10.2 g, 13.4 g)	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%, 55%.	When possible, avoid chronic coadministration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of dolutegravir or lamivudine on human male or female fertility. No studies on the effect on fertility have been conducted with DOVATO. Individually, animal studies indicate no effects of dolutegravir or lamivudine on male or female fertility. Dolutegravir did not affect male or female fertility in rats at doses up to 1,000 mg/kg/day, associated with an exposure level 33 times the clinical exposure based on AUC at the maximum recommended dose of 50 mg once daily (QD). Similarly, lamivudine did not affect male or female fertility in rats at doses up to 2,000 mg/kg twice daily, associated with exposure levels of up to 94 times based on AUC and up to 41 times based on C_{max}, the clinical exposure at 300 mg QD.

Use in pregnancy
(Category B3)
DOVATO should be used during pregnancy only if the benefit to the mother outweighs the possible risk to the foetus. Women of childbearing potential (WOCBP) should undergo pregnancy testing before initiation of DOVATO and should be informed about the potential risk of neural tube defects with dolutegravir and counselled about the use of effective contraception. It is recommended that pregnancy testing is conducted prior to initiation of DOVATO. If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on DOVATO, the risks and benefits of continuing DOVATO versus switching to another antiretroviral regimen should be discussed with the patient. Factors to consider should include feasibility of switching, tolerability, ability to maintain viral suppression, actual gestational age, risk of transmission to the infant and the available data around the potential risk of neural tube defects and other pregnancy outcomes for dolutegravir and alternative antiretroviral drugs.

No studies on the effect on embryofetal development have been conducted with DOVATO.

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

The seven neural tube defect cases reported with dolutegravir included three cases of myelomeningocele, two cases of encephalocele, and one case each of anencephaly and iniencephaly. In the same study, an increased risk of neural tube defects was not identified in women who started dolutegravir during pregnancy. Two infants out of 4,448 (0.04%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with five infants out of 6,748 (0.07%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy.

Further safety data from other sources including the Antiretroviral Pregnancy Registry, clinical trials, and post-marketing data are currently insufficient to further address the risk of neural tube defects with dolutegravir. There have been spontaneous reports of neural tube defects with use of dolutegravir-containing regimens. A causal relationship of these events to the use of dolutegravir has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As most neural tube defects occur within the first 4 weeks of foetal development (approximately 6 weeks after the last menstrual period) this potential risk would concern women exposed to dolutegravir at the time of conception and in early pregnancy.

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

In animal reproductive toxicity studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified. Dolutegravir was shown to cross the placenta in animals.

Oral administration of dolutegravir to pregnant rats at doses up to 1,000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (38 times the human clinical exposure based on AUC at the maximum recommended dose of 50 mg QD).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation was associated with marked maternal toxicity but did not elicit developmental toxicity or teratogenicity in the offspring (0.56 times the clinical exposure based on AUC).

Lamivudine was associated with findings in animal reproductive toxicity studies. Lamivudine was not teratogenic in animal studies, but there were indications of an increase in early embryonic deaths in rabbits at exposure levels comparable to those achieved in man (based on C_{max} and AUC). However, there was no evidence of embryonic loss in rats at exposure levels of approximately 21 times the clinical exposure (based on C_{max}).

Dolutegravir and lamivudine use during pregnancy have been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 600 and 12,500 women, respectively (as of July 2019). Available human data from the APR do not show an increased risk of major birth defects for dolutegravir or lamivudine compared to the background rate (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

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

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

It is expected that dolutegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans.

A study in lactating rats showed that the concentration of lamivudine in milk, was more than four times higher than that in maternal plasma.

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

concentrations to those found in serum. In other studies, following repeat oral dose of 150 mg lamivudine twice daily (given either in combination with 300 mg zidovudine or as Combivir or Trizivir) the breast milk: maternal plasma ratio ranged between 0.6 and 3.3. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/mL and were not detectable in one of the studies (assay sensitivity 7 ng/mL). Intracellular lamivudine triphosphate (active metabolite of lamivudine) levels in breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compound measured is unknown.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data
DOVATO contains dolutegravir plus lamivudine, therefore the adverse drug reactions (ADRs) associated with these individual components may be expected.

Clinical safety data with DOVATO are limited. The safety assessment of DOVATO in HIV–1-infected treatment-naïve adult subjects with viral load ≤500,000 HIV-1 RNA copies/mL, is based on the pooled Week 96 analyses of data from 2 identical, multicentre, double-blind, controlled trials, GEMINI-1 and GEMINI-2. A total of 716 HIV-1 infected adults with no antiretroviral treatment history received at least one dose of dolutegravir 50 mg plus lamivudine 300 mg with a mean duration of exposure of 99 weeks (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

The safety of DOVATO in virologically suppressed adults was based on Week 48 data from 740 subjects in a randomized, parallel-group, open-label, multicenter, non-inferiority controlled trial (TANGO). Subjects who were on a stable suppressive tenofovir alafenamide-based regimen (TBR) were randomized to receive DOVATO once daily or continue with TBR for up to 200 weeks (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product. A causal relationship does not necessarily exist between an AE and the medicinal product, but is at least suspected. An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended and for which a causal relationship is at least a reasonable possibility and cannot be ruled out.

Adverse events

The most common adverse events reported in ≥5% of subjects in the group that received DOVATO in the GEMINI studies were: nasopharyngitis, diarrhoea, headache, upper respiratory tract infection, syphilis, pharyngitis, back pain, influenza, bronchitis, insomnia and Vitamin D deficiency. A summary of adverse events greater than or equal to 3% is provided in Table 3.

