1. NAME OF THE MEDICINAL PRODUCT

Dovato

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg dolutegravir and 300 mg lamivudine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dovato is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine and viral load ≤500,000 c/mL (see section 5.1).

4.2 Posology and method of administration

Dovato should be prescribed by physicians experienced in the management of HIV infection.

Posology

Adults and adolescents (above 12 years of age weighing at least 40 kg).

The recommended dose of Dovato in adults and adolescents is one 50 mg/300 mg tablet once daily.

Dose adjustments
A separate preparation of dolutegravir is available where a dose adjustment is indicated due to drug-drug interactions (e.g. rifampicin, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St. John’s wort, etravirine (without boosted protease inhibitors), efavirenz, nevirapine, or tipranavir/ritonavir, see sections 4.4 and 4.5). In these cases the physician should refer to the individual product information for dolutegravir.

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

Elderly
There are limited data available on the use of Dovato in patients aged 65 years and over. No dose adjustment is necessary (see section 5.2).

Renal impairment
Dovato is not recommended for use in patients with a creatinine clearance < 50 mL/min (see section 5.2). No dose adjustment is required in patients with mild renal impairment.

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 in patients with severe hepatic impairment (Child-Pugh grade C); therefore Dovato should be used with caution in these patients (see section 5.2).

Paediatric population
Dovato is not indicated for children under 12 years old. 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.

Method of administration

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

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

Transmission of HIV

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.

Hypersensitivity reactions

Hypersensitivity reactions have been reported with dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including severe liver reactions. Dovato and other suspect medicinal products should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, eosinophilia, angioedema). Clinical status including liver aminotransferases and bilirubin should be monitored. Delay in stopping treatment with Dovato or other suspect active substances after the onset of hypersensitivity may result in a life-threatening allergic reaction.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Liver disease

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.

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.

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

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

Immune Reactivation Syndrome

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

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of dolutegravir therapy. Monitoring of liver chemistries is recommended in patients with hepatitis B and/or C co-infection. (See 'Liver disease' earlier in this section and also see section 4.8).

Mitochondrial dysfunction following exposure *in utero*

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues, these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), and metabolic disorders (hyperlactatemia, hyperlipasemia). These reactions have often been transitory. Some late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown aetiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Osteonecrosis

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

Opportunistic infections

Patients should be advised that dolutegravir, lamivudine or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Drug interactions

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

Dovato should not be co-administered with polyvalent cation-containing antacids. Polyvalent cation-containing antacids are recommended to be taken 2 hours after or 6 hours before Dovato (see section 4.5).

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted using Dovato. Dovato contains dolutegravir and lamivudine, therefore any interactions identified for these individually are relevant to Dovato. No clinically significant drug interactions are expected between dolutegravir and lamivudine.

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

Dolutegravir is eliminated mainly through metabolism by uridine diphosphate glucuronosyl transferase (UGT) 1A1. Dolutegravir is also a substrate of UGT1A3, UGT1A9, CYP3A4, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). Co-administration of Dovato and other medicinal products that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or P-gp may, therefore, increase dolutegravir plasma

concentration. Medicinal products that induce those enzymes or transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

The absorption of dolutegravir is reduced by certain metal cation-containing anti-acid substances and supplements (see Table 1).

Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through the OCT2 and multidrug and toxin extrusion transporters (MATE1 and MATE2-K). Trimethoprim (an inhibitor of these transporters) has been shown to increase lamivudine plasma concentrations, however the resulting increase was not clinically significant (see Table 1). Dolutegravir is an OCT2 and MATE1 inhibitor; however, lamivudine concentrations were similar with or without co-administration of dolutegravir based on a cross study analysis, indicating that dolutegravir has no relevant effect on lamivudine exposure *in vivo*. Lamivudine is also substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

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

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

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

In vitro, dolutegravir inhibited the renal transporters OCT2 and MATE1. *In vivo*, a 10-14% decrease of creatinine clearance (secretory fraction is dependent on OCT2 and MATE1 transport) was observed in patients. *In vivo*, dolutegravir may increase plasma concentrations of medicinal products in which excretion is dependent upon OCT2 and/or MATE1 (e.g. fampridine [also known as dalfampridine], metformin) (see Table 1 and section 4.3).

