NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DOVATO 50 mg/300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

DOVATO tablets also contain mannitol.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Oval, (approximately 18.5 x 9.5 mm), biconvex, white, film coated tablet, debossed with “SV 137” on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOVATO is indicated for the treatment of Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents from 12 years of age weighing at least 40 kg, who have no known or suspected resistance to either antiretroviral component (see Section 5.1 Pharmacodynamic properties, Clinical efficacy and safety).

4.2 Dose and method of administration

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

Dose

Adults and Adolescents

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

DOVATO is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments, such as those with creatinine clearance less than 50 mL/min.

A separate preparation of dolutegravir and lamivudine is available where a dose adjustment is required due to drug-drug interactions (see Section 4.5 Interaction with other medicines and other forms of interaction).

For patients with integrase inhibitor resistance DOVATO is not recommended. In this case the physician should refer to the dolutegravir datasheet.

Special Populations

Paediatric Population

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 datasheets for dolutegravir and lamivudine.

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 (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

Whilst no dosage adjustment of dolutegravir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to decreased clearance. Therefore DOVATO is not recommended for use in patients with a creatinine clearance less than 50 mL/min (see Section 5.2 Pharmacokinetic Properties, Special patient populations).

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh grade A or B). No data are available for dolutegravir in patients with severe hepatic impairment (Child-Pugh grade C) (see Section 5.2 Pharmacokinetic Properties, Special patient populations).

Method of administration

DOVATO can be taken with or without food.

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 (also known as dalfampridine; see Section 4.5 Interaction with other medicines and other forms of interaction).

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 characterized 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.

Immune Reconstitution Syndrome:

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral 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-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

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

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

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

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

Opportunistic infections:

Patients receiving 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.

Drug 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 (see Section 4.5 Interaction with other medicines and other forms of interaction).

The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir, (see Section 4.5 Interaction with other medicines and other forms of interaction).

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 (see Section 4.5 Interaction with other medicines and other forms of interaction).

DOVATO is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements, or alternatively, administered with food (see Section 4.5 Interaction with other medicines and other forms of interaction).

Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of DOVATO with metformin, to maintain glycaemic control (see Section 4.5 Interaction with other medicines and other forms of interaction).

4.5 Interaction with other medicines and other forms of interaction

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 Dolutegravir and Lamivudine 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, UGT1A1 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 (e.g., reverse transcriptase and protease inhibitors, abacavir, zidovudine, maraviroc, opioid analgesics, antidepressants, statins, azole antifungals, proton pump inhibitors, erectile dysfunction agents, aciclovir, valaciclovir, sitagliptin, adefovir).

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

In vitro, dolutegravir inhibited the renal OCT2 (IC50 = 1.93 µM), multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 µM) and MATE2-K (IC_{50} = 24.8 µM). Given

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

In vitro, dolutegravir inhibited the basolateral renal transporters: OAT1 (IC_{50} = 2.12 µM) and OAT3 (IC_{50} = 1.97 µM). However, dolutegravir had no notable effect on the pharmacokinetics *in vivo* of the OAT substrates tenofovir and para aminohippurate, and therefore has low propensity to cause drug interactions via inhibition of OAT transporters.

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 Dolutegravir and Lamivudine

Dolutegravir is eliminated mainly through metabolism by UGT1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, Pgp, and BCRP; therefore drugs that induce these enzymes or transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir. Co-administration of dolutegravir and other drugs that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or Pgp may increase dolutegravir plasma concentration (see Table 1).

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

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 (TIVICAY) is available where a dose adjustment is required due to drug-drug interactions. An additional dose of 50 mg dolutegravir (TIVICAY) should be administered, approximately 12 hours after DOVATO. In these cases the physician should refer to the TIVICAY datasheet.