Table 3: Summary of adverse events reported in ≥3% of subjects in any treatment group by overall frequency in GEMINI-1 and GEMINI-2 (Week 96 pooled analysis)

Preferred Term	Dolutegravir plus lamivudine N=716 n(%)	Dolutegravir plus TDF*/emtricitabine N=717 n(%)
Infections and infestations		
Nasopharyngitis	71 (10%)	114 (16%)
Upper respiratory tract	70 (10%)	56 (8%)
Syphilis	49 (7%)	52 (7%)
Pharyngitis	47 (7%)	48 (7%)
Influenza	35 (5%)	36 (5%)
Bronchitis	36 (5%)	30 (4%)
Gastroenteritis	31 (4%)	29 (4%)
Tonsillitis	24 (3%)	21 (3%)
Sinusitis	23 (3%)	19 (3%)
Gonorrhoea	22 (3%)	19 (3%)
Gastrointestinal disorders		
Diarrhoea	89 (12%)	93 (13%)
Nausea	29 (4%)	58 (8%)
Haemorrhoids	29 (4%)	25 (3%)
Abdominal pain	22 (3%)	27 (4%)
Nervous system disorders		
Headache	79 (11%)	87 (12%)
Dizziness	17 (2%)	25 (3%)
Psychiatric disorders		
Insomnia	34 (5%)	56 (8%)
Anxiety	30 (4%)	24 (3%)
Depression	25 (3%)	23 (3%)
Musculoskeletal and connective tissue disorders		
Back pain	41 (6%)	39 (5%)
Arthralgia	20 (3%)	38 (5%)
Respiratory, thoracic and mediastinal disorders		
Cough	23 (3%)	33 (5%)
Oropharyngeal pain	24 (3%)	26 (4%)
General disorders and administration site conditions		
Influenza like illness	29 (4%)	25 (3%)
Fatigue	26 (4%)	20 (3%)
Pyrexia	27 (4%)	19 (3%)
Metabolism and nutrition disorders		
Vitamin D deficiency	34 (5%)	25 (3%)

Preferred Term	Dolutegravir plus lamivudine N=716 n(%)	Dolutegravir plus TDF*/emtricitabine N=717 n(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Anogenital warts	23 (3%)	31 (4%)

* tenofovir disoproxil fumarate

The rates of adverse events leading to discontinuation in the pooled analysis were 3% of subjects in both treatment arms. The most common adverse events leading to discontinuation were psychiatric disorders: 1% of subjects in both treatment arms. The incidence of serious adverse events was 9% in both treatment arms.

Adverse drug reactions

The ADRs observed for the combination of dolutegravir and lamivudine in an analysis of pooled data from Phase 3 clinical trials (GEMINI-1 and GEMINI-2) were generally consistent with the ADR profiles and severities for the individual components when administered with other antiretroviral agents.

Treatment emergent ADRs (all grades) observed in at least 2% of subjects in either treatment arm of the Week 96 pooled analysis from GEMINI-1 and GEMINI-2 trials are provided in Table 4.

Table 4: Adverse Reactions (All Grades) ≥1% Frequency in either Treatment Arm in Treatment-Naïve Subjects in GEMINI-1 and GEMINI-2 (Week 96 Pooled Analysis)

Adverse Reaction	Dolutegravir plus Lamivudine (N = 716) N (%)	Dolutegravir plus TDF*/emtricitabine (N = 717) N (%)
Nervous System		
Headache[a]	21 (3%)	30 (4%)
Dizziness	8 (1%)	13 (2%)
Somnolence	8 (1%)	7 (<1%)
Gastrointestinal		
Diarrhoea	15 (2%)	19 (3%)
Nausea	14 (2%)	39 (5%)
Psychiatric Disorders		
Insomnia	15 (2%)	19 (3%)
Anxiety	11 (2%)	5 (<1%)

Adverse Reaction	Dolutegravir plus Lamivudine (N = 716) N (%)	Dolutegravir plus TDF*/emtricitabine (N = 717) N (%)
General disorders and administration site conditions		
Fatigue	11 (2%)	6 (<1%)

* tenofovir disoproxil fumarate

The ADRs observed for the combination of dolutegravir and lamivudine in these studies were generally consistent with the ADR profiles and severities for the individual components when administered with other antiretroviral agents. A single treatment emergent ADR [Nervous system disorders: somnolence; frequency common] was observed with the combination which was not listed in the product information for dolutegravir or lamivudine.

The ADRs observed in the Phase 3 clinical trial (TANGO) conducted in antiretroviral therapy experienced, virologically suppressed adult subjects who received DOVATO, were generally consistent with the ADR profiles and severities for the individual components when administered with other antiretroviral agents. Insomnia, observed in the DOVATO arm, was the only treatment emergent ADR observed in at least 2% of subjects in either treatment arm of the TANGO trial.

ADRs identified in an analysis of pooled data from Phase 2b and Phase 3 clinical trials of the individual components are listed in Table 5 below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000) and very rare (<1/10,000), including isolated reports.

In addition to the adverse reactions included from clinical trial data, adverse reactions identified during post-marketing use of dolutegravir and/or lamivudine with other antiretroviral agents have also been listed in Table 5 below. These events have been chosen for inclusion due to a potential causal connection to dolutegravir and/or lamivudine.