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

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

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

Interaction table

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

Table 1: Drug Interactions

Medicinal products by therapeutic areas	**Interaction geometric mean change (%)**	**Recommendations concerning co-administration**
Antiretroviral medicinal products		

Non-nucleoside reverse transcriptase inhibitors		
Etravirine without boosted protease inhibitors / Dolutegravir	Dolutegravir ↓ AUC ↓ 71% C_{max} ↓ 52% Cτ ↓ 88% Etravirine ↔ (induction of UGT1A1 and CYP3A enzymes)	Etravirine without boosted protease inhibitors decreased plasma dolutegravir concentration. The recommended dose of dolutegravir is 50 mg twice daily for patients taking etravirine without boosted protease inhibitors. As Dovato is a fixed-dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Dovato for the duration of the etravirine without boosted protease inhibitor co-administration (a separate formulation of dolutegravir is available for this dose adjustment, see section 4.2).
Lopinavir+ritonavir+etravirine/ Dolutegravir	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 7% Cτ ↑ 28% Lopinavir ↔ Ritonavir ↔ Etravirine ↔	No dose adjustment is necessary.
Darunavir+ritonavir+etravirine/ Dolutegravir	Dolutegravir ↓ AUC ↓ 25% C_{max} ↓ 12% Cτ ↓ 36% Darunavir ↔ Ritonavir ↔ Etravirine ↔	No dose adjustment is necessary.
Efavirenz/Dolutegravir	Dolutegravir ↓ AUC ↓ 57% C_{max} ↓ 39% Cτ ↓ 75% Efavirenz ↔ (historical controls) (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with efavirenz. As Dovato is a fixed-dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Dovato for the duration of the efavirenz co-administration (a separate formulation of dolutegravir is available for this dose adjustment, see section 4.2).
Nevirapine/Dolutegravir	Dolutegravir ↓ (Not studied, a similar reduction in exposure as observed with efavirenz is expected, due to induction)	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with nevirapine. As Dovato is a fixed-dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Dovato for the duration of the nevirapine co-administration (a separate formulation of dolutegravir is available for this dose adjustment, see section 4.2).

Rilpivirine/Dolutegravir	Dolutegravir ↔ AUC ↑ 12% C_{max} ↑ 13% Cτ ↑ 22% Rilpivirine ↔	No dose adjustment is necessary.
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Tenofovir disoproxil Emtricitabine, didanosine, stavudine, tenofovir alafenamide, zidovudine	Dolutegravir ↔ AUC ↑ 1% C_{max} ↓ 3% Cτ ↓ 8% Tenofovir ↔ Interaction not studied	No dose adjustment is necessary when Dovato is combined with tenofovir, didanosine, stavudine or zidovudine. Dovato is not recommended for use in combination with emtricitabine containing products, since both lamivudine (in Dovato) and emtricitabine are cytidine analogues (i.e. risk for intracellular interactions), see section 4.4.
Protease inhibitors		
Atazanavir/Dolutegravir	Dolutegravir ↑ AUC ↑ 91% C_{max} ↑ 50% Cτ ↑ 180% Atazanavir ↔ (historical controls) (inhibition of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Atazanavir+ ritonavir/ Dolutegravir	Dolutegravir ↑ AUC ↑ 62% C_{max} ↑ 34% Cτ ↑ 121% Atazanavir ↔ Ritonavir ↔	No dose adjustment is necessary.
Tipranavir+ritonavir/ Dolutegravir	Dolutegravir ↓ AUC ↓ 59% C_{max} ↓ 47% Cτ ↓ 76% Tipranavir ↔ Ritonavir ↔ (induction of UGT1A1 and CYP3A enzymes)	The recommended dose of-dolutegravir is 50 mg twice daily when co administered with tipranavir/ritonavir. As Dovato is a fixed-dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Dovato for the duration of the tipranavir/ritonavir co-administration (a separate formulation of dolutegravir is available for this dose adjustment, see section 4.2).
Fosamprenavir+ritonavir/ Dolutegravir	Dolutegravir↓ AUC ↓ 35% C_{max} ↓ 24% Cτ ↓ 49% Fosamprenavir↔ Ritonavir ↔	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.

