SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Twinaqt Tablets (Dolutegravir and Lamivudine Tablets 50 mg/300 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains

Lamivudine USP ..... 300 mg

Dolutegravir Sodium is Eq. to Dolutegravir... 50 mg

Colors: Indigo Carmine Aluminum Lake, Titanium

Dioxide USP Excipients..... Q.S.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Twinaqt is indicated as a complete regimen for the treatment of HIV-1 infection in adults with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Twinaqt.

4.2 Posology and method of administration

Testing Prior to or When Initiating Treatment with Twinaqt

Prior to or when initiating Twinaqt, test patients for HBV infection Pregnancy testing is recommended before initiation of Twinaqt in individuals of childbearing potential.

Posology

Twinaqt is a fixed-dose combination product containing 50 mg of dolutegravir and 300 mg of lamivudine. The recommended dosage regimen of Twinaqt in adults is one tablet taken orally

once daily with or without food.

Recommended Dosage with Certain Co administered Drugs

The dolutegravir dose (50 mg) in Twinaqt is insufficient when co administered with drugs listed in Table 1 that may decrease dolutegravir concentrations; the following dolutegravir dosage regimen is recommended.

Table 1. Dosing Recommendations for Twinaqt with Co administered Drugs

Co administered Drug	Dosing Recommendation
Carbamazepine, rifampin	An additional dolutegravir 50-mg tablet, separated by 12 hours from Twinaqt, should be taken.

Special population

Renal Impairment

Twinaqt is not recommended for patients with creatinine clearance <30 mL/min because it is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of Twinaqt, is required for patients with creatinine clearance <30 mL/min, then the individual components should be used.

Hepatic Impairment

No dosage adjustment of Twinaqt is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Score A or B). Dolutegravir has not been studied in patients with severe hepatic impairment (Child-Pugh Score C); therefore, Twinaqt is not recommended for patients with severe hepatic impairment.

Pediatric Use

The safety and efficacy of the fixed dose combination of dolutegravir and lamivudine have not been established in pediatric patients.

Geriatric Use

Clinical trials of the fixed dose combination of dolutegravir and lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of Twinaqt in elderly patients reflecting the

greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Method of administration

Twinaqt tablets are for oral administration.

4.3 Contraindications

Hypersensitivity

Twinaqt is contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to dolutegravir and lamivudine or any component of the product.

In patients receiving dofetilide there may be a potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events.

4.4 Special warnings and precautions for use

WARNING: PATIENTS CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV-1): EMERGENCE OF LAMIVUDINE-RESISTANT HBV AND EXACERBATIONS OF HBV

All patients with HIV-1 should be tested for the presence of HBV prior to or when initiating Twinaqt. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. If Twinaqt is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen. Severe acute exacerbations of HBV have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued lamivudine, a component of Twinaqt. Closely monitor hepatic function in these patients and, if appropriate, initiate anti-HBV treatment.

Patients Co-infected with HIV-1 and HBV: Emergence of Lamivudine-Resistant HBV and the Risk of Post treatment Exacerbations of HBV

All patients with HIV-1 should be tested for the presence of HBV prior to or when initiating Twinaqt.

Emergence of Lamivudine-Resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic HBV in subjects dually infected with HIV-1 and HBV. Emergence of HBV variants associated with resistance to lamivudine has been reported in HIV-1–infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with HBV. If a decision is made to administer Twinaqt to patients co-infected with HIV-1 and HBV, additional treatment should be considered for

appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.

Severe Acute Exacerbations of HBV in Patients Co-infected with HIV-1 and HBV

Severe acute exacerbations of HBV have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued products containing lamivudine, and may occur with discontinuation of Twinaqt. Patients who are co-infected with HIV-1 and HBV who discontinue Twinaqt should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with Twinaqt. If appropriate, initiation of anti-HBV therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with the use of dolutegravir, a component of Twinaqt, and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. These events were reported in <1% of subjects receiving dolutegravir in Phase 3 clinical trials.

Discontinue Twinaqt 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 or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with Twinaqt or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying

hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of Twinaqt. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or HBV reactivation particularly in the setting where antihepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure, have also been reported in patients receiving a dolutegravir-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with fixed dose combination of abacavir, dolutegravir, and lamivudine. Monitoring for hepatotoxicity is recommended.

Embryo-Fetal Toxicity

An ongoing observational study showed an association between dolutegravir and an increased risk of neural tube defects when dolutegravir was administered at the time of conception and in early pregnancy. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform individuals of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with Twinaqt. Assess the risks and benefits of Twinaqt and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester.

Pregnancy testing is recommended before initiation of Twinaqt in individuals of childbearing potential.

Individuals of childbearing potential should be counseled on the consistent use of effective contraception.