Table 5: Adverse Reactions with the Individual Components of DOVATO

System	Frequency*	Dolutegravir	Lamivudine
Blood and lymphatic systems disorders	Uncommon		Neutropenia Anaemia Thromobocytopenia
	Very rare		Pure red cell aplasia#
Immune system disorders	Uncommon	Hypersensitivity Immune Reconstitution Syndrome (*see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*)	

Psychiatric disorders	Common	Suicidal ideation (particularly in patients with a pre-existing history of depression or psychiatric illness) Depression Anxiety Insomnia Abnormal dreams	
	Uncommon	suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)	
Metabolism and nutrition	Common		Hyperlactataemia[#]
	Rare		Lactic acidosis[1#]
Nervous system disorders	Very common	Headache	
	Common	Dizziness	Headache
	Very rare		Paraesthesiae[#] Peripheral neuropathy has been reported although a causal relationship to treatment is uncertain[#]
Gastrointestinal disorders	Very common	Nausea Diarrhoea	
	Common	Abdominal pain Vomiting Flatulence Upper abdominal pain Abdominal discomfort	Nausea Vomiting Upper abdominal pain Diarrhoea
	Rare		Rises in serum amylase[#] Pancreatitis, although a causal relationship to lamivudine is uncertain[#]
Hepatobiliary disorders	Uncommon	Hepatitis	Transient rises in liver enzymes (AST, ALT)
	Rare	Acute hepatic failure[2#]	
Skin and subcutaneous tissue disorders	Common	Rash Pruritus	Rash
	Common		Alopecia[#]
Musculoskeletal and connective tissue disorders	Common		Arthralgia[#] Muscle disorders[#]
	Uncommon	Arthralgia[#] Myalgia[#]	
	Rare		Rhabdomyolysis[#]

Investigations	Uncommon	Weight increased#	
General disorders and administration site conditions	Common	Fatigue	Fatigue Malaise Fever

* Frequencies are assigned based on the maximum frequencies observed in the pooled GEMINI studies, studies with the individual components or post-marketing use of the individual components.

Post marketing events reported with individual components

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

[2]Acute hepatic failure has been reported in a dolutegravir-containing regimen. The contribution of dolutegravir in these cases is unclear.

Laboratory abnormalities

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity in ≥2% of subjects are presented in Table 6. The mean change from baseline observed for selected lipid values is presented in Table 7.

Table 6: Selected Laboratory Abnormalities (Grades 2 to 4) in GEMINI-1 and GEMINI-2 (Week 96 Pooled Analysis)

Laboratory Parameter Preferred Term	Dolutegravir plus lamivudine (n = 716)	Dolutegravir plus TDF*/emtricitabine (n = 717)
ALT Grade 2 (> 2.5 – 5.0 x ULN) Grade 3 to 4 (> 5.0 x ULN)	 3% 3%	 4% 3%
AST Grade 2 (> 2.5 – 5.0 x ULN) Grade 3 to 4 (> 5.0 x ULN)	 4% 3%	 4% 3%
Total Bilirubin Grade 2 (1.6 – 2.5 x ULN) Grade 3 to 4 (> 2.5 x ULN)	 2% 1%	 3% < 1%
Creatine kinase Grade 2 (6.0 – 9.9 x ULN) Grade 3 to 4 (> 10.0 x ULN)	 4% 6%	 4% 7%
Hyperglycaemia Grade 2 (6.95-13.89 mmol/L) Grade 3 to 4 (> 13.89 mmol/L)	 9%	 6%

Laboratory Parameter Preferred Term	Dolutegravir plus lamivudine (n = 716)	Dolutegravir plus TDF*/emtricitabine (n = 717)
	< 1%	< 1%
Hypophosphataemia Grade 2 (0.65-0.81 mmol/L) Grade 3 to 4 (< 0.65 mmol/L)	9% 1%	10% 1%
Lipase Grade 2 (> 1.5 – 3.0 x ULN) Grade 3 to 4 (> 3.0 x ULN)	6% 2%	6% 4%

ULN = Upper Limit of Normal * tenofovir disoproxil fumarate

Table 7: Mean Change from Baseline in Fasted Lipid Values in GEMINI-1 and GEMINI-2 (Week 96 Pooled Analysis[a])

Laboratory Parameter Preferred Term	Dolutegravir plus lamivudine (n = 716)	Dolutegravir plus TDF*/emtricitabine (n = 717)
Cholesterol (mmol/L)	0.39	-0.14
HDL cholesterol (mmol/L)	0.19	0.08
LDL cholesterol (mmol/L)	0.16	-0.17
Triglycerides (mmol/L)	0.13	-0.12
Total cholesterol/HDL cholesterol ratio	-0.13	-0.42

[a] Subjects on lipid-lowering agents at baseline are excluded (dolutegravir plus lamivudine, n = 30; dolutegravir plus tenofovir/emtricitabine FDC, n = 23). Lipid last observation carried forward data were used such that the last available fasted, on-treatment lipid value prior to the initiation of a lipid-lowering agent is used in place of future observed values. A total of 40 and 16 subjects receiving dolutegravir plus lamivudine and dolutegravir plus tenofovir/emtricitabine FDC, respectively, initiated lipid-lowering agents post-baseline.

* tenofovir disoproxil fumarate

Paediatric population

There are no clinical study data with DOVATO in the paediatric population.

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

Lamivudine has been investigated separately, and as a part of a dual nucleoside backbone, in combination antiretroviral therapy to treat ART- naïve and ART- experienced HIV- infected

paediatric patients (data available on the use of lamivudine in children less than three months are limited). No additional types of undesirable effects have been observed beyond those characterised for the adult population.

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

4.9 OVERDOSE

Symptoms and signs

There is currently limited experience with over-dosage in dolutegravir. Limited experience of single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs, apart from those listed as adverse reactions.

