Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Abacavir, Dolutegravir and Lamivudine Tablets for Oral Suspension 60mg/5mg/30mg)

2. Qualitative and quantitative composition

Each film-coated tablet for oral suspension contains: Abacavir sulfate USP equivalent to 60 mg of abacavir, Dolutegravir sodium equivalent to 5 mg of dolutegravir and 30 mg of Lamivudine USP.
Excipients with known effect
Mannitol and Propylene glycol
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet for oral suspension.

Pink colored, oval shaped, strawberry cream flavored, biconvex, film coated tablet, debossed with 'ADL' on one side and plain on other side, the tablets are free from physical defects and delamination.

4. Clinical particulars

4.1 Therapeutic indications

Abacavir, dolutegravir and lamivudine tablets for oral suspension are indicated for the treatment of HIV-1 infection in pediatric patients aged at least 3 months and weighing at least 6 kg to less than 25 kg.

Limitations of Use

Abacavir, dolutegravir and lamivudine tablets for oral suspension alone are 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 and lamivudine tablets for oral suspension is insufficient in these subpopulations. See full prescribing information for dolutegravir.

4.2 Posology and method of administration

Posology

Abacavir, dolutegravir and lamivudine as a fixed combination is available in two dosage forms.

Do not interchange abacavir, dolutegravir and lamivudine tablets and abacavir, dolutegravir and lamivudine tablets for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles for the dolutegravir component *[see Warnings and Precautions (4.4)*.

Because abacavir, dolutegravir and lamivudine tablets for oral suspension are fixed-dose tablets and the dosage of individual components cannot be

adjusted, it may lead to a suboptimal dosing for patients weighing ≥ 25 kg. Abacavir, dolutegravir and lamivudine tablets for oral suspension are not recommended in patients weighing 25 kg or more.

Recommended Dosage in Adults

Do not use abacavir, dolutegravir and lamivudine tablets for oral suspension in adults because it may lead to suboptimal dosing.

Recommended Dosage and Administration Instructions for Pediatric Patients Weighing at Least 6 kg

The dosage recommended for pediatric patients varies by weight as shown in Table 1 below.

Table 1. Recommended Dosage of Abacavir, Dolutegravir and Lamivudine Tablets for Oral Suspension in Pediatric Patients

Body Weight	Abacavir, Dolutegravir and Lamivudine Tablets for Oral Suspension[a] Number of Tablets	Total Daily Dose
6 kg to < 10 kg	3 tablets once daily	180 mg abacavir, 15 mg dolutegravir, and 90 mg lamivudine once daily
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
≥ 25 kg	Not recommended	

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

Administer abacavir, dolutegravir and lamivudine tablets for oral suspension with or without food. Instruct patients (or instruct caregivers) to fully **disperse the tablets for oral suspension in 20 mL of drinking water** (if using 4, 5, or 6 tablets for oral suspension) **or 15 mL** (if using 3 tablets for oral suspension) in a small cup; swirl the suspension so that no lumps remain. After full dispersion, administer the oral suspension within 30 minutes of mixing.

Do not swallow the tablets for oral suspension whole, and do not chew, cut, or crush the tablets for oral suspension.

For children unable to use a small cup, an appropriate-sized oral syringe may be used to administer the oral suspension.

Dosage Recommendation with Certain Concomitant Medications

The dolutegravir dose in abacavir, dolutegravir and lamivudine tablets 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 and Lamivudine Tablets for Oral Suspension with Coadministered Medications

Coadministered Drug	Dosing Recommendation
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, carbamazepine, or rifampin	In pediatric patients **weighing 6 kg to < 25 kg,** an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir, dolutegravir and lamivudine tablets for oral suspension. 6 to < 10 kg: administer an additional 15-mg dose of dolutegravir (3 dolutegravir 5-mg tablets for oral suspension or 1½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, 10 to < 14 kg: administer an additional 20-mg dose of dolutegravir (4 dolutegravir 5-mg tablets for oral suspension or 2 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, 14 to < 20 kg: administer an additional 25-mg dose of dolutegravir (5 dolutegravir 5-mg tablets for oral suspension or 2½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, 20 to < 25 kg: administer an additional 30-mg dose of dolutegravir (6 dolutegravir 5-mg tablets for oral suspension or 3 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension.

