1. NAME OF TIIE MEDICINAL PRODUCT

Abacavir/Dolutegravir/Lamivudine 60 mg/5 mg/30 mg tablets for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 60 mg of abacavir (as sulfate), 5 mg of dolutegravir (as sodium) and 30 mg of lamivudine.

Excipient with known effect

Each dispersible tablet contains 9.5 mg of aspartame.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

Pink coloured, oval shaped biconvex film coated tablet debossed with "C" on one side and plain on other side.

Approximate tablet dimensions

Length (mm):	12.00 ± 0.20 (11.80 to 12.20)
Breath (mm):	6.00 ± 0.20 (5.80 to 6.20)
Thickness (mm):	4.50 ± 0.50 (4.00 to 5.00)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abacavir/dolutegravir/lamivudine tablet for oral suspension is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in paediatric patients weighing 10 kg to less than 25 kg.

Limitations of use

- Abacavir/dolutegravir/lamivudine tablet for oral suspension alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor (INSTI) resistance because the dose of dolutegravir in Abacavir/dolutegravir/lamivudine tablet for oral suspension is insufficient in these subpopulations.

4.2 Posology and method of administration

Posology

*Screening for HLA-B*5701 allele prior to initiating Abacavir/Dolutegravir/Lamivudine tablet for oral suspension*

Screen for the HLA-B*5701 allele prior to initiating therapy with abacavir/dolutegravir/lamivudine tablet for oral suspension (see section 4.4).

Testing prior to or when initiating treatment with Abacavir/Dolutegravir/Lamivudine tablet for oral suspension

Prior to or when initiating abacavir/dolutegravir/lamivudine tablets for oral suspension, test patients for HBV infection (see section 4.4).

Pregnancy testing is recommended before initiation of abacavir/dolutegravir/lamivudine tablets for oral suspension in adolescents of childbearing potential (see sections 4.4 and 4.6).

Overview of abacavir, dolutegravir and lamivudine dosage forms

Abacavir/dolutegravir/lamivudine is available in two dosage forms. **Do not interchange abacavir/dolutegravir/ lamivudine (tablets) and abacavir/dolutegravir/lamivudine (tablets for oral suspension) on a milligram-per-milligram basis due to differing pharmacokinetic profiles for the dolutegravir component** (see sections 4.4 and 5.2).

- Abacavir/dolutegravir/lamivudine tablets for oral suspension: 60 mg of abacavir, 5 mg of dolutegravir, and 30 mg of lamivudine. Abacavir/dolutegravir/lamivudine tablet for oral suspension is recommended in paediatric patients weighing 10 kg to less than 25 kg.
- Because abacavir/dolutegravir/lamivudine tablet for oral suspension is a fixed-dose tablet and the dosage of individual components cannot be adjusted, it may lead to a suboptimal dosing for patients weighing ≥25 kg. Abacavir/dolutegravir/lamivudine tablet for oral suspension is not recommended in patients weighing 25 kg or more.

Recommended dosage and administration instructions for paediatric patients weighing 10 kg to less than 25 kg

The dosage and dosage form recommended for paediatric patients varies by weight as shown in Table 1 below.

Table 1. Recommended Dosage of Abacavir/Dolutegravir/Lamivudine tablets for oral suspension in Paediatric Patients

Body Weight	**Abacavir/Dolutegravir/Lamivudine tablets for oral suspension[a] Number of Tablets**	**Total Daily Dose**
10 kg to <14 kg	4 tablets once daily	240 mg abacavir, 20 mg dolutegravir, and 120 mg lamivudine once daily
14 kg to <20 kg	5 tablets once daily	300 mg abacavir, 25 mg dolutegravir, and 150 mg lamivudine once daily
20 kg to <25 kg	6 tablets once daily	360 mg abacavir, 30 mg dolutegravir, and 180 mg lamivudine once daily

[a] Abacavir/dolutegravir/lamivudine tablets for oral suspension is a fixed-dose combination product containing 60 mg of abacavir, 5 mg of dolutegravir, and 30 mg of lamivudine.

Dosage recommendation with certain concomitant medications

The dolutegravir dose in abacavir/dolutegravir/lamivudine tablet for oral suspension (5 mg) is insufficient when coadministered with medications listed in Table 2 that may decrease dolutegravir concentrations; the following dolutegravir dosage regimen is recommended.