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

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

If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM. *In vitro,* dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex ($t_{½}$ 71 hours).

Lamivudine is a NRTI, and is a potent, selective inhibitor of HIV-1 and HIV-2. Lamivudine is metabolised sequentially by intracellular kinases to the respective triphosphate (TP) which is the active moiety with an extended intracellular half-life supporting once daily dosing (see 5.2 PHARMACOKINETIC PROPERTIES, Excretion). Lamivudine-TP is a substrate for and competitive inhibitor of HIV reverse transcriptase (RT). However, its main antiviral activity is

through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine-TP shows significantly less affinity for host cell DNA polymerases.

Pharmacodynamic effects

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

Antiviral activity in cell culture
Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 in peripheral blood mononuclear cells (PBMCs) and MT-4 cells with mean EC_{50}s of 0.5 nM to 2.1 nM.

In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse clade B isolates, dolutegravir demonstrated antiviral potency similar to laboratory strains, with a mean EC_{50} of 0.52 nM. When tested in PBMC assays against a panel consisting of 24 HIV-1 clinical isolates [group M (clade A, B, C, D, E, F and G) and group O] and 3 HIV-2 clinical isolates, the geometric mean EC_{50} was 0.20 nM and EC_{50} values ranged from 0.02 to 2.14 nM for HIV-1, while the geometric mean EC_{50} was 0.18 nM and EC_{50} values ranged from 0.09 to 0.61 nM for HIV-2 isolates.

The antiviral activity of lamivudine against HIV 1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 0.17 µM. The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.002 to 0.120 µM in PBMCs.

Antiviral activity in combination with other antiviral agents
In vitro data with dolutegravir combined with lamivudine are not available.

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

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

Effect of human serum and serum proteins
The protein adjusted EC_{90} (PA-IC_{90}) in PBMCs for dolutegravir was estimated to be 64 ng/mL. Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve subjects was 1.20 μg/mL, 19 times higher than the estimated PA-EC_{90}.

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

Resistance in vitro and in vivo (dolutegravir)
Dolutegravir-resistant viruses were selected in studies of potential resistance using different wild type strains and clades of HIV-1. Amino acid substitutions that emerged during passaging included E92Q, G193E, G118R, S153F or Y and R263K, and were associated with decreased susceptibility to dolutegravir of 1.3- to 10-fold.

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

Treatment-naïve HIV-1 infected subjects receiving dolutegravir: No INI-resistant mutations or treatment emergent resistance to the NRTI backbone therapy were isolated with dolutegravir 50 mg once daily in treatment–naïve studies.

Resistance in vitro and in vivo (lamivudine)

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*. Studies in vitro indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Resistance in vivo (dolutegravir plus lamivudine)

None of the eleven subjects in the dolutegravir plus lamivudine group or the seven subjects in the dolutegravir plus tenofovir disoproxil/emtricitabine group that met the protocol-defined confirmed virologic withdrawal (CVW) criteria across the pooled GEMINI-1 and GEMINI-2 studies through Week 96 had emergent INSTI or NRTI resistance substitutions. No subjects in the dolutegravir plus lamivudine group, and one subject in the tenofovir alafenamide based regimen group met the protocol-defined CVW criteria in the TANGO study through Week 48, and there were no emergent INSTI or NRTI resistance substitutions.

Cross-resistance
Site-directed INSTI mutant virus: Dolutegravir activity was determined against a panel of 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions). The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and

substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference).

Recombinant clinical isolates: Dolutegravir activity was measured for 705 raltegravir resistant recombinant isolates from clinical practice; 93.9% (662/705) of the isolates had a dolutegravir FC ≤ 10. Dolutegravir had a ≤ 10 FC against 67 (73%) of the 92 clinical isolates with Q148 + ≥ 2 INSTI-resistance substitutions and 168 (91%) of the 184 isolates with Q148 + 1 INSTI resistance substitutions.

Cross-resistance conferred by the M184V reverse transcriptase: Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors. Viruses containing lamivudine resistance-associated mutations (including M184V/I, and K65R/E/N) may exhibit cross-resistance *in vitro* and *in vivo*. The M184V mutation can confer resistance to abacavir, didanosine and emtricitabine; the K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, stavudine, and tenofovir.

Resistance patterns may change, and the most up-to-date information in conjunction with resistance testing should be used to inform the choice of therapy.

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

Similar studies were not conducted with lamivudine.

Effects on renal function
The effect of dolutegravir on serum creatinine clearance (CrCl), glomerular filtration rate (GFR) using iohexol as the probe and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was evaluated in an open-label, randomised, 3 arm, parallel, placebo-controlled study in 37 healthy subjects, who were administered dolutegravir 50 mg once daily (n=12), 50 mg twice daily (n=13) or placebo once daily (n=12) for 14 days. A modest decrease in CrCl was observed with dolutegravir within the first week of treatment, consistent with that seen in clinical trials. Dolutegravir at both doses had no significant effect on GFR or ERPF. These data support *in vitro* studies which suggest that the small increases in creatinine observed in clinical trials are due to the nonpathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

Clinical trials

Antiretroviral naïve subjects
The efficacy of DOVATO is supported by data from two identical 148-week, Phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority controlled trials (GEMINI-1 [204861] and GEMINI-2 [205543]). A total of 1433, HIV-1 infected antiretroviral treatment-naïve adult subjects, defined as having had ≤10 days of prior therapy with any

antiretroviral agent following a diagnosis of HIV-1 infection, received treatment in the trials. Subjects with pre-existing viral resistance (based on the presence of any major resistance-associated mutation), severe hepatic or renal impairment, HBV positive status or those requiring hepatitis C virus (HCV) therapy were excluded from the trials. HIV-2 infected subjects were not evaluated.