Twinaqt may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including lamivudine (a component of the fixed dose combination of dolutegravir and lamivudine). A majority of these cases have been in women. Female sex and obesity may be risk factors for the development of lactic acidosis

and severe hepatomegaly with steatosis in patients treated with antiretroviral nucleoside analogues. Monitor closely when administering Twinaqt to any patient with known risk factors for liver disease. Treatment with Twinaqt should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The co administration of Twinaqt and other drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Loss of therapeutic effect of Twinaqt and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of coadministered drugs.

Consider the potential for drug interactions prior to and during therapy with Twinaqt, review co administered drugs during therapy with Twinaqt, and monitor for the adverse reactions associated with the co administered drugs.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including fixed dose combination of dolutegravir and lamivudine. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Coadministration with Other Antiretroviral Drugs
Twinaqt is a complete regimen for the treatment of HIV-1 infection; therefore, Coadministration with other antiretroviral drugs for the treatment of HIV-1 infection is not recommended. Information regarding potential drug-drug interactions with other antiretroviral drugs is not provided).

Potential for Twinaqt to Affect Other Drugs
Dolutegravir, a component of Twinaqt, inhibits the renal organic cation transporters (OCT)2 and multidrug and toxin extrusion transporter (MATE)1; thus, it may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 such as dofetilide, dalfampridine, and metformin.

Potential for Other Drugs to Affect the Components of Twinaqt
Dolutegravir is metabolized by uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1 with some contribution from cytochrome P450 (CYP)3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of Twinaqt. Coadministration of Twinaqt and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.
Coadministration of dolutegravir with polyvalent cation-containing products may lead to decreased absorption of dolutegravir.

Established and Other Potentially Significant Drug Interactions
No drug interaction studies were conducted with the fixed dose combination of dolutegravir and lamivudine. The drug interactions described are based on studies conducted with dolutegravir or lamivudine when administered alone. Information regarding potential drug interactions with the fixed dose combination of dolutegravir and lamivudine are provided in Table 2. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 2. Established and Other Potentially Significant Drug Interactions for the fixed dose combination of dolutegravir

and lamivudine: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Coadministered Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Antiarrhythmic: Dofetilide	↑ Dofetilide	Coadministration is contraindicated with Twinaqt.
Anticonvulsant: Carbamazepine[a]	↓ Dolutegravir	An additional dolutegravir 50-mg dose should be taken, separated by 12 hours from Twinaqt
Anticonvulsants: Oxcarbazepine Phenytoin Phenobarbital	↓ Dolutegravir	Avoid coadministration with Twinaqt because there are insufficient data to make dosing recommendations.
Antidiabetic: Metformin[a]	↑ Metformin	Refer to the prescribing information for metformin for assessing the benefit and risk of concomitant use of Twinaqt and metformin.
Antimycobacterial: Rifampin[a]	↓ Dolutegravir	An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from Twinaqt
Herbal product: St. John's wort (*Hypericum perforatum*)	↓ Dolutegravir	Avoid coadministration with Twinaqt because there are insufficient data to make dosing recommendations.

Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacidsa or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer Twinaqt 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium and iron supplements, including multivitamins containing calcium or iron[a]	↓ Dolutegravir	When taken with food, Twinaqt and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, Twinaqt should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.

Potassium channel blocker: Dalfampridine	↑ Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with Twinaqt should be considered against the risk of seizures in these patients.
Sorbitol[a]	↓ Lamivudine	When possible, avoid use of sorbitol-containing medicines with Twinaqt.

↑ = Increase, ↓ = Decrease.

4.6 Fertility pregnancy, lactation

Risk summary
Data from an ongoing birth outcome surveillance study have identified an increased risk of neural tube defects when dolutegravir, a component of Twinaqt, is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

Advise individuals of childbearing potential, including those actively trying to become pregnant, of the potential risk of neural tube defects with use of Twinaqt. Assess the risks and benefits of Twinaqt and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester. A benefit-risk assessment should consider factors such as feasibility of switching to another antiretroviral regimen, tolerability, ability to maintain viral suppression, and risk of HIV-1 transmission to the infant against the risk of neural tube defects associated with in utero dolutegravir exposure during critical periods of fetal development.

There are insufficient human data on the use of the fixed dose combination of dolutegravir and lamivudine during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data:
Dolutegravir: In a birth outcome surveillance study in Botswana, there were 7 cases of neural tube defects reported out of 3,591 deliveries (0.19%) to women who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.11% (21/19,361 deliveries) in the non-dolutegravir arm and 0.07% (87/119,630 deliveries) in the HIV-uninfected arm. Seven cases reported with

dolutegravir included 3 cases of myelomeningocele, 2 cases of encephalocele, and one case each of anencephaly and iniencephaly. In the same study, no increased risk of neural tube defects was identified in women who started dolutegravir during pregnancy. Two infants out of 4,448 (0.04%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 5 infants out of 6,748 (0.07%) deliveries to women who started non-dolutegravir containing regimens during pregnancy. The reported risks of neural tube defects by treatment groups were based on interim analyses from the ongoing surveillance study in Botswana. It is unknown if baseline characteristics were balanced between the study treatment groups. The observed trends of association could change as data accumulate.