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 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 or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine (ETR) without boosted protase inhibitors	Dolutegravir ↓ AUC ↓ 71% Cmax ↓ 52% Cτ ↓ 88% ETR ↔	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of dolutegravir is 50 mg twice daily for patients taking etravirine without boosted protease inhibitors. As DTG/3TC is a fixed- dose tablet, an additional dose of 50 mg dolutegravir (*TIVICAY*) should be administered, approximately 12 hours after DOVATO. In this case the physician should refer to the individual product information for *TIVICAY*.
Protease Inhibitor: Lopinavir/ritonavir + Etravirine (LPV/RTV+ETR)	Dolutegravir ↔ AUC ↑ 11% Cmax ↑ 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% Cmax ↓ 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% Cmax ↓ 39% Cτ ↓ 75% EFV ↔	Efavirenz decreased dolutegravir plasma concentrations. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. As DTG/3TC is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (*TIVICAY*) should be administered, approximately 12 hours after DOVATO. In this case the physician should refer to the individual product information for *TIVICAY*.
Non-nucleoside Reverse Transcriptase Inhibitor: Nevirapine	Dolutegravir ↓	Co-administration with nevirapine has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. Effect of nevirapine on dolutegravir exposure is likely similar to or less than that of efavirenz. The recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. As DTG/3TC is a fixed- dose tablet, an additional dose of 50 mg dolutegravir (*TIVICAY*) should be administered, approximately 12 hours after DOVATO. In this case the physician should refer to the individual product information for *TIVICAY*.
Protease Inhibitor: Atazanavir (ATV)	Dolutegravir ↑ AUC ↑ 91% Cmax ↑ 50% Cτ ↑ 180% ATV ↔	Atazanavir increased dolutegravir plasma concentration. No dose adjustment is necessary.
Protease Inhibitor: Atazanavir/ritonavir (ATV+RTV)	Dolutegravir ↑ AUC ↑ 62% Cmax ↑ 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% Cmax ↓ 47% Cτ ↓ 76% TPV ↔ RTV ↔	Tipranavir/ritonavir decreases dolutegravir concentrations. The recommended dose of dolutegravir is 50 mg twice daily for patients taking tipranavir/ritonavir. As DTG/3TC is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (*TIVICAY*) should be administered, approximately 12 hours after DOVATO. In this case the physician should refer to the individual product information for *TIVICAY*.
Protease Inhibitor: Fosamprenavir/ ritonavir (FPV+RTV)	Dolutegravir ↓ AUC ↓ 35% Cmax ↓ 24% Cτ ↓ 49% FPV ↔ RTV ↔	Fosamprenavir/ritonavir decreases dolutegravir concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients.
Protease Inhibitor: Nelfinavir	Dolutegravir ↔	This interaction has not been studied. Although an inhibitor of CYP3A4, based on data from other inhibitors, an increase is not expected. No dose adjustment is necessary.
Protease Inhibitor: Lopinavir/ritonavir (LPV+RTV)	DTG ↔ AUC ↓ 4% Cmax ↔ 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% Cmax ↓ 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 ↔ Cmax ↓3% Cτ ↓ 8%	Tenofovir did not change dolutegravir plasma concentration to a clinically relevant extent. No dose adjustment is necessary.

	Tenofovir ↔ AUC ↑ 12% Cmax ↑ 9% Cτ ↑ 19%	
Other Agents		
Dofetilide Pilsicainide	Dofetilide ↑ Pilsicainide ↑	Co-administration of dolutegravir has the potential to increase dofetilide or pilsicainide plasma concentration via inhibition of OCT2 transporter; co- administration has not been studied. Dofetilide or pilsicainide co-administration with dolutegravir is contraindicated due to potential life-threatening toxicity caused by high dofetilide or pilsicainide concentration.
Fampridine (also known as dalfampridine)	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co- administration with dolutegravir is contraindicated.
Carbamazepine	Dolutegravir ↓ AUC ↓ 49% Cmax ↓ 33% Cτ ↓ 73%	Carbamazepine decreased dolutegravir plasma concentration. The recommended dose of dolutegravir is 50 mg twice daily for patients taking carbamazepine. As DTG/3TC is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered, approximately 12 hours after DOVATO. In this case the physician should refer to the individual product information for TIVICAY.
Phenytoin Phenobarbital St. John's wort	Dolutegravir ↓	Co-administration with these metabolic inducers has the potential to decrease dolutegravir plasma concentration due to enzyme induction and has not been studied. The effect of these metabolic inducers on dolutegravir exposure is likely similar to carbamazepine. The recommended dose of dolutegravir is 50 mg twice daily for patients taking these metabolic inducers. As DTG/3TC is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered, approximately 12 hours after DOVATO. In this case the physician should refer to the individual product information for TIVICAY.