Subjects were enrolled with a screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL. Subjects were randomised to a two-drug regimen of dolutegravir 50 mg plus lamivudine 300 mg administered once daily or dolutegravir 50 mg plus tenofovir/emtricitabine 300/200 mg FDC administered once daily. The primary efficacy endpoint for each GEMINI trial was the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 (Snapshot algorithm for the ITT-E population).

At baseline, in the pooled analysis, the median age of subjects was 33 years (18 – 72 years), 15% were female, 69% were white, 9% were CDC Stage 3 (AIDS), 20% had HIV-1 RNA >100,000 copies/mL, and 8% had CD4+ cell count less than 200 cells per mm3; these characteristics were similar between studies and treatment arms.

In the primary week 48 analysis, dolutegravir plus lamivudine was non-inferior to dolutegravir plus tenofovir/emtricitabine FDC in GEMINI-1 and GEMINI-2 studies. This was supported by the pooled analysis, see Table 8.At 96 weeks in the GEMINI-1 and GEMINI-2 studies, the dolutegravir plus lamivudine group (86% with plasma HIV-1 RNA < 50 copies/mL [pooled data]) remained non-inferior to the dolutegravir plus tenofovir/emtricitabine FDC group (90% with plasma HIV-1 RNA < 50 copies/mL [pooled data]). The adjusted difference in proportions and 95% CI was -3.4% (6.7, 0.0) (Table 8). The results of the pooled analysis were in line with those of the individual studies, for which the secondary endpoint (difference in proportion of subjects with <50 copies/mL plasma HIV-1 RNA at Week 96 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus tenofovir/emtricitabine FDC) was met. The adjusted differences of -4.9 (95% CI: -9.8; 0.0) for GEMINI-1 and -1.8 (95% CI: -6.4; 2.7) for GEMINI-2 were within the prespecified non-inferiority margin of -10%.

Table 8: Virologic Outcomes of Randomised Treatment of GEMINI at Week 48 and 96 (Snapshot algorithm for the ITT-E population)

	GEMINI-1 and GEMINI-2 Pooled Data*			
	Week 48		Week 96	
	DTG + LAM N=716	DTG + TDF/FTC N=717	DTG + LAM N=716	DTG + TDF/FTC N=717
HIV-1 RNA <50 copies/mL	91%	93%	86%	90%
Treatment Difference† (95% confidence intervals)	-1.7 (-4.4, 1.1)		-3.4% (-6.7, 0.0)	
Virologic non response	3%	2%	3%	2%
Reasons				
Data in window and ≥50 copies/mL	1%	<1%	<1%	<1%
Discontinued for lack of efficacy	<1%	<1%	1%	<1%
Discontinued for other reasons and ≥50 copies/mL	<1%	<1%	<1%	<1%
Change in ART	<1%	<1%	<1%	<1%
No virologic data	6%	5%	11%	9%
Reasons				
Discontinued study due to adverse event or death	1%	2%	3%	3%
Discontinued study for other reasons	4%	3%	8%	5%
Missing data during window but on study	<1%	0%	0%	<1%
HIV-1 RNA <50 copies/mL by baseline covariates				
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Baseline Plasma Viral Load (copies/mL)				
≤100,000	526 / 576 (91%)	531 / 564 (94%)	499 / 576 (87%)	510 / 564 (90%)
>100,000	129 / 140 (92%)	138 / 153 (90%)	117 / 140 (84%)	132 / 153 (86%)

Baseline CD4+ (cells/ mm^3)				
≤200	50 / 63 (79%)	51 / 55 (93%)	43 / 63 (68%)	48 / 55 (87%)
>200	605 / 653 (93%)	618 / 662 (93%)	573 / 653 (88%)	594 / 662 (90%)
Gender				
Male	555 / 603 (92%)	580 / 619 (94%)	523 / 603 (87%)	557 / 619 (90%)
Female	100 / 113 (88%)	89 / 98 (91%)	93 / 113 (82%)	85 / 98 (87%)
Race				
White	451 / 484 (93%)	473 / 499 (95%)	429 / 484 (89%)	453 / 499 (91%)
African-American/African Heritage/Other	204 / 232 (88%)	196 / 218 (90%)	187 / 232 (81%)	189 / 218 (87%)
Age (years)				
<50	597 / 651 (92%)	597 / 637 (94%)	561 / 651 (86%)	572 / 637 (90%)
≥50	58 / 65 (89%)	72 / 80 (90%)	55 / 65 (85%)	70 / 80 (88%)

*The results of the pooled analysis are in line with those of the individual studies, for which the primary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus tenofovir/emtricitabine FDC) was met. The adjusted difference was -2.6 (95% CI: -6.7; 1.5) for GEMINI-1 and -0.7 (95% CI: -4.3; 2.9) for GEMINI-2 with a prespecified non-inferiority margin of 10%.
†Based on CMH-stratified analysis adjusting for the following baseline stratification factors: Plasma HIV-1 RNA (≤100,000 c/mL vs. >100,000 c/mL) and CD4+ cell count (≤200 cells/mm3 vs. >200◦cells/mm3). Pooled analysis also stratified by study.
Assessed using a non-inferiority margin of 10%.
N = Number of subjects in each treatment group, DTG = Dolutegravir, LAM = Lamivudine,
TDF/FTC = Tenofovir disoproxil fumarate /Emtricitabin

Virologic outcomes by baseline CD4$^+$ (cells/mm^3) in GEMINI-1 and GEMINI-2 at Week 96 are shown in Table 9. In both trials, lower response rates (HIV-1 RNA <50 copies/mL) were observed in subjects with baseline CD4$^+$ ≤200 cells/mm^3. These findings were seen irrespective of baseline plasma HIV-1 RNA.