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to definitively address the risk of neural tube defects with dolutegravir. Data from the birth outcome surveillance study described above and postmarketing sources with more than 1,000 pregnancy outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens and 4.8% (95% CI: 2.8% to 7.8%) following second-/third- trimester exposure to dolutegravir-containing regimens. In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%.

Dolutegravir has been shown to cross the placenta. In a clinical trial in Uganda and South Africa in women during the last trimester of pregnancy receiving dolutegravir 50 mg once daily, the ratio of median dolutegravir concentration in fetal umbilical cord to that in maternal peripheral plasma was 1.21 (range 0.51-2.11) (n = 15).

Lamivudine:
Based on prospective reports to the APR of exposures to lamivudine

during pregnancy resulting in live births (including over 5,300 exposed in the first trimester and over 7,400 exposed in the second/third trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1% (95% CI: 2.7% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.9% (95% CI: 2.5% to 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lactation

The Centers for Disease Control and Prevention recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Dolutegravir and lamivudine are present in human milk. There is no information on the effects of the fixed dose combination of dolutegravir and lamivudine or the components of the fixed dose combination of dolutegravir and lamivudine on the breastfed infant or the effects of the drugs on milk production.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving the fixed dose combination of dolutegravir and lamivudine.

Females and Males of Reproductive Potential

In individuals of childbearing potential currently on Twinaqt who are actively trying to become pregnant or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing Twinaqt and discuss with the patient if an alternative treatment should be considered.

Pregnancy Testing

Pregnancy testing is recommended in individuals of childbearing potential before initiation of Twinaqt.

Contraception

Individuals of childbearing potential who are taking Twinaqt should be counseled on the consistent use of effective contraception.

4.7 Effects on ability to drive and use machines

Twinaqt 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 Twinaqt 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.

Tabulated list of adverse reactions

The adverse reactions from clinical study and post-marketing experience are listed in Table 3 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 3: Tabulated summary of adverse reactions to the fixed dose combination of dolutegravir and lamivudine based on clinical study and postmarketing experience with the fixed dose combination of dolutegravir and lamivudine 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, immune reconstitution syndrome
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, weight increased
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 w 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.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.

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.

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.

Paediatric population

There are no clinical study data on the effects of the fixed dose combination of dolutegravir and lamivudine 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:
Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org ' or the relevant regulatory Authority

4.8 Overdose

There is no known specific treatment for overdose with Twinaqt. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Dolutegravir
As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Lamivudine
Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

5 PHARMACOLOGICAL PROPERTIES

5.4 Pharmacodynamic properties

Mechanism of Action
Dolutegravir: Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified recombinant HIV-1 integrase and pre-processed substrate DNA resulted in IC50 values of 2.7 nM and 12.6 nM.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue.

Antiviral Activity in Cell Culture

Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentrations of drug necessary to affect viral replication by 50 percent (EC50) values of 0.5 nM (0.21 ng/mL) to 2.1 nM (0.85 ng/mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells.

Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC50 value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M [clades A-G], and 3 in group O) with EC50 values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC50 values against three HIV2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC50 values were in the range of 3 to 15,000 nM (1 nM = 0.23 ng/mL). The EC50 values of lamivudine against different HIV-1 clades (A-G) and group O viruses ranged from 1 to 120 nM, and against HIV-2 isolates from 3 to 120 nM in PBMCs.

Antiviral Activity in Combination with Other Antiviral Agents

Neither dolutegravir nor lamivudine were antagonistic to all tested anti-HIV agents.

Resistance

ell Culture: *Dolutegravir*: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions emerged in different passages; the substitution G118R emergence conferred decreased susceptibility to

dolutegravir of 10-fold, while substitutions E92Q, S153F or Y, G193E, or R263K conferred decreased susceptibility to dolutegravir of up to 4-fold.

Lamivudine: HIV-1 resistance to lamivudine involves the development of a M184V or M184I amino acid change close to the active site of the viral RT. This variant arises both in cell culture and in HIV-1–infected patients treated with lamivudine-containing antiretroviral therapy. Substitutions M184V or I confer high-level resistance to lamivudine.

Clinical Subjects: At Week 144, none of the 12 subjects in the dolutegravir plus lamivudine group or the 9 subjects in the dolutegravir plus TDF/FTC group who met the protocol-defined confirmed virologic withdrawal criteria across the pooled GEMINI-1 and GEMINI-2 trials had emergent INSTI- or NRTI-resistance substitutions.