Oxcarbazepine	Dolutegravir ↓	This interaction has not been studied. Although an inducer of CYP3A4, based on data from other inducers, a clinically 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% Cmax ↓ 72% C_{24} ↓ 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% Cmax ↓ 37% C_{24} ↓ 39%	. - When taken with food, Dovato and supplements or multivitamins containing calcium, iron or magnesium can be taken at the same time. - If Dovato is taken in a fasted state, such supplements should be taken a minimum 2 hours after or 6 hours before the intake of Dovato. The stated reductions in dolutegravir exposure were observed with the intake of dolutegravir and these supplements during fasted conditions. In fed state, the changes in exposure following intake together with calcium or iron supplements were modified by the food effect, resulting in an exposure similar to that obtained with dolutegravir administered in the fasted state.
Iron supplements	Dolutegravir ↓ AUC ↓ 54% Cmax ↓ 57% C_{24} ↓ 56%	
Multivitamins (containing calcium, iron and magnesium) /Dolutegravir (fasted intake)	Dolutegravir ↓ AUC ↓ 33% Cmax ↓ 35% C_{24} ↓ 32%	
Metformin	Metformin ↑ When co-administered with dolutegravir 50 mg QD: Metformin	Co-administration of dolutegravir increased metformin plasma concentration. A dose adjustment of metformin should be considered when starting and stopping co-administration of DOVATO with metformin, to maintain glycaemic control.

	AUC ↑ 79% Cmax ↑ 66% When co-administered with dolutegravir 50 mg BID: Metformin AUC ↑ 145% Cmax ↑ 111%	
Rifampicin	Dolutegravir ↓ (by rifampicin) AUC ↓ 54% Cmax ↓ 43% Cτ ↓ 72%	Rifampicin decreased dolutegravir plasma concentration. The recommended dose of dolutegravir is 50 mg twice daily for patients taking rifampicin. As DTG/3TC is a fixed-dose tablet, an additional dose of 50 mg dolutegravir (TIVICAY) should be administered, approximately 12 hours after DOVATO. In this case the physician should refer to the individual product information for TIVICAY.
Oral contraceptives (Ethinyl estradiol (EE) and Norelgestromin (NGMN))	Effect of dolutegravir: EE ↔ AUC ↑ 3% Cmax ↓ 1% Cτ ↑ 2% Effect of dolutegravir: NGMN ↔ AUC ↓ 2% Cmax ↓ 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% Cmax ↔ 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% Cmax ↑ 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, C24 = concentration at 24 hours post-dose

Table 2 Drug Interactions studied with lamivudine

Concomitant Drug Class: Drug Name	**Effect on Concentration of lamivudine or Concomitant Drug**	**Clinical Comment**
Trimethoprim/sulfa methoxazole (Co-trimoxazole) (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see Section 4.2 Dose and method of administration). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. The effect of co-administration of lamivudine with higher doses of co- trimoxazole used for the treatment of Pneumocystis jiroveci pneumonia and toxoplasmosis has not been studied. DOVATO is not recommended for subjects with CrCl of <50 mL/min.
Emtricitabine		Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine- containing fixed-dose combinations.
Other Agents		
Sorbitol solution (3.2 g, 10.2 g, 13.4 g)	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14%; 32%; 36% Cmax ↓ 28%; 52%, 55%.	When possible, avoid chronic co-administration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Information on individual components

Two large birth outcome surveillance studies in Botswana (Tsepamo) and Eswatini, which together include over 14,000 women taking dolutegravir-containing regimens at conception, show no increased risk of neural tube defects with dolutegravir exposure at conception. Data from the Tsepamo study show no significant difference in neural tube defect prevalence in infants whose mothers were exposed to dolutegravir at conception compared to those taking non-dolutegravir containing antiretroviral regimens at conception or compared to women without HIV. Data from the Eswatini study show similar rates of neural tube defects between infants whose mothers were on dolutegravir at conception compared with women without HIV. These studies refute an initial finding from a preliminary analysis of the Tsepamo study, which suggested a possible increased risk. Data analysed to date from these studies and other sources do not support a causal relationship between dolutegravir and neural tube defects.