Table 9. Virologic Outcomes by Baseline CD4$^+$ in GEMINI-1 and GEMINI-2 Trials at Week 96 in Subjects with No Antiretroviral Treatment History

	GEMINI-1		**GEMINI-2**	
	DTG + LAM (n = 356)	**DTG + TDF/FTC (n = 358)**	**DTG + LAM (n = 360)**	**DTG + TDF/FTC (n = 359)**
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL[a]				
Baseline CD4$^+$ (cells/mm^3)				

≤200	65% (20/31)	90% (26/29)	72% (23/32)	85% (22/26)
>200	86% (280/325)	89% (294/329)	89% (293/328)	90% (300/333)

[a] Four subjects treated with dolutegravir plus lamivudine were withdrawn for treatment-related reasons (3 due to confirmed loss of virologic response and 1 due to drug-related adverse reactions). Two subjects also had HIV-1 RNA ≥50 copies/mL at Week 96 but remained in the study. The other 14 subjects treated with dolutegravir plus lamivudine who did not have HIV-1 RNA <50 copies/mL at Week 96 (based on Snapshot Algorithm) were discontinued for non–treatment-related reasons by Week 96. One subject in GEMINI-1 whose last HIV-1 RNA was 64,366 copies/mL was lost to follow-up. Three subjects receiving dolutegravir plus lamivudine with HIV-1 RNA ≥50 copies/mL at Week 48 remained in the study, all with <50 copies/mL at Week 96, 1 of which had a Week 96 HIV-1 RNA of 46 copies/mL.

The adjusted mean change from baseline in $CD4^+$ cell count based on the pooled analysis at Week 96 was 269 cells/mm^3 for the group receiving dolutegravir plus lamivudine and 259 cells/mm^3 for the group receiving dolutegravir plus tenofovir/emtricitabine FDC.

Virologically suppressed subjects

The efficacy of DOVATO in HIV-infected, antiretroviral therapy experienced, virologically suppressed subjects is supported by data from a 200-week, Phase III, randomised, open-label, multicentre, parallel-group, non-inferiority controlled trial (TANGO [204862]). A total of 741 adult HIV-1 infected subjects who were on a stable suppressive TBR received treatment in the studies. Subjects were randomised in a 1:1 ratio to receive DOVATO once daily or continue with TBR for up to 200 weeks. Randomisation was stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INSTI], or nonnucleoside reverse transcriptase inhibitor [NNRTI]). The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL (virologic nonresponse) as per the FDA Snapshot category at Week 48 (Snapshot algorithm adjusting for randomization stratification factor: Baseline Third Agent Class [INSTI, PI, NNRTI]).

At baseline the median age of subjects was 39 years, 8% were female and 21% non-white, 5% were CDC Class C (AIDS) and 98% subjects had Baseline CD4+ cell count ≥200 cells/mm3; these characteristics were similar between treatment arms. Subjects had been on ART for a median of 2.8 years and 2.9 years prior to Day 1 for the DOVATO and TBR arms, respectively. Most subjects were on INSTI-based TBR, 78% and 80% in the DOVATO and TBR arms, respectively.

The primary analysis demonstrated that DOVATO is non-inferior to TBR, with <1% of subjects in both arms experiencing virologic failure (HIV-1 RNA ≥50 c/mL) at Week 48 based on the Snapshot algorithm (Table 10).

Table 10 Virologic Outcomes of Randomised Treatment of TANGO at Week 48 (Snapshot algorithm)

	Dovato N=369	Tenofovir alafenamide based regimen N=372
HIV-1 RNA <50 copies/mL*	93%	93%
Virologic non response (≥50 copies/mL)**	<1%	<1%
Treatment Difference† (95% confidence intervals)	-0.3 (-1.2, 0.7)	
Reasons for virologic non response:		
Data in window and ≥50 copies/mL	0%	0%
Discontinued for lack of efficacy	0%	<1%
Discontinued for other reasons and ≥50 copies/mL	<1%	0%
Change in ART	0%	0%
No virologic data at Week 48 window	7%	6%
Reasons		
Discontinued study due to adverse event or death	3%	<1%
Discontinued study for other reasons	3%	6%
Missing data during window but on study	0%	<1%

*Based on an 8% non-inferiority margin, Dovato is non-inferior to TBR at Week 48 in the secondary analysis (proportion of subjects achieving <50 copies/mL plasma HIV-1 RNA) because the lower bound of the 95% CI for the adjusted treatment difference is greater than -8%, based on the Snapshot algorithm. Adjusted difference (95% CI) 0.2 (-3.4, 3.9).

**Based on a 4% non-inferiority margin, Dovato is non-inferior to TBR at Week 48 in the primary analysis (proportion of subjects with plasma HIV-1 RNA ≥50 c/mL) because the upper bound of the 95% CI for the adjusted treatment difference is less than 4%

†Based on CMH-stratified analysis adjusting for Baseline third agent class (PI, NNRTI, INSTI).

N = Number of subjects in each treatment group;

In TANGO, treatment outcomes between treatment arms were similar across the stratification factor, Baseline Third agent class (INSTI/NNRTI/PI), and across subgroups by age, sex, race, baseline CD4 cell count, CDC HIV disease stage and countries. The median change from baseline in CD4+ count at Week 48 was 22.5 cells per mm3 in subjects who switched to DOVATO and 11.0 cells per mm3 in subjects who stayed on TBR.