Table 2. Dosing Recommendations for Abacavir/Dolutegravir/Lamivudine tablets for oral suspension with Coadministered Medications

Coadministered Drug	Dosing Recommendation
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, carbamazepine, or rifampin	In paediatric patients **weighing 10 kg to <25 kg**, an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir/dolutegravir/lamivudine tablets for oral suspension. • 10 to <14 kg: administer an additional 20-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine tablets for oral suspension, • 14 to <20 kg: administer an additional 25-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine tablets for oral suspension, • 20 to <25 kg: administer an additional 30-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine tablets for oral suspension.

Special populations

Renal impairment

Abacavir/dolutegravir/lamivudine tablet for oral suspension is not recommended for patients with creatinine clearance <30 mL/min because abacavir/dolutegravir/lamivudine tablet for oral suspension is a fixed-dose combination, and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of abacavir/dolutegravir/lamivudine tablet for oral suspension, is required for patients with creatinine clearance <30 mL/min, then the individual components should be used (see section 5.2).

Hepatic impairment

Abacavir/dolutegravir/lamivudine tablet for oral suspension is a fixed-dose combination, and the dosage of the individual components cannot be adjusted. If a dose reduction of abacavir, a component of abacavir/dolutegravir/lamivudine tablet for oral suspension, is required for patients with mild hepatic impairment (Child-Pugh Score A), then the individual components should be used (see section 5.2).

The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate (Child-Pugh Score B) or severe (Child-Pugh Score C) hepatic impairment; therefore, abacavir/dolutegravir/lamivudine tablet for oral suspension is contraindicated in these patients (see section 4.3).

Paediatric population

The safety and efficacy of abacavir/dolutegravir/lamivudine tablet for oral suspension have not been established in paediatric patients weighting < 10 kg.

Method of administration

Oral use.

Abacavir/dolutegravir/lamivudine tablet for oral suspension can be taken with or without food.

4.3 Contraindications

Abacavir/dolutegravir/lamivudine tablet for oral suspension are contraindicated in patients:

- who have the HLA-B*5701 allele (see section 4.4).
- with prior hypersensitivity reaction to abacavir, dolutegravir (see section 4.4), or lamivudine.

- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir (see section 4.5).
- with moderate or severe hepatic impairment (see sections 4.4 and 5.2).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Hypersensitivity reactions have been reported with the use of abacavir or dolutegravir, components of abacavir/dolutegravir/lamivudine tablet for oral suspension.

Abacavir

Abacavir hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with abacavir (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment (see section 4.8). Patients who carry the HLA-B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making.

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir:

- All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with abacavir/dolutegravir/lamivudine or reinitiation of therapy with abacavir/dolutegravir/lamivudine, unless patients have a previously documented HLA-B*5701 allele assessment.
- Abacavir/dolutegravir/lamivudine are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- Before starting abacavir/dolutegravir/lamivudine, review medical history for prior exposure to any abacavir-containing product. NEVER restart abacavir/dolutegravir/lamivudine or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status.
- To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue abacavir/dolutegravir/lamivudine immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications). Clinical status, including liver chemistries, should be monitored and appropriate therapy initiated.
- If a hypersensitivity reaction cannot be ruled out, do not restart abacavir/dolutegravir/lamivudine or any other abacavir-containing products because more severe symptoms, which may include life-threatening hypotension and death, can occur within hours.
- Clinically, it is not possible to determine whether a hypersensitivity reaction with abacavir/dolutegravir/lamivudine would be caused by abacavir or dolutegravir. Therefore, never restart abacavir/dolutegravir/lamivudine or any other abacavir- or dolutegravir-containing product in patients who have stopped therapy with abacavir/dolutegravir/lamivudine due to a hypersensitivity reaction.
- If a hypersensitivity reaction is ruled out, patients may restart abacavir/dolutegravir/lamivudine. Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of

abacavir/dolutegravir/lamivudine, or any other abacavir-containing product, is recommended only if medical care can be readily accessed.

- A patient information leaflet and alert card that provide information about recognition of abacavir hypersensitivity reactions should be dispensed with each new prescription and refill.

Dolutegravir

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in <1% of subjects receiving dolutegravir in Phase 3 clinical trials. Discontinue abacavir/dolutegravir/lamivudine and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters 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 abacavir/dolutegravir/lamivudine or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Clinically, it is not possible to determine whether a hypersensitivity reaction with abacavir/dolutegravir/lamivudine would be caused by abacavir or dolutegravir. Therefore, never restart abacavir/dolutegravir/lamivudine or any other abacavir- or dolutegravir-containing product in patients who have stopped therapy with abacavir/dolutegravir/lamivudine due to a hypersensitivity reaction.