Not Recommended Due to Lack of Dosage Adjustment

Because abacavir, dolutegravir and lamivudine tablets for oral suspension are fixed-dose tablets and cannot be dose adjusted, abacavir, dolutegravir and lamivudine tablets for oral suspension are not recommended in:

Patients with creatinine clearance < 30 mL/min and pediatric patients with a similar degree of renal impairment based on age-appropriate renal function

assessment. There are no data available on the use of lamivudine, a component of abacavir, dolutegravir and lamivudine tablets for oral suspension, in pediatric patients with renal impairment.

Patients with mild hepatic impairment. Abacavir, dolutegravir and lamivudine tablets for oral suspension are contraindicated in patients with moderate or severe hepatic impairment *[see Contraindications (4.3)]*.

Method of administration

For oral use

4.3 **Contraindications**

Abacavir, dolutegravir and lamivudine tablets for oral suspension are contraindicated in patients:

- who have the HLA-B*5701 allele *[see Warnings and Precautions (4.4)]*.
- with prior hypersensitivity reaction to abacavir, dolutegravir *[see Warnings and Precautions (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 Drug Interactions (4.5)]*.
- with moderate or severe hepatic impairment.
- With hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 and lamivudine tablets for oral suspension.

*Abacavir**:***

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing regimens.

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 Undesirable effects (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 abacavircontaining 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 and lamivudine tablets for oral suspension or reinitiation of therapy with abacavir, dolutegravir and lamivudine tablets for oral suspension, unless patients have a previously documented HLA-B*5701 allele assessment.

Abacavir, dolutegravir and lamivudine tablets for oral suspension are contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLAB*5701-positive patients.

Before starting abacavir, dolutegravir and lamivudine tablets for oral suspension, review medical history for prior exposure to any abacavir-containing product. NEVER restart abacavir, dolutegravir and lamivudine tablets for oral suspension 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 and lamivudine tablets for oral suspension 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 and lamivudine tablets for oral suspension or any other abacavircontaining 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 and lamivudine tablets for oral suspension would be caused by abacavir or dolutegravir. Therefore, never restart abacavir, dolutegravir and lamivudine tablets for oral suspension or any other abacavir-

or dolutegravir-containing product in patients who have stopped therapy with abacavir, dolutegravir and lamivudine tablets for oral suspension due to a hypersensitivity reaction.

If a hypersensitivity reaction is ruled out, patients may restart abacavir, dolutegravir and lamivudine tablets for oral suspension. 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 and lamivudine tablets for oral suspension, or any other abacavir-containing product, is recommended only if medical care can be readily accessed.

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 and lamivudine tablets for oral suspension 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 and lamivudine tablets for oral suspension 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 and lamivudine tablets for oral suspension would be caused by abacavir or dolutegravir. Therefore, never restart abacavir, dolutegravir and lamivudine tablets for oral suspension or any other abacavir- or dolutegravircontaining product in patients who have stopped therapy with abacavir, dolutegravir and lamivudine tablets for oral suspension 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 and lamivudine tablets 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 and lamivudine tablets for oral suspension 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 and lamivudine tablets for oral suspension.

Patients who are co-infected with HIV-1 and HBV who discontinue abacavir, dolutegravir and lamivudine tablets for oral suspension should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with abacavir, dolutegravir and lamivudine tablets for oral suspension.

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 Undesirable effects (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 and lamivudine tablets for oral suspension *[see Undesirable effects (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 pediatric patients receiving a dolutegravir-containing regimen who had no preexisting hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with abacavir, dolutegravir and 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 and lamivudine tablets 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 and lamivudine tablets for oral suspension 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.

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

The concomitant use of abacavir, dolutegravir and lamivudine tablets for oral suspension and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4.3), Drug Interactions (4.5)]***:**

- Loss of therapeutic effect of abacavir, dolutegravir and lamivudine tablets for oral suspension and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 6 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 and lamivudine tablets for oral suspension, review concomitant medications during therapy with abacavir, dolutegravir and lamivudine tablets for oral suspension, 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 and lamivudine tablets for oral suspension.