No subject who received the fixed dose combination of dolutegravir and lamivudine in the TANGO trial met the protocol-defined confirmed virologic withdrawal criteria through Week
144. No emergent INSTI- or NRTI-resistance was detected by genotypic or phenotypic analyses of the last on-treatment isolate from one subject who received the fixed dose combination of dolutegravir and lamivudine with HIV-1 RNA ≥400 copies/mL at withdrawal. No emergent resistance was detected by genotypic or phenotypic analyses of HIV-1 integrase, protease, or reverse transcriptase at the time of virologic failure in 3 subjects in the TBR arm who met the confirmed virologic withdrawal criteria.

Cross-Resistance

Dolutegravir: The susceptibility of dolutegravir was tested against 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
>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 >2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference).

Lamivudine: Cross-resistance conferred by the M184V or I RT

has been observed within the NRTI class of antiretroviral agents. The M184V or I substitution confers resistance to emtricitabine and to abacavir, which selects M184V or I plus additional RT substitutions K65R, L74V, and Y115F. Zidovudine maintains its antiretroviral activities against lamivudine- resistant HIV-1. Abacavir and tenofovir maintain antiretroviral activity against lamivudine- resistant HIV1 harboring only the M184V or I substitution.

Pharmacodynamic effects

Cardiac Electrophysiology

The effect of combination therapy as the fixed dose combination of dolutegravir and lamivudine or lamivudine given alone on the QT interval has not been studied. At a 250-mg suspension dose (exposures approximately 3–fold that of the 50-mg once-daily dose at steady state), dolutegravir given alone did not prolong the QTc interval to any clinically relevant extent.

Effects of Dolutegravir on Renal Function

No clinically significant dolutegravir exposure-response relationship on the glomerular filtration rate or effective renal plasma flow was observed. The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days.

Clinical efficacy and safety

The efficacy of fixed dose combination of dolutegravir and lamivudine is supported by data from 2 randomized, double-blind, controlled trials (GEMINI-1 [NCT02831673] and GEMINI-2 [NCT02831764]) in HIV-1–infected adults with no antiretroviral treatment history, and data from a randomized, open-label, controlled trial (TANGO [NCT03446573]) in virologically suppressed HIV-1–infected adults.

Clinical Trial Results in HIV-1–Infected Adult Subjects with No Antiretroviral Treatment History

GEMINI-1 and GEMINI-2 are identical 148-week, Phase 3, randomized, multicenter, parallel- group, non-inferiority trials. A total of 1,433 HIV-1–infected adults with no antiretroviral treatment history received treatment in the trials. Subjects were enrolled with a screening plasma HIV-1 RNA of 1,000 to

≤500,000 copies/mL and without evidence of major resistance-associated mutations or evidence of HBV infection. Subjects were randomized to receive a 2- drug regimen of dolutegravir 50 mg plus lamivudine 300 mg administered once daily or dolutegravir 50 mg plus fixed-dose combination of emtricitabine-tenofovir 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) who were randomized and treated.

At baseline, in the pooled analysis, the median age of subjects was 33 years, 15% female, 69% white, 9% were CDC Stage 3 (AIDS), the median plasma HIV-1 RNA was 4.4 log10 copies/mL, 20% had HIV-1 RNA >100,000 copies/mL, the median CD4+ cell count was 432 cells/mm3, and 8% had CD4+ cell count ≤200 cells/mm3; these characteristics were similar between trials and treatment arms within each trial.

Week 144 outcomes (including outcomes by key baseline covariates) for the pooled GEMINI- 1 and GEMINI-2 trials are shown in Table 4. The results of the pooled analysis are consistent with the results from the individual trials, for which the secondary endpoint is the difference in proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 144 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus fixed-dose combination of emtricitabine-tenofovir. The proportions of subjects with plasma HIV-1 RNA <50 copies/mL in the group receiving dolutegravir plus lamivudine versus dolutegravir plus fixed-dose combination of emtricitabine-tenofovir were 79% and 83%, respectively, in GEMINI-1 and 84% in both treatment arms of GEMINI-2. The adjusted difference was -3.6% (95% CI: -9.4%, 2.1) for GEMINI-1 and 0.0% (95% CI: -5.3%, 5.3%) for GEMINI-2. At Week 144, no subjects who met the protocol-defined confirmed virologic withdrawal criteria had any treatment-emergent substitutions associated with resistance to dolutegravir or NRTIs.

Table 4. Pooled Virologic Outcomes of Randomized Treatment of HIV-1–Infected Adults with No Antiretroviral Treatment History in GEMINI-1 and GEMINI-2 Trials at Weeks 48 and 144 (Snapshot Algorithm)

	GEMINI-1 and GEMINI-2 Pooled Data[a]	
	Week 48	**Week 144**

Virologic Outcomes	Dolutegravir plus Lamivudine (n = 716)	Dolutegravir plus Emtricitabine- tenofovir (n = 717)	Dolutegravir plus lamivudine (n = 716)	Dolutegravirplus Emtricitabine-tenofovir (n = 717)
HIV-1 RNA <50 copies/mL	91%	93%	82%	84%