Patients co-infected with HIV-1 and HBV: emergence of lamivudine-resistant HBV and the risk of posttreatment exacerbations of HBV

All patients with HIV-1 should be tested for the presence of HBV prior to or when initiating abacavir/dolutegravir/lamivudine tablet for oral suspension.

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 abacavir/dolutegravir/lamivudine 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 abacavir/dolutegravir/lamivudine. Patients who are co-infected with HIV-1 and HBV who discontinue abacavir/dolutegravir/lamivudine should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with abacavir/dolutegravir/lamivudine. If appropriate, initiation of anti-HBV therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since posttreatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen (see section 4.8). Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of abacavir/dolutegravir/lamivudine (see section 4.8). In some cases, the elevations in transaminases were consistent with immune

reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure, have also been reported in patients, including paediatric 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 abacavir/dolutegravir/lamivudine. Monitoring for hepatotoxicity is recommended.

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 abacavir and lamivudine (components of abacavir/dolutegravir/lamivudine tablet for oral suspension). 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. Treatment with abacavir/dolutegravir/lamivudine 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.

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 adolescents of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with abacavir, dolutegravir and lamivudine. Assess the risks and benefits of abacavir/dolutegravir/lamivudine 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 (see section 4.6).

Pregnancy testing is recommended before initiation of abacavir/dolutegravir/lamivudine in adolescents of childbearing potential (see section 4.2).

Adolescents of childbearing potential should be counseled on the consistent use of effective contraception (see section 4.6).

Abacavir/dolutegravir/lamivudine 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.

Risk of adverse reactions or loss of virologic response due to drug interactions

The concomitant use of abacavir/dolutegravir/lamivudine and other drugs may result in known or potentially significant drug interactions, some of which may lead to (see sections 4.3 and 4.5):

- Loss of therapeutic effect of abacavir/dolutegravir/lamivudine and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 3 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with abacavir/dolutegravir/lamivudine, review concomitant medications during therapy with abacavir/dolutegravir/lamivudine, and monitor for the adverse reactions associated with the concomitant drugs.

Immune reconstitution syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir/dolutegravir/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, Guillain-Barré syndrome, autoimmune hepatitis) 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.

Different formulations are not interchangeable

Abacavir/dolutegravir/lamivudine (tablets) and abacavir/dolutegravir/lamivudine (dispersible tablets) are not bioequivalent and are not interchangeable on a milligram-per-milligram basis (see section 5.2). If a paediatric patient switches from the dispersible tablets to the tablets, the dosage must be adjusted (see section 4.2). Incorrect dosing of a given formulation may result in underdosing and loss of therapeutic effect and possible development of resistance or possible clinically significant adverse reactions from greater exposure to the individual components.

Myocardial infarction

Several prospective, observational, epidemiological studies have reported an association with the use of abacavir and the risk of myocardial infarction (MI). Meta-analyses of randomized, controlled clinical trials have observed no excess risk of MI in abacavir-treated subjects as compared with control subjects. To date, there is no established biological mechanism to explain a potential increase in risk. In totality, the available data from the observational studies and from controlled clinical trials show inconsistency; therefore, evidence for a causal relationship between abacavir and the risk of MI is inconclusive.

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

Excipients

Sodium

Abacavir/dolutegravir/lamivudine tablet for oral suspension contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Risks in patients with phenylketonuria

This medicinal product contains 9.5 mg aspartame in each tablet. Aspartame is a source of phenylalanine. It may be harmful if the patient has phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of dolutegravir on the pharmacokinetics of other agents

In vitro, dolutegravir inhibited the renal organic cation transporters (OCT)2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE)1 (IC_{50} = 6.34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide, dalfampridine, and metformin) (see sections 4.3).

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT)

1 (IC_{50} = 2.12 microM) and OAT3 (IC_{50} = 1.97 microM). However, *in vivo*, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} >50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2, or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

In drug interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following drugs: daclatasvir, tenofovir, methadone, midazolam, rilpivirine, and oral contraceptives containing norgestimate and ethinyl estradiol. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect the pharmacokinetics of the following drugs: atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, lopinavir, ritonavir, and boceprevir.

Effect of other agents on the pharmacokinetics of dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp *in vitro*. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir (Table 3).

In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, daclatasvir, prednisone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir.

Established and other potentially significant drug interactions

There were no drug-drug interaction trials conducted with the abacavir, dolutegravir, and lamivudine fixed-dose combination tablets.