In the Tsepamo study, which includes over 9,460 exposures to dolutegravir at conception, the prevalence of neural tube defects in infants delivered to women taking dolutegravir at conception was 0.11%. This was the same as the prevalence for non-dolutegravir containing regimens (0.11%), and did not differ significantly from the prevalence in infants delivered to women without HIV (0.07%).

In the Eswatini study, which includes over 4,800 exposures to dolutegravir at conception, the prevalence of neural tube defects in infants delivered to women taking dolutegravir at conception was 0.08%, which was the same as in infants delivered to women without HIV (0.08%).

The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. The prevalence of neural tube defects in infants born to women taking dolutegravir at conception in these two studies did not differ significantly from the background rate in women without HIV, or other ART exposure groups.

Data analysed from the Antiretroviral Pregnancy Registry (APR) in over 870 exposures to dolutegravir and over 5,600 exposures to lamivudine in the first trimester of pregnancy do not indicate an increased risk of major birth defects compared to the background rate (see Section 5.1 Pharmacodynamic properties, Antiretroviral Pregnancy Registry).

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

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

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peri- partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or

peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lamivudine was associated with findings in animal reproductive toxicity studies (see Section 5.3 Preclinical safety data, Reproductive toxicology).

Breast-feeding

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

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

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

Fertility

There are no data on the effects of dolutegravir or lamivudine on human male or female fertility. Animal studies indicate no effects of dolutegravir or lamivudine on male or female fertility (see Section 5.3 Preclinical safety data, Reproductive toxicology).

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 Undesirable effects

Summary of the safety profile

DOVATO contains dolutegravir and lamivudine, therefore the adverse drug

reactions (ADRs) associated with these may be expected (Table 3 and 4). For many of the adverse events listed it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process.

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

Clinical Trial Data

Description of selected adverse reactions

Clinical safety data with the DOVATO are limited. The ADRs observed for the combination of DTG+3TC in an analysis of pooled data from Phase 3 clinical trials (GEMINI-1 and GEMINI-2) conducted in antiretroviral naïve subjects, and from 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. A single treatment emergent adverse reaction [*Nervous system disorders*: somnolence; frequency common] was observed with the combination which was not listed in the prescriber information for dolutegravir or lamivudine. There was no difference between the combination and the individual components in severity for any observed adverse reactions. Treatment-emergent ADRs observed in at least 2% of subjects in either treatment arm of the pooled analysis of the GEMINI-1 and GEMINI-2 trials were nausea, headache, diarrhoea, insomnia and dizziness. Insomnia and weight increased, observed in the DOVATO arm, were the only treatment- emergent ADRs observed in at least 2% of subjects in either treatment arm of the TANGO trial.

Tabulated list of adverse reactions

Table 3 Adverse Reactions with the Individual Components of DOVATO

System organ class	Frequency*	Dolutegravir	Lamivudine
Blood and lymphatic systems disorders	Uncommon		neutropenia anaemia thrombocytopenia
Immune system disorders	Uncommon	hypersensitivity (see Section 4.4 Special warnings and precautions for use) 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)	
Nervous system disorders	Very common	headache	
	Common	dizziness	headache
Gastrointestinal disorders	Very common	nausea diarrhoea	
	Common	vomiting flatulence abdominal pain upper abdominal pain abdominal discomfort	nausea vomiting upper abdominal pain diarrhoea

Hepatobiliary disorders	Uncommon	hepatitis	transient rises in liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	Common	rash pruritus	rash
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 or studies with the individual components.

Changes in laboratory chemistries

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 Pharmacodynamic properties).

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) rate (see Section 5.1 Pharmacodynamic properties).

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

Post-marketing data

In addition to the adverse reactions included from clinical trial data, the adverse reactions listed in Table 4 below have been identified during post-approval use of dolutegravir and/or lamivudine in use with other antiretroviral agents. These events have been chosen for inclusion due to a potential causal connection to dolutegravir and/or lamivudine.