Treatment Difference (95% CI)[b]	-1.7% (-4.4%, 1.1%)		-1.8% (-5.8%, 2.1%)	
Virologic nonresponse	3%	2%	3%	3%
Reasons				
Data in window ≥50 copies/mL	1%	<1%	<1%	<1%
Discontinued for lack of efficacy	<1%	<1%	1%	<1%
Discontinued for other reasons and ≥50 copies/mL	<1%	<1%	<1%	2%
Change in ART	<1%	<1%	<1%	<1%
No virologic data at Week 48 or Week 144 window	6%	5%	15%	14%
Reasons				
Discontinued trial due to adverse event or death	1%	2%	4%	4%
Discontinued trial for other reasons	4%	3%	11%	9%
Missing data during window but on trial	<1%	0	<1%	<1%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category				
	% (n/N)	**% (n/N)**	**% (n/N)**	**% (n/N)**
Plasma Viral Load (copies/mL)				
≤100,000	91% (526/576)	94% (531/564)	81% (469/576)	84% (471/564)
>100,000	92% (129/140)	90% (138/153)	82% (115/140)	84% (128/153)
CD4+ (cells/mm3)				
≤200	79% (50/63)	93% (51/55)	67% (42/63)	76% (42/55)
>200	93% (605/653)	93% (618/662)	83% (542/653)	84% (557/662)

Gender				
Male	92% (555/603)	94% (580/619)	83% (500/603)	84% (517/619)
Female	88% (100/113)	91% (89/98)	74% (84/113)	84% (82/98)
Race				
White	93% (447/480)	95% (471/497)	85% (409/484)	86% (429/499)
African-American/African Heritage	84% (83/99)	84% (64/76)	67% (60/90)	73% (52/71)
Asian	94% (67/71)	94% (68/72)	79% (56/71)	82% (59/72)
Other	88% (58/66)	92% (66/72)	83% (59/71)	79% (59/75)
Ethnicity				
Hispanic or Latino	90% (193/215)	93% (216/232)	83% (178/215)	85% (197/232)
Not Hispanic or Latino	92% (462/501)	93% (453/485)	81% (406/501)	83% (402/485)
Age (years)				
<50	92% (597/651)	94% (597/637)	81% (530/651)	84% (533/637)

≥50	89% (58/65)	90% (72/80)	83% (54/65)	83% (66/80)

[a] The results of the pooled analysis are similar to the individual trials, for which the primary endpoint (proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus fixed-dose combination of emtricitabine-tenofovir) 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.

[b] Based on Cochran–Mantel–Haenszel-stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 copies/mL versus >100,000 copies/mL) and CD4+ cell count (≤200 cells/mm3 versus >200 cells/mm3). Pooled analysis also stratified by trial. The other Snapshot outcomes (HIV-1 RNA ≥50 copies/mL and no virologic data in the visit window) were combined into a single category for the analysis.

The primary endpoint was assessed at Week 48 and the virologic success rate was 91% in the group receiving dolutegravir plus lamivudine and 93% in the group receiving dolutegravir plus fixed-dose combination of emtricitabine-tenofovir, with a treatment difference of -1.7% (95% CI: -4.4%, 1.1%) in the pooled data. The results of the pooled analysis are similar to the individual trials, for which the primary endpoint (proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus fixed-dose combination of fixed-dose combination of emtricitabine-tenofovir) 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.

The adjusted mean change from baseline in CD4+ cell count based on the pooled analysis at Week 144 was 302 cells/mm3 for the group receiving dolutegravir plus lamivudine and 300 cells/mm3 for the group receiving dolutegravir plus fixed-dose combination of emtricitabine- tenofovir.

Clinical Trial Results in HIV-1–Infected Virologically Suppressed Adult Subjects Who Switched to fixed dose combination of dolutegravir and lamivudine

The efficacy of fixed dose combination of dolutegravir and lamivudinein HIV-1–infected, antiretroviral treatment-experienced, virologically suppressed subjects is supported by data from a 200-week, Phase 3, randomized, open-label, multicenter, parallel-group, non-inferiority controlled trial

(TANGO). A total of 741 adult HIV-1–infected subjects who were on a stable suppressive TBR received treatment in the trial. Subjects were randomized in a 1:1 ratio to receive fixed dose combination of dolutegravir and lamivudine once daily or continue with their TBR for up to 148 weeks; at Week 148, the subjects randomized to continue with their TBR were switched to fixed dose combination of dolutegravir and lamivudine once daily. All subjects are followed up to Week 200. Randomization was stratified by baseline third-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 copies/mL (virologic non-response) at Week 48 (Snapshot algorithm adjusting for randomization stratification factor).