Information regarding potential drug interactions with the individual components of abacavir/dolutegravir/lamivudine are provided below. 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 (see section 4.3).

Table 3. Established and Other Potentially Significant Drug Interactions for Dolutegravir: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration**	**Clinical Comment**

HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine	↓ Dolutegravir	Use of abacavir/dolutegravir/lamivudine with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz	↓ Dolutegravir	In paediatric patients **weighing 10 to <25 kg**, an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir/dolutegravir/lamivudine. • 10 to <14 kg: administer an additional 20-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine, • 14 to <20 kg: administer an additional 25-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine, • 20 to <25 kg: administer an additional 30-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with abacavir/dolutegravir/lamivudine because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir Tipranavir/ritonavir	↓ Dolutegravir	In paediatric patients **weighing 10 to <25 kg**, an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir/dolutegravir/lamivudine. • 10 to <14 kg: administer an additional 20-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine, • 14 to <20 kg: administer an additional 25-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine, • 20 to <25 kg: administer an additional 30-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine.
Other Agents		
Antiarrhythmic: Dofetilide	↑ Dofetilide	Coadministration is contraindicated with abacavir/dolutegravir/lamivudine (see section 4.3).
Potassium channel blocker: Dalfampridine	↑ Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with abacavir/dolutegravir/lamivudine should be considered against the risk of seizures in these patients.
Carbamazepine	↓ Dolutegravir	In paediatric patients **weighing 10 to < 25 kg**, an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir/dolutegravir/lamivudine. • 10 to <14 kg: administer an additional 20-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine, • 14 to <20 kg: administer an additional 25-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine, • 20 to <25 kg: administer an additional 30-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine.
Oxcarbazepine Phenytoin Phenobarbital	↓ Dolutegravir	Avoid coadministration with abacavir/dolutegravir/lamivudine because there are insufficient data to make dosing recommendations.

St. John's wort (*Hypericum perforatum*)		
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer abacavir/dolutegravir/lamivudine 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium and iron supplements, including multivitamins containing calcium or iron	↓ Dolutegravir	When taken with food, abacavir/dolutegravir/lamivudine and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, abacavir/dolutegravir/lamivudine should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.
Metformin	↑ Metformin	Refer to the package insert for metformin for assessing the benefit and risk of concomitant use of abacavir/dolutegravir/lamivudine and metformin.
Rifampin	↓ Dolutegravir	In paediatric patients **weighing 10 to < 25 kg**, an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir/dolutegravir/lamivudine. • 10 to <14 kg: administer an additional 20-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine, • 14 to <20 kg: administer an additional 25-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine, • 20 to <25 kg: administer an additional 30-mg dose of dolutegravir, 12 hours after abacavir/dolutegravir/lamivudine.

Methadone

Abacavir: In a trial of 11 HIV-1–infected subjects receiving methadone-maintenance therapy with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased. This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Sorbitol

Lamivudine: Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with lamivudine-containing medicines.

Riociguat

Abacavir: Coadministration with abacavir, dolutegravir and lamivudine resulted in increased riociguat exposure, which may increase the risk of riociguat adverse reactions. The riociguat dose may need to be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 antiretroviral pregnancy registry (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 over 1,000 exposures to dolutegravir during pregnancy resulting in live births (including 634 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 2.1% to 5.0%) following first-trimester exposure to dolutegravir-containing regimens and 5.1% (95% CI: 3.2% to 7.7%) 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).

Abacavir: Based on prospective reports to the APR of over 2,700 exposures to abacavir during pregnancy resulting in live births (including 1,391 exposed in the first trimester), there was no difference between the overall risk of birth defects for abacavir 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 3.2% (95% CI: 2.3% to 4.2%) following first trimester exposure to abacavir-containing regimens and 3.0% (95% CI: 2.1% to 4.0%) following second/third trimester exposure to abacavir-containing regimens.

Abacavir has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery.

Lamivudine: Based on prospective reports to the APR of over 12,900 exposures to lamivudine during pregnancy resulting in live births (including 5,472 exposed in the first 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 birth 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%, 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

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 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks' gestation using 150 mg lamivudine 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).

Breast-feeding

Abacavir, dolutegravir and lamivudine are present in human milk. There is no information on the effects of abacavir/dolutegravir/lamivudine tablet for oral suspension or its components on the breastfed infant or the effects of the drug on milk production.

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, abacavir or lamivudine on human male or female fertility.