Table 4 Adverse reactions based on post-marketing experience

System organ class	Frequency	Dolutegravir	Lamivudine
Blood and lymphatic systems disorders	Very rare	sideroblastic anaemia[1]	pure red cell aplasia
Metabolism and nutrition disorders	Common		hyperlactataemia
	Rare		lactic acidosis[2]
Nervous system disorders	Very rare		paraesthesiae peripheral neuropathy has been reported although a causal relationship to treatment is uncertain
Gastrointestinal disorders	Rare		rises in serum amylase pancreatitis, although a causal relationship to lamivudine is uncertain
Hepatobiliary disorders	Rare	acute hepatic failure[3]	
Skin and subcutaneous tissue disorders	Common		alopecia
Musculoskeletal and connective tissue disorders	Common		arthralgia muscle disorders
	Uncommon	arthralgia myalgia	
	Rare		rhabdomyolysis
Investigations	Common	weight increased	

[1]Reversible sideroblastic anaemia has been reported with dolutegravir-containing regimens. The contribution of dolutegravir in these cases is unclear.

[2]Lactic acidosis (see Section 4.4 Special warnings and precautions for use).

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

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- naive 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Symptoms and Signs

There is currently limited experience with overdosage in dolutegravir. Limited experience of single higher doses (up to 250 mg in healthy 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, Antivirals for treatment of HIV infections, combinations.

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 and12.6 nM. *In vitro*, dolutegravir dissociates slowly from the active site of the wild type integrase-DNA complex (t½ 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 Section 5.2 Pharmacokinetic properties, Elimination). 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 with mean concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells.

In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse clade B isolates, dolutegravir demonstrated antiviral potency similar to reference 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

No drugs with inherent anti-HIV activity were antagonistic with dolutegravir (*in vitro* assessments were conducted in checkerboard format in combination with stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, maraviroc, adefovir

and raltegravir). In addition, antivirals without inherent anti-HIV activity (ribavirin) had no apparent effect on dolutegravir activity.

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

In vitro studies suggested a 75-fold shift in EC_{50} of dolutegravir in the presence of 100% human serum (by method of extrapolation), and the protein adjusted EC_{90} (PA-EC_{90}) in PBMCs 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)

Viruses highly resistant to dolutegravir were not observed during the 112 day passage of strain IIIB, with a 4.1-fold maximum fold change (FC) observed for the passaged resistant virus populations with substitutions at the conserved IN positions S153Y and S153F. Passage of the wild type HIV-1 strain NL432 in the presence of dolutegravir selected for E92Q (passage population virus FC=3.1) and G193E (passage population virus FC=3.2) substitutions on Day 56. Additional passage of wildtype clade B, C, and A/G viruses in the presence of dolutegravir selected for G118R (site-directed mutant FC=10), S153T, and R263K (site-directed mutant FC=1.5).

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–naive 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 during *in vitro* selection 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*.

Resistance in vivo (dolutegravir plus lamivudine)

No subjects that met the protocol-defined confirmed virologic withdrawal (CVW) criteria across the pooled GEMINI-1 and GEMINI-2 studies through Week 144 or in the TANGO study through Week 144 had emergent INSTI or NRTI resistance substitutions. In patients with prior failed therapies, but naïve to the integrase class (SAILING study), integrase inhibitor substitutions were observed in 4/354 patients (follow-up 48 weeks) treated with dolutegravir, which was given in combination with an investigator selected background regimen. Of these four, two subjects had a unique R263K integrase substitution, with a maximum fold change of 1.93, one subject had a polymorphic V151V/I integrase substitution, with fold change of 0.92, and one subject had pre-existing integrase mutations and is assumed to have been integrase experienced or infected with integrase resistant virus by transmission. In patients naïve to the integrase class and failing first line NNRTI + 2 NRTI treatment (DAWNING study) through Week 48, 2/314 subjects treated with dolutegravir had integrase inhibitor G118R pathway substitutions conferring DTG fold changes of 15 and 30, and

respective viral replication capacity decreases of 6.6 fold and 18 fold compared with baseline. The G118R and R263K mutations were also selected *in vitro* (see above).

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 and 1.8% had a DTG FC >25. Mutants with Y143 and N155 pathway had mean FCs of 1.2 and 1.5, respectively, while Q148 + 1 mutant and Q148 + ≥2 mutants mean FCs were 4.8 and 6.0, respectively.

Cross-resistance conferred by the M184V reverse transcriptase: Cross-resistance is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir and tenofovir maintain antiretroviral activity against lamivudine-resistant HIV-1 harbouring only the M184V mutation.