At baseline, the median age of subjects was 39 years, 8% were female, 21% non-white, 5% were CDC Class C (AIDS), and 98% of subjects had baseline CD4+ cell count ≥200 cells/mm^3
; these characteristics were similar between treatment arms. Subjects receiving the fixed dose combination of dolutegravir and lamivudine and a TBR had been on an antiretroviral regimen for a median of 2.8 and 2.9 years, respectively, prior to Day 1. Most subjects were on an integrase inhibitor-based TBR (78% and 80% of subjects who received fixed dose combination of dolutegravir and lamivudine and a TBR, respectively).

In the primary 48 week analysis, <1% of subjects in both arms experienced virologic failure (HIV-1 RNA ≥50 copies/mL) at Week 48 based on the Snapshot algorithm. Based on a 4% noninferiority margin, fixed dose combination of dolutegravir and lamivudine was non-inferior to TBR in the primary analysis (proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL), as the upper bound of the 95% CI for the adjusted treatment difference (-1.2%, 0.7%) was less than 4%.

At Week 144, the proportion of subjects with HIV-1 RNA ≥50 copies/mL (Snapshot) was 0.3% and 1.3% in fixed dose combination of dolutegravir and lamivudineand TBR treatment arms, respectively (Table 5).

Table 5 Virologic Outcomes of Randomized Treatment in TANGO Trial at Weeks 48 and 144 in Virologically Suppressed Subjects Who Switched to fixed dose combination of dolutegravir and lamivudine

	Week 48[a]		Week 144	
Virologic Outcomes	**fixed dose combination of dolutegravir and lamivudine (n = 369)**	**TBR (n = 372)**	**fixed dose combination of dolutegravir and lamivudine (n = 369)**	**TBR (n = 372)**
Virologic nonresponse (≥50 copies/mL)	<1%	1%	<1%	1%
Treatment Difference (95% CI)[b]	-0.3% (-1.2%, 0.7%)		-1.1% (-2.4%, 0.2%)	
HIV-1 RNA <50 copies/mL[c]	93%	93%	86%	82%
Reasons for virologic nonresponse				
Data in window ≥50 copies/mL	0	0	0	0
Discontinued for lack of efficacy	0	1%	0	1%
Discontinued for other reasons and ≥50 copies/mL	<1%	0	<1%	0
Change in ART	0	0	0	<1%
Reasons for no virologic data at Week 48 or Week 144 window	7%	6%	14%	17%
Discontinued trial due to adverse event or death	3%	<1%	6%	2%
Discontinued trial for other reasons	3%	6%	7%	15%
Missing data during window but on trial[d]	0	<1%	1%	0

TBR = Tenofovir alafenamide-based regimen.

[a] Based on a 4% non-inferiority margin, fixed dose combination of dolutegravir and lamivudine is non-inferior to TBR at Week 48 in the primary analysis (proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL) because the upper bound of the 95% CI for the adjusted treatment difference is less than 4%.

[b] Based on Cochran–Mantel–Haenszel-stratified analysis adjusting for baseline third-agent class (PI, INSTI, or NNRTI). The other Snapshot outcomes (HIV-1 RNA <50 copies/mL and no virologic data in the visit window) were combined into a single category for the analysis, and subjects who had no virologic data at Week 144 were assumed to have virologic response (<50 copies/mL).

[c] At Week 144 in the secondary analysis (proportion of subjects achieving plasma HIV-1 RNA
<50 copies/mL), the adjusted treatment difference was 4.2% (95% CI: -1.1%, 9.5%).

[d] Five (5) and 2 subjects in the fixed dose combination of dolutegravir and lamivudine and TBR arms, respectively, had no Week 144 Snapshot data due to Coronavirus Disease 2019 (COVID-19).

In TANGO, treatment outcomes between treatment arms were similar across the stratification factor, baseline third-agent class (PI, INSTI, or NNRTI), and across subgroups by age, sex, race, baseline $CD4^+$ cell count, CDC HIV disease stage, and countries. The median change from baseline in CD4+ T-cell count at Week 144 was 36.0 cells/mm3 in the fixed dose combination of dolutegravir and lamivudine arm and 35.0 cells/mm3 in the TBR arm.

5.5 Pharmacokinetic properties

The Cmax, Ctrough, and AUCtau parameters of the components of the fixed dose combination of dolutegravir and lamivudine are provided in Table 6.

Table 6. Multiple-Dose Pharmacokinetic Parameters of the Components of the fixed dose combination of dolutegravir and lamivudine

Parameter Mean (%CV)	Dolutegravir[a]	Lamivudine[b]
Cmax (mcg/mL)	3.67 (20%)	2.04 (26%)
Ctrough (mcg/mL)	1.11 (46%)	0.042 (38%)
AUCtau (mcg/h/mL)	53.6 (27%)	8.87 (21%)

Cmax = Maximum concentration; Ctrough = Lowest concentration before administration of the next dose; AUCtau = Area under the concentration-time curve integrated across the dosing interval.

[a] Based on dolutegravir 50-mg once-daily dosage administered to antiretroviral treatment-naive adults.

[b]Based on lamivudine 300-mg once-daily dosage administered to healthy subjects.