Antiretroviral Pregnancy Registry

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

The APR has received reports of over 12,500 exposures to lamivudine during pregnancy resulting in live birth, as of July 2019. These consist of over 5,200 exposures during the first trimester, over 7,400 exposures during the second/third trimester and included 161 and 216 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to

lamivudine in the first trimester was 3.1% (2.6, 3.6%) and in the second/third trimester, 2.9% (2.5, 3.3%).

The available data from the APR do not indicate a significant increase in risk of major birth defects for dolutegravir or lamivudine compared to the background rates in two population based surveillance systems (Metropolitan Atlanta Congenital Defects Program with defects of 2.72 per 100 live births and the Texas Birth Defects Registry with 4.17 per 100 live births). However, the APR data are currently insufficient to provide evidence regarding the risk of neural tube defects associated with dolutegravir.

Children
There are no clinical study data with DOVATO in the paediatric population.

Although adolescents were not included in the pivotal GEMINI studies evaluating treatment with DOVATO, both dolutegravir and lamivudine are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents. DOVATO consists of 50 mg dolutegravir and 300 mg lamivudine which are approved doses for adolescents ≥12 years of age weighing ≥40 kg. Prior studies have shown that dolutegravir and lamivudine pharmacokinetic (PK) exposures in adolescents are sufficiently similar to those in adults.

5.2 PHARMACOKINETIC PROPERTIES

When administered in fasted state, bioequivalence was achieved for dolutegravir, when comparing the DOVATO tablet to dolutegravir 50 mg co-administered with lamivudine 300 mg, for AUC and C_{max}.

When administered in fasted state, bioequivalence was achieved for lamivudine AUC, when comparing the DOVATO tablet to lamivudine 300 mg co-administered with dolutegravir 50 mg. Lamivudine C_{max} for the DOVATO tablet was 32% higher than lamivudine 300 mg co-administered with dolutegravir 50 mg. Following multiple oral doses of DOVATO in HIV-infected, treatment experienced subjects in the Phase III TANGO study, the steady state dolutegravir and lamivudine AUC and Cmax were similar to historical exposure.

Absorption
Dolutegravir and lamivudine are rapidly absorbed following oral administration. The absolute bioavailability of dolutegravir has not been established. The absolute bioavailability of oral lamivudine in adults is 80 to 85%. For DOVATO, the median time to maximal plasma concentrations (t_{max}) is 2.5 hours for dolutegravir and 1.0 hour for lamivudine, when dosed under fasted conditions.

Following multiple oral doses of dolutegravir 50 mg once daily, the geometric mean steady state pharmacokinetic parameter estimates are 53.6 micrograms.h/mL for AUC_{24}, 3.67 micrograms/mL for C_{max}, and 1.11 microgram/mL for C_{24}. Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days the mean steady-state C_{max} is 2.04 micrograms/mL and the mean AUC_{24} is 8.87 micrograms.h/mL.

Effect of food Administration of DOVATO with a high fat meal increased dolutegravir AUC and C_{max} by 33% and 21%, respectively, and decreased the lamivudine C_{max} by 30% compared to fasted conditions. The lamivudine AUC was not affected by a high fat meal.

These changes are not clinically significant. DOVATO may be administered 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 lamivudine showed that the mean apparent volume of distribution is 1.3 L/kg.

Dolutegravir is highly bound (approximately 99.3%) to human plasma proteins based on *in vitro* data. Binding of dolutegravir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. Free fraction of dolutegravir in plasma is estimated at approximately 0.2 to 1.1% in healthy subjects, approximately 0.4 to 0.5% in subjects with moderate hepatic impairment, and 0.8 to 1.0% in subjects with severe renal impairment and 0.5% in HIV-1 infected patients. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36%).

Dolutegravir and lamivudine are present in cerebrospinal fluid (CSF). In 12 treatment-naïve subjects receiving a regimen of dolutegravir plus abacavir/lamivudine for 16 weeks, dolutegravir concentration in CSF averaged 16.2 ng/mL at Week 2 and 12.6 ng/mL at Week 16, ranging from 3.7 to 23.2 ng/mL (comparable to unbound plasma concentration). CSF:plasma concentration ratio of dolutegravir ranged from 0.11 to 2.04%. Dolutegravir concentrations in CSF exceeded the IC_{50}, supporting the median reduction from baseline in CSF HIV-1 RNA of 2.2 log after 2 weeks and 3.4 log after 16 weeks of therapy (see Section 5.1 PHARMACODYNAMIC PROPERTIES). The mean ratio of CSF/serum lamivudine concentrations 2 to 4 h after oral administration was approximately 12%. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

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

Metabolism
Dolutegravir is primarily metabolized via UGT1A1 with a minor CYP3A component (9.7% of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged drug is low (<1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-one percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions with lamivudine is low due to the small extent of hepatic metabolism (less than 10%).

Excretion
Dolutegravir has a terminal half-life of ~14 hours and an apparent clearance (CL/F) of 0.56 L/hr.

The observed half-life of elimination for lamivudine 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 (greater than 70%) via the organic cationic transport system.

Special patient populations

Paediatric population
DOVATO has not been studied in the paediatric population.

In a paediatric study including 23 antiretroviral treatment-experienced HIV-1 infected adolescents aged 12 to 18 years of age, the pharmacokinetics of dolutegravir was evaluated in 10 adolescents and showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir exposure in paediatric subjects comparable to that observed in adults who received dolutegravir 50 mg once daily (Table 11).