	(induction of UGT1A1 and CYP3A enzymes)	
Lopinavir+ritonavir/ Dolutegravir	Dolutegravir ↔ AUC ↓ 4% C_{max} ↔ 0% C_{24} ↓ 6% Lopinavir ↔ Ritonavir ↔	No dose adjustment is necessary.
Darunavir+ritonavir/ Dolutegravir	Dolutegravir ↓ AUC ↓ 22% C_{max} ↓ 11% Cτ ↓ 38% Darunavir ↔ Ritonavir ↔ (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Other antiviral active substances		
Daclatasvir/Dolutegravir	Dolutegravir ↔ AUC ↑ 33% C_{max} ↑ 29% Cτ ↑ 45% Daclatasvir ↔	Daclatasvir did not change dolutegravir plasma concentration to a clinically relevant extent. Dolutegravir did not change daclatasvir plasma concentration. No dose adjustment is necessary.
Ledipasvir/Sofosbuvir/ Lamivudine (with abacavir)	Lamivudine ↔ Ledipasvir ↔ Sofosbuvir ↔	No dosage adjustment necessary.
Sofosbuvir/ Velpatasvir/Dolutegravir	Dolutegravir ↔ Sofosbuvir ↔ Velpatasvir↔	No dosage adjustment necessary.
Ribavirin	Interaction not studied. Clinically significant interaction unlikely.	No dosage adjustment necessary.
Anti-infective products		
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑ 43% C_{max} ↑ 7% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	No dosage adjustment necessary.
Antimycobacterials		
Rifampicin/Dolutegravir	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 43% Cτ ↓ 72%	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin. As Dovato is a fixed-dose tablet, an additional 50 mg tablet of dolutegravir

	(induction of UGT1A1 and CYP3A enzymes)	should be administered, approximately 12 hours after Dovato for the duration of the rifampicin co-administration (a separate formulation of dolutegravir is available for this dose adjustment, see section 4.2).
Rifabutin/Dolutegravir	Dolutegravir ↔ AUC ↓ 5% C_{max} ↑ 16% Cτ ↓ 30% (induction of UGT1A1 and CYP3A enzymes)	No dose adjustment is necessary.
Anticonvulsants		
Carbamazepine/Dolutegravir	Dolutegravir ↓ AUC ↓ 49% C_{max} ↓ 33% Cτ ↓ 73%	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with these metabolic inducers. As Dovato is a fixed-dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Dovato for the duration of the co-administration with these metabolic inducers (a separate formulation of dolutegravir is available for this dose adjustment, see section 4.2).
Phenobarbital/Dolutegravir Phenytoin/Dolutegravir Oxcarbazepine/Dolutegravir	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected).	
Antihistamines (histamine H2 receptor antagonists)		
Ranitidine	Interaction not studied. Clinically significant interaction unlikely.	No dosage adjustment necessary.
Cimetidine	Interaction not studied. Clinically significant interaction unlikely.	No dosage adjustment necessary.
Cytotoxics		
Cladribine/Lamivudine	Interaction not studied. *In vitro* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine.	Concomitant use of Dovato with cladribine is not recommended (see section 4.4).
Miscellaneous		
Sorbitol		