The absorption, distribution, and elimination pharmacokinetic parameters of the components of the fixed dose combination of dolutegravir and lamivudine are provided in Table 7.

Table 7. Pharmacokinetic Properties of the Components of the fixed dose combination of dolutegravir and lamivudine

Pharmacokinetic Parameters	**Dolutegravir**	**Lamivudine**
Absorption		
T_{max} (h), median[a]	2.5	1
Effect of Food		
High-fat meal[b] (relative to fasting)	No clinically significant differences in the pharmacokinetics of either component (after administration of the fixed dose combination of dolutegravir and lamivudine) were observed[c]	
Distribution		
Plasma protein binding[d]	Approximately 99%	36%
Blood-to-plasma ratio	0.44 - 0.54	1.1 - 1.2
Elimination		
$t_{1/2}$ (h)	Approximately 14	13 - 19
Metabolism		
Metabolic pathways	UGT1A1 (primary) CYP3A (minor)	Not significantly metabolized
Excretion		
Major route of elimination	Metabolism	Renal, by OCT system
Urine (unchanged)	31% (<1%)[e]	Approximately 70%[f]
Feces (unchanged)	64% (53%)[e]	–

T_{max} = Time to maximum concentration (C_{max}); $t_{1/2}$ = Elimination half-life; UGT Uridine diphosphate glucuronosyl transferase; CYP = Cytochrome P450; OCT = Organic cation transporter.

[a] After administration of the fixed dose combination of dolutegravir and lamivudine (fasted state).

[b] High-fat meal is approximately 900 kcal, 56% fat.

[c] The geometric mean (90% confidence interval) AUC ratio (fed/fasted) of dolutegravir and lamivudine is 1.33 (1.18, 1.48) and 0.91 (0.87, 0.96), respectively.

[d] Based on in vitro data.

[e] Based on single-dose, mass balance study of radiolabeled dolutegravir.

[f] Based on 24-hour urine collection obtained after

oral or IV administration. Specific Populations

No clinically significant differences in the pharmacokinetics of the components of the fixed dose combination of dolutegravir and lamivudine were observed based on age, sex, or race. Pharmacokinetic data for dolutegravir and lamivudine in subjects aged 65 years and older are limited.

Renal impairment

Patients with a creatinine clearance between 30 and 49 mL/min receiving fixed dose combination of dolutegravir and lamivudine may experience a 1.6- to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min. There are no safety data from randomized, controlled trials comparing the fixed dose combination and the individual components dolutegravir and lamivudine in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of hematologic toxicities (neutropenia and anemia), although discontinuations due to neutropenia or anemia each occurred in <1% of subjects. Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive Twinaqt should be monitored for hematologic toxicities. If new or worsening neutropenia or anemia develop, dose adjustment of lamivudine, per lamivudine prescribing information, is recommended. If lamivudine dose adjustment is indicated, Twinaqt should be discontinued and the individual components should be used to construct the treatment regimen. Because Twinaqt is a fixed-dose tablet and cannot be dose adjusted, Twinaqt is not recommended in patients with creatinine clearance less than 30 mL per minute.

Drug Interaction Studies

Clinical Studies: No drug interaction studies were conducted with fixed dose combination of dolutegravir and lamivudine. The drug interaction studies described below were conducted with dolutegravir or lamivudine when used alone. Table 8 summarizes the effects of dolutegravir on the pharmacokinetics of coadministered drugs. Table 9 summarizes the effect of other drugs on the pharmacokinetics of dolutegravir when used alone and Table 10 summarizes the effect of sorbitol on the pharmacokinetics of lamivudine when used alone.

Table 8. Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	**Dose of Dolutegravir**	**Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00**		
		Cmax	**AUC**	**Ctau or C24**
Daclatasvir 60 mg once daily	50 mg once daily	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Ethinyl estradiol 0.035 mg	50 mg twice daily	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin[a] 500 mg twice daily	50 mg once daily	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin[a] 500 mg twice daily	50 mg twice daily	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	_	0.95 (0.79 to 1.15)	_
Norelgestromin[b] 0.25 mg	50 mg twice daily	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	0.88 (0.80, 0.98) 1.01	0.92 (0.85, 0.99) 0.99	NA 0.99 (0.97, 1.01)

		(0.93, 1.10)	(0.97, 1.01)	
Velpatasvir 100 mg once daily	50 mg once daily	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

[a] OCT2 or multidrug and toxin extrusion (MATE)1 substrate.

[b] Norelgestromin is the active metabolite of norgestimate.

No clinically significant differences in the pharmacokinetics of tenofovir (organic anion transporter [OAT]1 and OAT3 substrates) or para-amino hippurate (OAT1 and OAT3 substrates) were observed when coadministered with dolutegravir.

No clinically significant differences in the pharmacokinetics of trimethoprim/sulfamethoxazole were observed when coadministered with lamivudine.