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with dolutegravir. The clinical status of the patient and the adverse reaction profile of abacavir/dolutegravir/lamivudine 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 severe adverse events possibly related to the treatment with abacavir and dolutegravir are associated with a risk for hypersensitivity reactions (HSR). Hypersensitivity reaction observed for each of these medicinal products (described below)

Dolutegravir hypersensitivity

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

Abacavir hypersensitivity

The signs and symptoms of this HSR are listed below.

Skin	Rash
Gastrointestinal tract	Nausea, vomiting, diarrhoea, abdominal pain
Respiratory tract	Dyspnoea, cough, pharyngitis
Miscellaneous	Fever, lethargy, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry	Headache, paraesthesia
Haematological	Lymphopenia
Liver/pancreas	Elevated liver function tests, hepatic failure
Musculoskeletal	Myalgia, myolysis, arthralgia, elevated creatine phosphokinase
Urology	Elevated creatinine

Tabulated list of adverse reactions

Tabulated summary of adverse reactions associated with the combination of dolutegravir + abacavir/lamivudine in an analysis of pooled data from: Phase II to Phase III clinical trials; and adverse reactions to treatment with dolutegravir, abacavir and lamivudine from clinical studies when used with other antiretrovirals

Gastrointestinal disorders	Abdominal pain, abdominal distention, abdominal discomfort, dyspepsia, flatulence, gastroesophageal reflux disease, upper abdominal pain, vomiting.
General disorders	Fever, lethargy
Hepatobiliary disorders	Hepatitis.
Metabolism and nutrition disorders	Anorexia, hypertriglyceridemia.
Musculoskeletal disorders	Arthralgia, myositis.
Nervous system disorders	Somnolence.
Psychiatric disorders	Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness. Nightmare and sleep disorder.
Renal and urinary disorders	Renal impairment.
Skin and subcutaneous tissue disorders	Pruritus

Paediatric population

Abacavir and lamivudine: The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as abacavir/lamivudine, was assessed in the ARROW trial (n = 336). Primary safety assessment in the ARROW (COL105677) trial was based on Grade 3 and Grade 4 adverse events. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator. No additional safety issues were identified in paediatric subjects compared with historical data in adults.

Dolutegravir: The safety of dolutegravir in paediatric subjects with HIV-1 infection weighing at least 10 kg was evaluated in the IMPAACT P1093 trial. Overall, the safety data in this paediatric study was similar to that seen in adults.

IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of paediatric subjects with HIV-1 infection, aged <18 years. One hundred and five subjects weighing at least 10 kg were enrolled in this trial (see section 5.1).

The safety analysis through Week 24 included 40 subjects from Cohorts I (n = 19), IIA (n = 5), III-DT (n = 15), and IV-DT (n=1) weighing at least 10 kg at enrollment who received the recommended dose (determined by weight and age) and formulation. This analysis showed that 6 subjects (all from Cohort I) experienced drug-related clinical adverse reactions. There were no Grade 3 or 4 drug-related adverse reactions reported. No adverse reactions led to discontinuation.

All laboratory abnormalities considered to be drug-related in subjects weighing at least 10 kg at enrollment were Grade 1 or 2 in severity. Only one grade 3 laboratory abnormality was reported in more than 1 subject (decreased blood bicarbonate, n = 2). Changes in median serum creatinine were similar to those observed in adults.

Postmarketing experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use with one or more of the components of abacavir/dolutegravir/lamivudine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or

establish a causal relationship to drug exposure.

Blood and lymphatic systems disorders	Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.
Gastrointestinal disorders	Stomatitis, Pancreatitis.
General disorders	Weakness.
Hepatobiliary disorders	Acute liver failure, liver transplant (see section 4.4).
Hypersensitivity	Sensitization reactions (including anaphylaxis), urticaria (see section 4.4).
Investigations	Weight increased.
Metabolism and nutrition disorders	Hyperlactemia.
Musculoskeletal and connective tissue disorders	CPK elevation, muscle weakness, myalgia, rhabdomyolysis.
Nervous system disorders	Paresthesia, peripheral neuropathy, seizures.
Psychiatric disorders	Anxiety.
Respiratory, thoracic and mediastinal disorders	Abnormal breath sounds/wheezing.
Skin and subcutaneous tissue disorders	Alopecia, erythema multiforme. Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

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. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

4.9 Overdose

There is no known specific treatment for overdose with abacavir/dolutegravir/lamivudine. 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.

Abacavir

It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infections, combinations. ATC code: J05AR13

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 IC_{50} values of 2.7 nM and 12.6 nM.

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA.

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 RT via DNA chain termination after incorporation of the nucleotide analogue.