Sorbitol solution (3.2 g, 10.2 g, 13.4 g)/Lamivudine	Single dose lamivudine oral solution 300 mg. Lamivudine: AUC ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%, 55%.	When possible, avoid chronic coadministration of Dovato with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (eg: xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.
Potassium channel blockers		
Fampridine (also known as dalfampridine)/Dolutegravir	Fampridine ↑	Co-administration of dolutegravir has the potential to cause seizures due to increased fampridine plasma concentration via inhibition of OCT2 transporter; co-administration has not been studied. Fampridine co-administration with Dovato is contraindicated (see section 4.3).
Antacids and supplements		
Magnesium/ aluminium-containing antacids/Dolutegravir	Dolutegravir ↓ AUC ↓ 74% C_{max} ↓ 72% (Complex binding to polyvalent ions)	Magnesium/ aluminium-containing antacids should be taken well separated in time from the administration of Dovato (minimum 2 hours after or 6 hours before).
Calcium supplements/Dolutegravir (fasted intake)	Dolutegravir ↓ AUC ↓ 39% C_{max} ↓ 37% C_{24} ↓ 39% (Complex binding to polyvalent ions)	- 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 (fasted intake)	Dolutegravir ↓ AUC ↓ 54% C_{max} ↓ 57% C_{24} ↓ 56% (Complex binding to polyvalent ions)	
Multivitamins (containing calcium, iron and magnesium) /Dolutegravir (fasted intake)	Dolutegravir ↓ AUC ↓ 33% C_{max} ↓ 35% C_{24} ↓ 32% (Complex binding to polyvalent ions)	
Proton pump inhibitors		
Omeprazole	Dolutegravir ↔	No dosage adjustment necessary.
Corticosteroids		
Prednisone/Dolutegravir	Dolutegravir ↔ AUC ↑ 11% C_{max} ↑ 6% Cτ ↑ 17%	No dose adjustment is necessary.
Antidiabetics		

Metformin/Dolutegravir	Metformin ↑ Dolutegravir ↔ When co-administered with dolutegravir 50 mg QD: Metformin AUC ↑ 79% C_{max} ↑ 66% When co-administered with dolutegravir 50 mg BID: Metformin AUC ↑ 145 % C_{max} ↑ 111%	A dose adjustment of metformin should be considered when starting and stopping coadministration of Dovato with metformin, to maintain glycaemic control. In patients with moderate renal impairment a dose adjustment of metformin should be considered when coadministered with Dovato, because of the increased risk for lactic acidosis in patients with moderate renal impairment due to increased metformin concentration (section 4.4).
Herbal products		
St. John's wort/Dolutegravir	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is expected).	The recommended dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. As Dovato is a fixed-dose tablet, an additional 50 mg tablet of dolutegravir should be administered, approximately 12 hours after Dovato for the duration of the St. John's wort co-administration (a separate formulation of dolutegravir is available for this dose adjustment, see section 4.2).
Oral contraceptives		
Ethinyl estradiol (EE) and Norgestromin (NGMN)/Dolutegravir	Effect of dolutegravir: EE ↔ AUC ↑ 3% C_{max} ↓ 1% Effect of dolutegravir: NGMN ↔ AUC ↓ 2% C_{max} ↓ 11%	Dolutegravir had no pharmacodynamic effect on Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and progesterone. No dose adjustment of oral contraceptives is necessary when co-administered with Dovato.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

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

Pregnancy

The safety and efficacy of a dual regimen has not been studied in pregnancy.

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

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

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

In animal reproductive toxicology studies with dolutegravir, no adverse development outcomes, including neural tube defects, were identified (see section 5.3). Dolutegravir was shown to cross the placenta in animals.

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

A large amount of data on the use of lamivudine in pregnant women (more than 5200 outcomes from first trimester) indicates no malformative toxicity.

Animal studies showed lamivudine may inhibit cellular DNA replication (see section 5.3). The clinical relevance of these findings is unknown.

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

Breast-feeding

Dolutegravir is excreted in human milk in small amounts. There is insufficient information on the effects of dolutegravir in neonates/infants.