Effects on Electrocardiogram

In a randomized, 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, randomized, 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 studies. Dolutegravir at both doses had no significant effect on GFR or ERPF. These data support *in vitro* studies which suggest that the small increases in creatinine observed in clinical studies are due to the nonpathologic inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine.

In the pooled analysis of GEMINI-1 and GEMINI-2 studies in treatment-naïve adult patients at the week 144 analysis, dolutegravir plus lamivudine was associated with lower impact on renal safety parameters compared to dolutegravir plus tenofovir/emtricitabine FDC. The dolutegravir plus lamivudine group had a significantly greater increase in the estimated GFR using cystatin C adjusted CKD-EPI equation, compared with the dolutegravir plus tenofovir/emtricitabine FDC group (adjusted mean change from baseline of 12.2 and 10.6 mL/min/1.73 m2, respectively; p = 0.008). Change from baseline analysis showed that urine albumin/creatinine and protein/creatinine ratios were lower in the dolutegravir plus lamivudine group compared with the dolutegravir plus tenofovir/emtricitabine FDC group; the difference was significantly significant for the protein/creatinine ratio (urine albumin/creatinine week 144/ baseline ratio of 1.046 and 1.104, respectively; p = 0.261 and protein/creatinine week 144/baseline ratio of 0.994 and 1.193, respectively; p <0.001). Withdrawals from study for renal function-related adverse events or for meeting predefined renal toxicity criteria (eGFR <50 ml/min/1.73m^2) were more frequently observed in subjects in the dolutegravir plus tenofovir/emtricitabine FDC group compared with the dolutegravir plus lamivudine group.

Clinical efficacy and safety

Antiretroviral naïve subjects

The efficacy of DOVATO is supported by data from 2 identical 148-week, Phase III, randomised, double-blind, multicenter, 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 received treatment in the trials. 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 plus lamivudine administered once daily or dolutegravir plus tenofovir/emtricitabine 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, 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 mm^3; 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 5.

Table 5 Virologic Outcomes of Randomised Treatment of GEMINI at Week 48 (Snapshot algorithm)

	GEMINI-1 and GEMINI-2 Pooled Data*	
	DTG + 3TC N=716	DTG + TDF/FTC N=717
HIV-1 RNA <50 copies/mL	91%	93%
Treatment Difference† (95% confidence intervals)	-1.7 (-4.4, 1.1)	
Virologic non response	3%	2%

Reasons		
Data in window and ≥50 copies/mL	1%	<1%
Discontinued for lack of efficacy	<1%	<1%
Discontinued for other reasons and ≥50 copies/mL	<1%	<1%
Change in ART	<1%	<1%
No virologic data at Week 48 window	6%	5%
Reasons		
Discontinued study due to adverse event or death	1%	2%
Discontinued study for other reasons	4%	3%
Missing data during window but on study	<1%	0%
HIV-1 RNA <50 copies/mL by baseline covariates		
	n/N (%)	n/N (%)
Baseline Plasma Viral Load (copies/mL)		
≤100,000	526 / 576 (91%)	531 / 564 (94%)
>100,000	129 / 140 (92%)	138 / 153 (90%)
Baseline CD4+ (cells/ mm^3)		
≤200	50 / 63 (79%)	51 / 55 (93%)
>200	605 / 653 (93%)	618 / 662 (93%)
Gender		
Male	555 / 603 (92%)	580 / 619 (94%)
Female	100 / 113 (88%)	89 / 98 (91%)
Race		
White	451 / 484 (93%)	473 / 499 (95%)
African-American/African Heritage/Other	204 / 232 (88%)	196 / 218 (90%)
Age (years)		
<50	597 / 651 (92%)	597 / 637 (94%)
≥50	58 / 65 (89%)	72 / 80 (90%)

*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/mm^3 vs. >200 cells/mm^3). Pooled analysis also stratified by study. Assessed using a non-inferiority margin of 10%.

N = Number of subjects in each treatment group.

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). The results of the pooled analysis were in line with those of the individual studies, for which the secondary endpoint (difference in proportion <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%.

The mean increase in CD4+ T-cell counts was 269 cells/mm^3 in the DTG+3TC arm and 259 cells/mm^3 in the DTG+FTC/TDF arm, at week 96.