Table 11: Paediatric pharmacokinetic parameters (n=10)

Age/weight	Dolutegravir Dose	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (CV%)		
		$AUC_{(0-24)}$ µg.hr/mL	C_{max} µg/mL	C_{24} µg/mL
12 to < 18 years ≥ 40 kg [a]	50 mg once daily [a]	46 (43)	3.49 (38)	0.90 (59)

[a] One patient weighing 37 kg received 35 mg once daily.

Limited data are available in adolescents receiving a daily dose of 300 mg of lamivudine. Pharmacokinetic parameters are comparable to those reported in adults.

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

Pharmacokinetic data for dolutegravir and lamivudine in subjects > 65 years old are limited.

Renal impairment
Pharmacokinetic data have been obtained for dolutegravir and lamivudine alone.

Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (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.

Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction (creatinine clearance < 50 ml/min) due to decreased clearance.

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

Hepatic impairment
Pharmacokinetic data has been obtained for dolutegravir and lamivudine individually.

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

Dolutegravir is primarily metabolised and eliminated by the liver. In a study comparing 8 subjects with moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. The effect of severe hepatic impairment (Child-Pugh score C) on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in drug metabolising enzymes
There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical trials 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). Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the pharmacokinetics of dolutegravir.

Gender
The dolutegravir exposure in healthy subjects appears to be slightly higher (~20%) in women than men based on data obtained in a healthy subject study (males n=17, females n=24). Population pharmacokinetic 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.

No clinically relevant differences in the pharmacokinetics of lamivudine have been observed between men and women.

Race
Population pharmacokinetic analyses using pooled pharmacokinetic data from Phase IIb and Phase III adult trials for dolutegravir 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 or lamivudine would be required based on the effects of race on PK parameters.

Co-infection with hepatitis B or C

Population PK analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited pharmacokinetic data on subjects with hepatitis B co-infection (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Patients co-infected with hepatitis B virus (HBV)).

Pregnancy
The pharmacokinetics of lamivudine during pregnancy are similar to that of non-pregnant adults. In humans, consistent with passive transmission of lamivudine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

There are no pharmacokinetic data on the use of dolutegravir in pregnancy.

5.3 PRECLINICAL SAFETY DATA

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

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

Lamivudine was not mutagenic in bacterial tests, but induced mutations in a mouse lymphoma assay and was clastogenic in human peripheral lymphocytes *in vitro*. In rats, lamivudine did not cause chromosomal damage in bone marrow cells *in vivo* or cause DNA damage in primary hepatocytes.

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

In long-term oral carcinogenicity studies conducted with dolutegravir no drug-related increases in tumour incidence were found in mice at doses up to 500 mg/kg/day (20 times the human systemic exposure based on AUC at the maximum recommended dose of 50 mg QD) or in rats at doses up to 50 mg/kg/day (17 times the human systemic exposure based on AUC at the maximum recommended dose).

When lamivudine was administered orally in the diet to separate groups of rodents at doses up to 2000 (mice and male rats) and 3000 (female rats) mg/kg/day, there was no evidence of a carcinogenic effect due to lamivudine in the mouse study. In the rat study there was an increased incidence of endometrial tumours at the highest dose (approximately 70 times the estimated human exposure at the recommended therapeutic dose of 300 mg daily, based on AUC). However, the relationship of this increase to treatment is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol
Magnesium stearate
Microcrystalline cellulose

Povidone
Sodium starch glycollate Type A,
Sodium stearylfumarate
Hypromellose
Macrogol 400
Titanium dioxide

6.2 INCOMPATIBILITIES

No incompatibilities have been identified.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

DOVATO tablets are supplied in opaque, white HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closures. Each bottle contains 30 film-coated tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Dolutegravir:
The chemical (IUPAC) name for dolutegravir sodium is Sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate.

Molecular formula: $C_{20}H_{18}F_2N_3NaO_5$

Molecular weight of 441.36 g/mol.

The partition coefficient (log P) for dolutegravir sodium is 2.2 and the pKa is 8.2.

Dolutegravir sodium is slightly soluble in water.

Lamivudine:
The chemical name of lamivudine is (2R,cis)-4-amino-1-[2- (hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine.

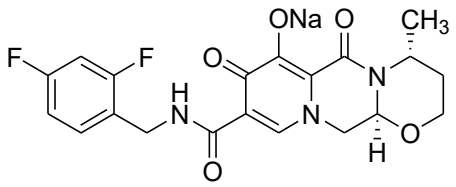
Molecular formula: $C_8H_{11}N_3O_3S$

Molecular weight of 229.3 g/mol

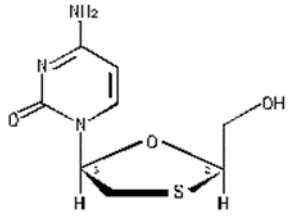
Lamivudine is highly soluble in water.

Chemical structure

The structural formula of dolutegravir sodium is:



The structural formula of lamivudine is:



CAS number
1051375-19-9 (dolutegravir sodium); 134678-17-4 (lamivudine).

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

ViiV Healthcare Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

12 September 2019

10 DATE OF REVISION

3 August 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Updated recommendation for patients with creatinine clearance of 30-49 mL/min

4.4	Updated recommendation for patients with creatinine clearance of 30-49 mL/min
4.5	Updated recommendation for patients with creatinine clearance of 30-49 mL/min
5.2	Updated recommendation for patients with creatinine clearance of 30-49 mL/min

Version 5.0