Pharmacodynamic effects

Effects on electrocardiogram

A thorough QT trial has been conducted for dolutegravir. Neither the effects of abacavir nor lamivudine as single entities or the combination of abacavir, dolutegravir, and lamivudine on the QT interval have been evaluated.

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3–fold of the 50-mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours postdose.

Effects on renal function

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. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

Antiviral activity in cell culture

Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of drug necessary to affect viral replication by 50% (EC_{50}) 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 median EC_{50} value of 0.54 nM (range: 0.41 to 0.60 nM) in a viral 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 with median EC_{50} values of 0.18 nM (n = 3, range: 0.09 to 0.5 nM), 0.08 nM (n = 5, range: 0.05 to 2.14 nM), 0.12 nM (n = 4, range: 0.05 to 0.51 nM), 0.17 nM (n = 3, range: 0.16 to 0.35 nM), 0.24 nM (n = 3, range: 0.09 to 0.32 nM), 0.17 nM (n = 4, range: 0.07 to 0.44 nM), 0.2 nM (n = 3, range: 0.02 to 0.87 nM), and 0.42 nM (n = 3, range: 0.41 to 1.79 nM) for clades A, B, C, D, E, F, and G, and group O viruses, respectively. Dolutegravir EC_{50} values against three HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Abacavir: The antiviral activity of abacavir against HIV-1 was assessed in a number of cell lines including in primary monocytes/macrophages and PBMCs. EC_{50} values ranged from 3,700 to 5,800 nM (1 nM = 0.28 ng/mL) and 70 to 1,000 nM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and the mean EC_{50} value was 260 ± 180 nM against 8 clinical isolates. The median EC_{50} values of abacavir were 344 nM (range: 14.8 to 676 nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4), ranged from 24 to 490 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. EC_{50} values were in the range of 3 to 15,000 nM (1 nM = 0.23 ng/mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC_{50} values against HIV-2 isolates (n = 4) from 3 to 120 nM in PBMCs. Ribavirin (50,000 nM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Antiviral activity in combination with other antiviral agents

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

Resistance in cell culture

Dolutegravir: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold.

Abacavir and Lamivudine: HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture with amino acid substitutions K65R, L74V, Y115F, and M184V/I in HIV-1 RT. M184V or I substitutions resulted in high-level resistance to lamivudine and approximately 2-fold decrease in susceptibility to abacavir. Substitutions K65R, L74V, or Y115F with M184V or I conferred a 7- to 8-fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility.

Resistance in clinical subjects

No subjects in the treatment arm receiving dolutegravir + abacavir/lamivudine in SINGLE (treatment-naive trial) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 11 with HIV-1 RNA >400 copies/mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1

subject with 275 copies/mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to abacavir and lamivudine, components of abacavir/dolutegravir/lamivudine tablet for oral suspension, was observed in the arm receiving dolutegravir + abacavir/lamivudine in the SINGLE trial through Week 144.

Cross-resistance

Dolutegravir: Cross-resistance has been observed among INSTIs. 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). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Abacavir and lamivudine: Cross-resistance has been observed among NRTIs. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with a K65R substitution with or without an M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutation (TAM) substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

Clinical efficacy and safety

Adult subjects

The efficacy of abacavir/dolutegravir/lamivudine is supported by data from a randomized, controlled trial (double-blind through 96 weeks and open-label phase from 96 to 144 weeks) in antiretroviral treatment-naive subjects, SINGLE (ING114467, NCT01263015) and other trials in treatment- naive subjects. The efficacy of dolutegravir, in combination with at least two active background regimens in treatment-experienced, INSTI-naive subjects is supported by data from SAILING (ING111762, NCT01231516).

Treatment-naive subjects

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily with fixed-dose abacavir and lamivudine or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate. At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA >100,000 copies/mL, and 53% had CD4+ cell count <350 cells/mm^3; these characteristics were similar between treatment groups.

Week 144 (open-label-phase analysis which followed the Week 96 double-blind phase) outcomes for SINGLE are provided in Table 4.