Table 9. Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	**Dose of Dolutegravir**	**Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00**		
		Cmax	**AUC**	**C□au or C24**
Antacid (MAALOX) simultaneous administration	50-mg single dose	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50-mg single dose	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50-mg single dose	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50-mg single dose	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50-mg single dose	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine	50 mg	0.67	0.51	0.27

300 mg twice daily	once daily	(0.61 to 0.73)	(0.48 to 0.55)	(0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50-mg single dose	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50-mg single dose	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50-mg single dose	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50-mg single dose	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50-mg single dose	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily

Table 10. Effect of Sorbitol on the Pharmacokinetics of Lamivudine

Coadministered Drug and Dose[a]		**Lamivudine Pharmacokinetic Parameters (% Decreased)**		
		Cmax	**AUC0-24**	**AUCinf**
Sorbitol (Excipient)	3.2 grams	28%	20%	14%
	10.2 grams	52%	39%	32%
	13.4 grams	55%	44%	36%

Cmax = Maximum concentration; AUC(0-24) = Area under the concentration-time curve integrated from time of administration

to 24 hours; $AUC_{(inf)}$ = Area under the concentration-time curve from the time of administration to infinity.

a Coadministered with a single dose of lamivudine 300 mg.

No clinically significant differences in the pharmacokinetics of lamivudine were observed when coadministered with trimethoprim (MATE1, MATE2-K, and OCT2 inhibitor)/sulfamethoxazole, interferon alfa, or ribavirin.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically: Dolutegravir: Dolutegravir does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. Dolutegravir does not induce CYP1A2, CYP2B6, or CYP3A4.

Dolutegravir is a substrate of UGT1A3 and UGT1A9.
Dolutegravir does not inhibit UGT1A1 or UGT2B7.

Dolutegravir is a substrate of BCRP and P-gp. Dolutegravir does not inhibit P-gp, BCRP, bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. Dolutegravir is not a substrate of OATP1B1 or OATP1B3.

Lamivudine: Lamivudine is a substrate of P-gp and BCRP. Lamivudine does not inhibit OATP1B1/3, BCRP, P-gp, MATE1, MATE2-K, OCT1, OCT2, or OCT3.

Lamivudine pharmacokinetics in pregnant women

Lamivudine: Lamivudine pharmacokinetics were studied in 36 pregnant women during 2 clinical trials conducted in South Africa. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks' gestation using lamivudine 150 mg twice daily with zidovudine, 10 women at 38 weeks' gestation using lamivudine 150 mg twice daily with zidovudine, and 10 women at 38 weeks' gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were

not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9-fold (1.2- to 12.8-fold) greater compared with paired maternal serum concentration (n = 8).

5.6 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility.

Carcinogenicity

Dolutegravir: Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg/kg, and rats were administered doses of up to 50 mg/kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 26 times higher than those in humans at the recommended dose. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 17 times higher than those in humans at the recommended dose.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the recommended dose.

Mutagenicity

Dolutegravir: Dolutegravir was not genotoxic in the bacterial reverse mutation assay, in a mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility

Dolutegravir or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44 or 112 times, respectively, higher than the exposures in humans at the

recommended dose.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and 50 times (rats) the exposure in humans at the recommended human dose (RHD). Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the RHD; however, no adverse developmental effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (Cmax) 35 times the RHD.

Animal Data: Dolutegravir: Dolutegravir was administered orally to pregnant rats and rabbits (up to 1,000 mg/kg/day) on Gestation Days 6 to 17 and 6 to 18, respectively, and also to rats on Gestation Day 6 to Lactation/Postpartum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the RHD and in rats were approximately 50 times the exposure in humans at the RHD. In the rat pre/postnatal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 50 times human exposure at the RHD).

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg/kg/day) and rabbits (at 90, 300 and 1,000 mg/kg/day and at 15, 40, and 90 mg/kg/day) during organogenesis (on Gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the RHD. Evidence of early embryolethality was seen in the rabbit at systemic exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human exposure at the RHD. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg/kg/day (from prior to mating through Postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by the maternal administration of lamivudine.

6 PHARMACEUTICAL PARTICULARS

6.4 List of excipients

Microcrystalline Cellulose
USPNF Mannitol USP
Sodium Starch Glycolate
USPNF Croscarmellose
Sodium USPNF Povidone
USP
Purified Water USP
Magnesium Stearate
USPNF Opadry II
Blue IH

6.5 Incompatibilities

Not Applicable.

6.6 Shelf life

Proposed 24 Months

6.7 Special precautions for storage

Store protected from moisture, at a temperature not exceeding 30°C.

6.8 Nature and contents of container

30's tablets packed in HDPE
Container 90's tablets
packed in HDPE Container

6.9 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Limited

8 MARKETING AUTHORISATION NUMBER(S)

CTD12587/26245

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06-01-2026

10 DATE OF REVISION OF THE TEXT

06-01-2026