At 144 weeks in the GEMINI-1 and GEMINI-2 studies, the dolutegravir plus lamivudine group (82% with plasma HIV-1 RNA < 50 copies/mL [pooled data]) remained non-inferior to dolutegravir plus tenofovir/emtricitabine FDC group (84% with plasma HIV-1 RNA < 50 copies/mL [pooled data]). The results of the pooled analysis were in line with those of the individual studies, for which the secondary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at Week 144 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus tenofovir/emtricitabine FDC) was met. The adjusted difference in proportions and 95% CI for the pooled data was 1.8% (5.8, 2.1). The adjusted differences of 3.6 (95% CI: 9.4, 2.1) for GEMINI-1 and 0.0 (95% CI: 5.3, 5.3) for GEMINI-2 were within the prespecified non-inferiority margin of 10%.

The mean increase in CD4+ T-cell counts was 302 cells/mm^3 in the DTG+3TC arm and 300 cells/mm^3 in the DTG+FTC/TDF arm, at Week 144.

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, multicenter, parallel-group, non-inferioritycontrolled trial (TANGO [204862]). A total of 741 adult HIV-1-infected subjects who were on a stable suppressive tenofovir alafenamide based regimen (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 non-nucleoside reverse transcriptase inhibitor [NNRTI]). The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL (virologic non-response) 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/mm^3; 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.

In the primary 48 week analysis, DOVATO was non-inferior to TBR, with <1% of subjects in both arms experiencing virologic failure (HIV-1 RNA ≥50 c/mL) based on the Snapshot algorithm (Table 6).

Table 6 Virologic Outcomes of Randomised Treatment of TANGO at Week 48 (Snapshot algorithm)

	DOVATO N=369	TBR 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%
HIV-1 RNA <50 copies/mL by baseline covariates		
	n/N (%)	n/N (%)
Baseline CD4+ (cells/ mm^3)		
<500	92 / 98 (94%)	68 / 74 (92%)
≥500	252 / 271 (93%)	278 / 298 (93%)
Baseline Third Agent Class		
NNRTI	49 / 51 (96%)	42 / 48 (88%)
INSTI	268 / 289 (93%)	276 / 296 (93%)
PI	27 / 29 (93%)	28 / 28 (100%)
Gender		
Male	323 / 344 (94%)	319 / 339 (94%)
Female	21 / 25 (84%)	27 / 33 (82%)
Race		
White	279 / 297 (94%)	272 / 289 (94%)
African-American/African Heritage/Other	65 / 72 (90%)	74 / 83 (89%)
Age (years)		
<50	271 / 290 (93%)	260 / 280 (93%)
≥50	73 / 79 (92%)	86 / 92 (93%)

*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; TBR = tenofovir alafenamide based regimen; DTG/3TC = dolutegravir plus lamivudine fixed dose combination; INSTI = Integrase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = Protease Inhibitor

At 96 weeks in the TANGO study, the proportion of subjects with HIV-1 RNA ≥ 50 c/mL (Snapshot) was 0.3% and 1.1% in the DTG/3TC FDC and TBR groups, respectively. Based on a non-inferiority margin of 4%, DTG/3TC FDC remained non-inferior to TBR, as the upper bound of the 95% CI for the adjusted treatment difference (-2.0%, 0.4%) was less than 4% for the ITT E Population.

The median change from baseline in CD4+ T-cell counts at Week 96 was 61 cells/mm^3 in the DTG+3TC FDC arm and 45 cells/mm^3 in the TBR arm.

At 144 weeks, the proportion of subjects with HIV-1 RNA ≥ 50 c/mL (Snapshot) was 0.3% and 1.3% in the DTG/3TC FDC and TBR groups, respectively. Based on a non-inferiority margin of 4%, DTG/3TC FDC remained non-inferior to TBR, as the upper bound of the 95% CI for the adjusted treatment difference (-2.4%, 0.2%) was less than 4% for the ITT E Population.

The median change from baseline in CD4+ T-cell counts at Week 144 was 36 cells/mm^3 in the DTG+3TC FDC arm and 55 cells/mm^3 in the TBR arm.