Table 4. Virologic Outcomes of Randomized Treatment in SINGLE at 144 Weeks (Snapshot Algorithm)

	Dolutegravir + Abacavir/Lamivudine Once Daily (n = 414)	**Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate Once Daily (n = 419)**
HIV-1 RNA <50	71%	63%

copies/mL		
Treatment difference[a]	8.3% (95% CI: 2.0%, 14.6%)[d]	
Virologic nonresponse	10%	7%
Data in window not <50 copies/mL	4%	<1%
Discontinued for lack of efficacy	3%	3%
Discontinued for other reasons while not suppressed	3%	4%
No virologic data	18%	30%
Reasons		
Discontinued study/study drug due to adverse event or death[b]	4%	14%
Discontinued study/study drug for other reasons[c]	12%	13%
Missing data during window but on study	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤100,000	73%	64%
≥100,000	69%	61%
Gender		
Male	72%	66%
Female	69%	48%
Race		
White	72%	71%
African American/African Heritage/Other	71%	47%

[a] Adjusted for pre-specified stratification factors.
[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.
[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.
[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 81% in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race. The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving dolutegravir + abacavir/lamivudine and 332 cells per mm^3 for the efavirenz/emtricitabine/tenofovir disoproxil fumarate group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm^3 (15.6 cells per mm^3, 78.2 cells per mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

Treatment-experienced

In SAILING, there were 715 subjects included in the efficacy and safety analyses. At Week 48, 71% of subjects randomized to dolutegravir plus background regimen versus 64% of subjects randomized to raltegravir plus background regimen had HIV-1 RNA <50 copies/mL (treatment difference and 95% CI: 7.4% [0.7%, 14.2%]).

Paediatric population

The efficacy of the individual components of abacavir/dolutegravir/lamivudine for the treatment of HIV-1 infection was evaluated in paediatric patients enrolled in the ARROW trial (NCT02028676) and IMPAACT P1093 trial (NCT01302847), as summarized below.

- Abacavir and lamivudine once daily, in combination with a third antiretroviral drug, were evaluated in a randomized, multicenter trial (ARROW) in treatment- naive paediatric subjects with HIV-1 infection. Subjects randomized to once-daily dosing (n = 336) and who weighed at least 25 kg received abacavir 600 mg and lamivudine 300 mg, as either the single entities or as abacavir/lamivudine. At Week 96, 67% of subjects receiving abacavir and lamivudine once-daily in combination with a third antiretroviral drug, had HIV-1 RNA <80 copies/mL.

- Dolutegravir , in combination with other antiretroviral drugs was evaluated in treatment naive or treatment-experienced, INSTI- naive, HIV-1–infected subjects aged at least 4 weeks to 18 years in an ongoing open-label, multicenter, dose-finding clinical trial, IMPAACT P1093. Subjects were stratified by age cohort; subjects aged 12 to <18 years were enrolled in Cohort I, subjects aged 6 to <12 years were enrolled in Cohort IIA, and subjects aged 2 to <6 years were enrolled in Cohort III-DT. Subjects weighing at least 10 kg from Cohorts I (n = 19), IIA (n = 5), and III-DT (n = 3) who received the recommended dose (determined by weight and age) and formulation contributed to the efficacy analysis at Week 48. Across all 3 cohorts, 67% (18/27) of subjects weighing at least 10 kg achieved HIV-1 RNA <50 copies/mL at Week 48 (Snapshot algorithm).

5.2 Pharmacokinetic properties

Pharmacokinetics in adults

One abacavir/dolutegravir/lamivudine tablet was bioequivalent to one dolutegravir tablet (50 mg) plus one abacavir and lamivudine fixed-dose combination tablet under fasted conditions in healthy subjects (n = 62).

Abacavir/dolutegravir/lamivudine tablet and abacavir/dolutegravir/lamivudine tablet for oral suspension are bioequivalent for the abacavir and lamivudine components, but not for the dolutegravir component. The relative dolutegravir bioavailability of abacavir/dolutegravir/lamivudine tablet for oral suspension is approximately 1.7-fold higher than abacavir/dolutegravir/lamivudine tablet; therefore, the 2 dosage forms are not interchangeable on a milligram-per-milligram basis (see sections 4.2 and 4.4). The relative dolutegravir bioavailability is expected to be similar between abacavir/dolutegravir/lamivudine tablet for oral suspension and dolutegravir tablets.

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg/mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hour/mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration.

Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5′-carboxylic acid and glucuronyl transferase to form the 5′-glucuronide. In single-dose trials, the observed elimination half-life ($t_{½}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L/h/kg (mean ± SD).

Dolutegravir: Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and $C_{24\,h}$ ranging from 1.2 to 1.5. Dolutegravir is a P-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established. Dolutegravir is highly bound (≥98.9%) to human plasma proteins based on *in vivo* data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a

single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose is excreted unchanged in the feces. Thirty-one percent of the total oral dose is excreted in the urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was <1% of the dose. Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L/h based on population pharmacokinetic analyses.