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

It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

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).

4.7 Effects on ability to drive and use machines

Dovato has no or negligible influence on the ability to drive and use machines. Patients should be informed that dizziness and somnolence has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction 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

The most frequently reported adverse reactions are headache (3%), diarrhoea (2%), nausea (2%) and insomnia (2%).

The most severe adverse reaction reported with dolutegravir was a hypersensitivity reaction that included rash and severe liver effects (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions from clinical study and post-marketing experience are listed in Table 2 by body system, organ class and absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 2: Tabulated summary of adverse reactions to Dovato based on clinical study and post-marketing experience with Dovato and its individual components

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

	depression or psychiatric illness.
Nervous system disorders:	
Very common:	headache
Common:	dizziness, somnolence
Very rare:	peripheral neuropathy, paraesthesia
Gastrointestinal disorders:	
Very common:	nausea, diarrhoea
Common:	vomiting, flatulence, abdominal pain/ discomfort
Rare:	pancreatitis
Hepatobiliary disorders:	
Common:	alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations
Uncommon:	hepatitis
Rare:	acute hepatic failure[1], increased bilirubin[2]
Skin and subcutaneous tissue disorders:	
Common:	rash, pruritus, alopecia
Rare:	angioedema
Musculoskeletal and connective tissue disorders:	
Common:	arthralgia, muscle disorders (including myalgia)
Rare:	rhabdomyolysis
General disorders and administration site conditions:	
Common:	fatigue
Investigations:	
Common:	creatine phosphokinase (CPK) elevations
Rare:	amylase elevations
[1] This adverse reaction was identified through post-marketing surveillance for dolutegravir in combination with other ARVs. The frequency category of rare was estimated based on post-marketing reports. [2] In combination with increased transaminases.	

Description of selected adverse reactions

Changes in laboratory biochemistries
Dolutegravir has been associated with an increase in serum creatinine occuring in the first week of treatment when administered with other antiretroviral medicinal products. Increases in serum creatinine occurred within the first four weeks of treatment with dolutegravir plus lamivudine and remained stable through 48 weeks. In the pooled GEMINI studies 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 linked to the inhibiting effect of dolutegravir on renal tubular transporters of creatinine. The changes are not considered to be clinically relevant and do not reflect a change in glomerular filtration rate.

Co-infection with Hepatitis B or C

In the Phase III studies for the dolutegravir single agent, patients with hepatitis B and/or C co-infection were permitted to enrol provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal (ULN). Overall, the safety profile in patients co-infected with hepatitis B and/or C was similar to that observed in patients without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C co-infection for all treatment groups. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C co-infection at the start of dolutegravir therapy, particularly in those whose anti-hepatitis B therapy was withdrawn (see section 4.4).

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

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Immune response syndrome
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Paediatric population

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

Based on limited available data with the dolutegravir single entity or lamivudine single entity used in combination with other antiretroviral agents to treat adolescents (12 to 17 years), there were no additional types of adverse reactions beyond those observed in the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

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

There is no specific treatment for an overdose of Dovato. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infections, combinations. ATC code: J05AR25

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.

Lamivudine, via its active metabolite 5'-triphosphates (TP) (an analogue for cytidine), inhibits reverse transcriptase of HIV-1 and HIV-2 through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine triphosphate shows significantly less affinity for host cell DNA polymerases.

Pharmacodynamic effects

Antiviral activity in cell culture
Dolutegravir and lamivudine have been shown to inhibit replication of lab-strains and clinical isolates of HIV in a number of cell types, including transformed T cell lines, monocyte/macrophage derived lines and primary cultures of activated peripheral blood mononuclear cells (PMBCs) and monocyte/macrophages. The concentration of active substance necessary to effect viral replication by 50% (IC_{50} - half maximal inhibitory concentration) varied according to virus and host cell type.