Antiretroviral Pregnancy Registry

The APR has received reports of over 1300 exposures to dolutegravir during pregnancy resulting in live births. These consist of over 870 exposures during the first trimester, over 500 exposures during the second/third trimester and included 29 and 25 birth defects, respectively. The prevalence (95% CI) of defects among live births exposed to dolutegravir in the first trimester was 3.3% (2.2%, 4.7%) and in the second/third trimester, 5.0% (3.2%, 7.3%).

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

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

Paediatric population

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

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

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

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 C_{max} were similar to historical exposures.

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 the 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 microgram/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 the DOVATO tablet 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 15.4 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 5.2 Pharmacodynamics 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.

Biotransformation

Dolutegravir is primarily metabolized via UGT1A1 with a minor CYP3A component (9.7% of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged drug is low (<1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed 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%).

Elimination

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

Children

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 7).

Table 7 Paediatric pharmacokinetic parameters (n=10)

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

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

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

Elderly

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

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

Renal impairment

Pharmacokinetic data have been obtained for dolutegravir and lamivudine alone. DOVATO should not be used in patients with creatinine clearance of less than

50 mL/min because, whilst no dosage adjustment of dolutegravir is necessary in patients with renal impairment, dose reduction is required for the lamivudine component.

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

Renal clearance of unchanged drug is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr <30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr <30 mL/min) and matching healthy subjects were observed.

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 metabolized and eliminated by the liver. In a study comparing 8 subjects with

moderate hepatic impairment (Child-Pugh category B) to 8 matched healthy adult controls, the single 50 mg dose exposure of dolutegravir was similar between the two groups. The effect of severe hepatic impairment on the pharmacokinetics of dolutegravir has not been studied.

Polymorphisms in Drug Metabolising Enzymes

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

Gender

Population pharmacokinetic analyses 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 pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited pharmacokinetic data on subjects with hepatitis B co-infection (see Section 4.4 Special warnings and precautions for use).

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

Carcinogenesis/mutagenesis

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

Lamivudine was not mutagenic in bacterial tests, but like many nucleoside analogues it shows activity in the *in vitro* mammalian tests such as the mouse lymphoma assay. This is consistent with the known activity of other nucleoside analogues. The results from two *in vivo* rat micronucleus tests with lamivudine were negative.

Lamivudine did not show any genotoxic activity in additional *in vivo* studies in rats (metaphase analysis of bone marrow and unscheduled DNA synthesis). The results of long-term carcinogenicity studies in mice and rats did not show any carcinogenic potential at exposures approximately 12 to 72 times higher than clinical plasma levels.

Reproductive Toxicology

Fertility

Fertility studies in the rat have shown that dolutegravir and lamivudine had no effect on male or female fertility.

Dolutegravir did not affect male or female fertility in rats at doses up to 1000 mg/kg/day, the highest dose tested (33 times the 50 mg human clinical exposure, based on AUC).

Pregnancy

Dolutegravir and lamivudine were shown to cross the placenta in animal reproductive toxicity studies.

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (37.9 times the 50 mg human clinical exposure, based on AUC).

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.56 times the 50 mg human clinical exposure, based on AUC). In rabbits, maternal toxicity (decreased food consumption, scant/no faeces/urine, suppressed body weight gain) was observed at 1000 mg/kg (0.56 times the 50 mg human clinical exposure, based on AUC).

Lamivudine was not teratogenic in animal studies, but there were indications of an increase in early embryonic deaths in rabbits at exposure levels comparable to those achieved in man. However, there was no evidence of embryonic loss in rats at exposure levels of approximately 32 times the clinical exposure (based on C_{max}).

Animal toxicology and/or pharmacology

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 30 and 1.2 times the 50 mg human clinical exposure, based on AUC, respectively.

Because gastrointestinal intolerance is considered to be due to local drug administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 30 times the human mg/kg equivalent dose (based on 50 kg human), and 11 times the human mg/m^2 equivalent dose for a total daily clinical dose of 50 mg.

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

24 months.

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

GlaxoSmithKline NZ Limited
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9 DATE OF FIRST APPROVAL

18th November 2021

10 DATE OF REVISION OF THE TEXT

5 May 2025

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
4.8	Sideroblastic Anaemia is included as an Undesirable effects under 'Post- marketing data'.

Version 5.0