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1–infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects.

Table 5. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1–Infected Adults

Parameter	50 mg Once Daily Geometric Mean (%CV)
$AUC_{(0-24)}$ (mcg•h/mL)	53.6 (27)
C_{max} (mcg/mL)	3.67 (20)
C_{min} (mcg/mL)	1.11 (46)

Cerebrospinal fluid (CSF): In 11 treatment- naive subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng/mL (range: 4 ng/mL to 23.2 ng/mL) 2 to 6 hours postdose after 2 weeks of treatment. The clinical relevance of this finding has not been established.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg/mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hour/mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). In most single-dose trials with plasma sampling up to 48 or 72 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 13 to 19 hours. In HIV-1–infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD).

Effect of food on oral absorption

Abacavir/dolutegravir/lamivudine may be taken with or without food. Overall, when compared with fasted conditions, administration of abacavir/dolutegravir/lamivudine to healthy adult subjects with a high-fat meal (53% fat, 869 calories) resulted in decreased C_{max} for abacavir and increased C_{max} and AUC for dolutegravir. Lamivudine exposures were not affected by food. With a high-fat meal, the C_{max} of abacavir decreased 23% and the C_{max} and AUC of dolutegravir increased 37% and 48%, respectively. When compared with fasted conditions, administration of abacavir/dolutegravir/lamivudine tablet for oral suspension to healthy adult subjects with a high-fat meal (50% fat, 917 calories) resulted in decreased C_{max} for abacavir (55%), dolutegravir (29%) and lamivudine (36%). AUCs for all 3 components were not affected by food.

Specific populations

Paediatric population

The pharmacokinetics for the individual components of abacavir/dolutegravir/lamivudine tablet for oral suspension (abacavir, dolutegravir, and lamivudine) have been evaluated in paediatric subjects.

Dolutegravir: The pharmacokinetics of dolutegravir were evaluated in the IMPAACT P1093 trial and in 2 weight-band–based pharmacokinetic substudies from the ODYSSEY trial (see section 5.1).

Mean dolutegravir $AUC_{0\text{-}24h}$ and C_{24h} in HIV-1–infected paediatric subjects weighing at least 10 kg were comparable to those in adults after 50 mg once daily or 50 mg twice daily. Mean C_{max} is higher in paediatrics, but the increase is not considered clinically significant as the safety profiles were similar in paediatric and adult subjects (see section 4.8).

Abacavir and lamivudine: In paediatric patients weighing 10 to <25 kg, predicted exposures ($AUC_{0\text{-}24h}$) of abacavir and lamivudine at the recommended doses for abacavir, dolutegravir and lamivudine are within the observed exposure ranges at the recommended doses of individual products in adults and paediatrics.

5.3 Preclinical safety data

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-fold higher than those in humans at the recommended dose of 50 mg once daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 17-fold and 30-fold higher in males and females, respectively, than those in humans at the recommended dose of 50 mg once daily.

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 7 to 28 times the human exposure at the recommended dose of 600 mg.

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 of 300 mg.

Mutagenicity

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

Abacavir: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

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, abacavir, or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44, 9, or 112 times (respectively) higher than the exposures in humans at the doses of 50 mg, 600 mg, and 300 mg (respectively).

Animal toxicology and/or pharmacology

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 21 times the expected systemic exposure in humans at a dose of 600 mg. The clinical relevance of this finding has not been determined.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Aspartame,
Calcium sulphate dihydrate,
Colloidal silicon dioxide,
Crospovidone,
Iron oxide red,
Magnesium stearate,
Mannitol,
Microcrystalline cellulose,
Povidone,
Purified water,
Sodium starch glycolate,
Strawberry cream flavour permaseal.

Film-coat

Iron oxide red
Iron oxide yellow
Macrogol
Polyvinyl alcohol
Talc
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C (86°F). Keep bottle tightly closed. Protect from moisture. Do not remove desiccant.

6.5 Nature and contents of container

Each carton having Bottle of 30 tablets with desiccant and non-child-resistant closure. with one 40-mL dosing cup

Each carton having Bottle of 90 tablets with desiccant and non-child-resistant closure. with one 40-mL dosing cup

6.6 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

Cipla Ltd.
Cipla House,
Peninsula Business Park,
Ganapatrao Kadam Marg,
Lower Parel, Mumbai 400 013.
Maharashtra (INDIA).

8. MARKETING AUTHORISATION NUMBER(S)

[----]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[----]

10. DATE OF REVISION OF THE TEXT

This leaflet is prepared in October 2022