The IC_{50} for dolutegravir in various lab-strains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC_{50}s were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC_{50} value was 0.2 nM (range 0.02-2.14). The mean IC_{50} for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).

The median or mean IC_{50} values for lamivudine against lab-strains of HIV-1 ranged from 0.007 to 2.3 μM. The mean IC_{50} against lab-strains of HIV-2 (LAV2 and EHO) ranged from 0.16 to 0.51 μM for lamivudine. The IC_{50} values of lamivudine against HIV-1 subtypes (A-G) ranged from 0.001 to 0.170 μM, against Group O from 0.030 to 0.160 μM and against HIV-2 isolates from 0.002 to 0.120 μM in peripheral blood mononuclear cells.

HIV-1 isolates (CRF01_AE, n=12; CRF02_AG, n=12; and Subtype C or CRF_AC, n=13) from 37 untreated patients in Africa and Asia were susceptible to lamivudine (IC_{50} fold changes < 3.0). Group O isolates from antiviral naïve patients tested for lamivudine activity were highly sensitive.

Effect of human serum
In 100% human serum, the mean fold shift for dolutegravir activity was 75 fold, resulting in protein adjusted IC_{90} of 0.064 μg/mL. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36%).

Resistance

Dovato is indicated in the absence of documented or suspected resistance to the integrase inhibitor class and to lamivudine (see section 4.1). For information around in vitro resistance, and cross resistance to other agents of the integrase- and NRTI class, please refer to the SmPCs of dolutegravir and lamivudine.

None of the twelve subjects in the dolutegravir plus lamivudine group or the nine subjects in the dolutegravir plus tenofovir disoproxil/emtricitabine FDC group that met virological withdrawal criteria through Week 144 across the GEMINI-1 (204861) and GEMINI-2 (205543) studies had treatment emergent integrase inhibitor or NRTI class resistance.

In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase inhibitor class, or to the NRTI class was seen (n=1118 follow-up of 48-96 weeks).

Effects on electrocardiogram

No relevant effects were seen with dolutegravir on the QTc interval, with doses exceeding the clinical dose by approximately three fold. A similar study was not conducted with lamivudine.

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, 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 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 50 mg plus lamivudine 300 mg once daily or dolutegravir 50 mg plus tenofovir disoproxil/emtricitabine 245/200 mg 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). Double blind therapy will continue up to week 96, followed by open label therapy up to week 148.

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 disoproxil/emtricitabine FDC in GEMINI-1 and GEMINI-2 studies. This was supported by the pooled analysis, see Table 3.

Table 3 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%)
HIV-1 subtype		
B	424 / 467 (91%)	452 / 488 (93%)
A	84 / 86 (98%)	74 / 78 (95%)
Other	147 / 163 (90%)	143 / 151 (95%)
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%)

* 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 disoproxil /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 and at 144 weeks in the GEMINI studies, the lower bound of the 95% confidence interval for the adjusted treatment difference of proportion of subjects with HIV-1 RNA <50 copies/mL (Snapshot) was greater than the non-inferiority margin of -10%, for the individual studies as well as pooled analysis, see Table 4.

Table 4 Virologic Outcomes of Randomised Treatment of GEMINI at Weeks 96 and 144 (Snapshot algorithm)

	GEMINI-1 and GEMINI-2 Pooled Data*			
	DTG + 3TC N=716	**DTG + TDF/FTC N=717**	**DTG + 3TC N=716**	**DTG + TDF/FTC N=717**
	Week 96		Week 144	
HIV-1 RNA <50 copies/mL	86%	90%	82%	84%
Treatment Difference† (95% confidence intervals)	-3.4% (-6.7, 0.0)		-1.8% (-5.8; 2.1)	
Virologic non response	3%	2%	3%	3%
Reasons				
Data in window, ≥50 cps/mL	<1%	<1%	<1%	<1%
Discontinued, lack of efficacy	1%	<1%	1%	<1%
Discontinued, other reasons, ≥50 cps/mL	<1%	<1%	<1%	2%
Change in ART	<1%	<1%	<1%	<1%
No virologic data at Week 96/Week 144 window	11%	9%	15%	14%
Reasons				
Discontinued study due to AE or death	3%	3%	4%	4%
Discontinued study for other reasons	8%	5%	11%	9%
Loss to follow-up	3%	1%	3%	3%
Withdrew consent	3%	2%	4%	3%
Protocol deviations	1%	1%	2%	1%
Physicians decision	1%	<1%	2%	1%
Missing data in window, on study	0%	<1%	<1%	<1%

* The results of the pooled analysis are in line with those of the individual studies.
† 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

The mean increase in CD4+ T-cell counts through week 144 was 302 cells/mm^3 in the dolutegravir plus lamivudine arm and 300 cells/mm^3 in the dolutegravir plus tenofovir/emtricitabine arm.

Virologically suppressed subjects

The efficacy of dolutegravir/lamivudine in virologically suppressed subjects is supported by data from a randomised, open-label, trial (TANGO [204862]). A total of 741 adult HIV-1 infected subjects, without any evidence of resistance to the NRTI or integrase inhibitor (INSTI) class and 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 dolutegravir/lamivudine FDC or continue with TBR for up to 200 weeks. Randomisation was stratified by baseline core agent class (protease inhibitor [PI], 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 (adjusted for randomisation stratification factor).

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 around 3 years prior to Day 1 Around 80% were on INSTI-based TBR (mainly elvitegravir/c) at baseline.

In the primary 48 week analysis, dolutegravir/lamivudine was non-inferior to TBR, with <1% of subjects in both arms experiencing virologic failure (HIV-1 RNA ≥50 c/mL) (Table 5).

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

	DTG/3TC 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%

*Based on an 8% non-inferiority margin, DTG/3TC is non-inferior to TBR at Week 48 in the secondary analysis (proportion of subjects achieving <50 copies/mL plasma HIV-1 RNA).

**Based on a 4% non-inferiority margin, DTG/3TC is non-inferior to TBR at Week 48 in the primary analysis (proportion of subjects with plasma HIV-1 RNA ≥50 c/mL).

†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.

Treatment outcomes between treatment arms at week 48 were similar across the stratification factor, baseline third agent class 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 mm^3 in subjects who switched to dolutegravir/lamivudine and 11.0 cells per mm^3 in subjects who stayed on TBR.

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 dolutegravir/lamivudine and TBR groups, respectively. Based on a non-inferiority margin of 4%, dolutegravir/lamivudine 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 dolutegravir/lamivudine arm and 45 cells/mm^3 in the TBR arm.

Paediatric population

The efficacy of Dovato, or the dual combination of dolutegravir plus lamivudine (as single entities) has not been studied in children or adolescents.

5.2 Pharmacokinetic properties

When administered in fasted state, bioequivalence regarding C_{max} was achieved for dolutegravir, when comparing Dovato to dolutegravir 50 mg co-administered with lamivudine 300 mg. Dolutegravir AUC_{0-t} was 16% higher for Dovato than for dolutegravir 50 mg co-administered with lamivudine 300 mg. This increase is not considered clinically relevant.

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

32% higher than lamivudine 300 mg co-administered with dolutegravir 50 mg. The higher lamivudine C_{max}, is not considered clinically relevant.

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 approximately 80-85%. For Dovato, the median time to maximal plasma concentration (t_{max}) is 2.5 hours for dolutegravir and 1.0 hour for lamivudine, when dosed under fasted conditions.

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

Administration of a single Dovato tablet with a high fat meal increased dolutegravir $AUC_{(0-\infty)}$ and C_{max} by 33% and 21%, respectively, and decreased the lamivudine C_{max} by 30% compared to fasted conditions. The lamivudine $AUC_{(0-\infty)}$ 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 (Vd/F) is 17-20 L. Intravenous studies with lamivudine showed that the mean apparent volume of distribution is 1.3 L/kg.

Dolutegravir is highly bound (> 99%) to human plasma proteins based on *in vitro* data. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited plasma protein binding *in vitro* (< 16%- 36% to serum albumin).

Dolutegravir and lamivudine are present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on a stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC_{50}). The mean ratio of CSF/serum lamivudine concentrations 2-4 hours after oral administration was approximately 12%. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

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

Biotransformation

Dolutegravir is primarily 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 active substance is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of

total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of unchanged lamivudine. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5-10%).

Drug interactions

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50}>50 μM) of the enzymes cytochrome P_{450} (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, UGT1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OCT1, MATE2-K, multidrug resistance-associated protein (MRP) 2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters (see section 4.5).

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

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

Lamivudine was not significantly metabolised by CYP enzymes.

Elimination

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

The observed lamivudine half-life of elimination is 18 to 19 hours. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0.32 L/h/kg, predominantly by renal clearance (> 70%) via the organic cationic transport system. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance < 50 mL/min (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship(s)

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

Special patient populations

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

Limited data are available in adolescents receiving a daily dose of 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 >65 years of age are limited.

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

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (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. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

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

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

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

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

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

Polymorphisms in drug metabolising enzymes
There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).

Gender
Population PK analyses using pooled pharmacokinetic data from clinical studies where dolutegravir or lamivudine was administered to adults in combination with other ARVs revealed no clinically relevant effect of gender on the exposure of dolutegravir or lamivudine. There is no evidence that a dose adjustment of dolutegravir or lamivudine would be required based on the effects of gender on PK parameters.

Race
Population PK analyses using pooled pharmacokinetic data from clinical studies where dolutegravir was administered to adults in combination with other ARVs 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).

5.3 Preclinical safety data

There are no data available on the effects of the combination of dolutegravir and lamivudine in animals.

Carcinogenesis and mutagenesis

Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in viv*o rodent micronucleus assay. Lamivudine was not mutagenic in bacterial tests, but consistent with other nucleoside analogues, inhibits cellular DNA replication in *in vitro* mammalian tests such as the mouse lymphoma assay. The results from two in vivo rat micronucleus tests with lamivudine were negative. Lamivudine has not shown any genotoxic activity in the *in vivo* studies.

The carcinogenic potential of a combination of dolutegravir and lamivudine has not been tested. Dolutegravir was not carcinogenic in long term studies in the mouse and rat. In long-term oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential.

Reproductive toxicology studies

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

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (37.2 times the 50 mg human clinical exposure, based on AUC following single dose in the fasted state). 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 (0.55 times the 50 mg human clinical exposure, based on AUC following single dose in the fasted state). In rabbits, maternal toxicity (decreased food consumption, scant/no faeces/urine, suppressed body weight gain) was observed at 1000 mg/kg (0.55 times the 50 mg human clinical exposure, based on AUC following single dose in the fasted state).

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

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

Repeated dose toxicity

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 28.5 and 1.1 times the 50 mg human clinical exposure following single dose in the fasted state based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local active substance administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 30 times the human mg/kg equivalent dose (based on 50 kg human), and 11 times the human mg/m^2 equivalent dose for a total daily clinical dose of 50 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Mannitol
Sodium starch glycolate (Type A)
Povidone (K29/32)
Sodium stearyl fumarate
Magnesium Stearate

Tablet coating

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Opaque, white HDPE (high density polyethylene) bottles closed with child resistant polypropylene closures, with a polyethylene faced induction heat seal liner. Each pack consists of one bottle containing 30 film-coated tablets.

6.6 Special precautions for disposal

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

7. MANUFACTURER

Glaxo Wellcome S.A., Avenida De Extremadura 3, 09400 Aranda De Duero, Burgos, Spain.

8. MARKETING AUTHORISATION HOLDER

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

9. LICENSE NUMBER

165-26-36147-00

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Dov DR v6