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 and lamivudine tablets and abacavir, dolutegravir and lamivudine tablets for oral suspension are not bioequivalent and are not interchangeable on a milligram-per-milligram basis.

If a pediatric patient switches from the tablets for oral suspension to the tablets, the dosage must be adjusted. 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). Metaanalyses 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).

Pediatric Use

The clinical data supporting use of abacavir, dolutegravir and lamivudine tablets for oral suspension in pediatric patients with HIV-1 infection aged at least 3 months and weighing at least 6 kg is derived from the following previously conducted pediatric trials using abacavir, dolutegravir and lamivudine tablets and abacavir, dolutegravir and lamivudine tablets for oral suspension or the individual components:

The safety, pharmacokinetics, and antiviral activity (efficacy) of abacavir, dolutegravir and lamivudine tablets for oral suspension were established through an open-label, multicenter clinical trial (IMPAACT 2019), in which HIV-1–infected, treatment-naive or treatment-experienced, pediatric subjects younger than 12 years and weighing at least 6 kg to less than 40 kg were treated with abacavir, dolutegravir and lamivudine tablets or abacavir, dolutegravir and lamivudine tablets for oral suspension *[see Undesirable effects (4.8)]*.

The safety and efficacy of once-daily abacavir and lamivudine were established with a randomized, multicenter trial (ARROW [COL105677]) in HIV-1−infected, treatment-naive subjects aged 3 months to 17 years with a first-line regimen containing abacavir and lamivudine, using either the combination of lamivudine and abacavir or fixed dosed abacavir and lamivudine *[see Undesirable effects (4.8)]*.

The safety, pharmacokinetics, and antiviral activity (efficacy) of abacavir, dolutegravir and lamivudine tablets for oral suspension were established through an ongoing, open-label, multicenter, dose-finding clinical trial (IMPAACT P1093), in which HIV-1−infected, treatment-naive or treatment-experienced, INSTInaive, pediatric and adolescent subjects aged 4 weeks to < 18 years and weighing at least 3 kg were treated with dolutegravir plus optimized background therapy *[see Undesirable effects (4.8)]*.

Additional pharmacokinetics data were evaluated in 2 pharmacokinetic substudies in ODYSSEY, an ongoing open-label, randomized, non-inferiority trial to evaluate the safety, efficacy, and pharmacokinetic parameters of dolutegravir plus two nucleoside reverse transcriptase inhibitor (NRTIs) (mainly abacavir and lamivudine) compared with standard of care in HIV-1−infected, pediatric subjects younger than 18 years.

Overall, the safety, and efficacy profile of abacavir, dolutegravir and lamivudine tablets for oral suspension in pediatric patients is comparable to that observed in adults. There are no data available on the use of lamivudine in pediatric patients with renal impairment.

The safety and effectiveness of abacavir, dolutegravir and lamivudine tablets for oral suspension have not been established in pediatric patients aged less than 3 months or weighing less than 6 kg.

Patients with Impaired Renal Function

Abacavir, dolutegravir and lamivudine tablets for oral suspension are not recommended for patients with creatinine clearance < 30 mL/min and pediatric patients with a similar degree of renal impairment based on age appropriate assessment of renal function because abacavir, dolutegravir and lamivudine tablets for oral suspension are 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 and lamivudine tablets for oral suspension, is required for patients with creatinine clearance < 30 mL/min and in pediatric patients with a similar degree of renal impairment based on age-appropriate assessment of renal function, then the individual components should be used.

Patients with a creatinine clearance between 30 and 49 mL/min receiving abacavir, 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 abacavir, dolutegravir and lamivudine to the individual components in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. Additionally, there are no data available on the use of lamivudine in pediatric patients with renal impairment. 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 or pediatric patients with a similar degree of renal impairment based on age-appropriate assessment of renal function who receive abacavir, dolutegravir and lamivudine tablets for oral suspension 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, abacavir, dolutegravir and lamivudine tablets for oral suspension should be discontinued, and the individual components should be used to construct the treatment regimen.

Patients with Impaired Hepatic Function

Abacavir, dolutegravir and lamivudine tablets for oral suspension are 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 and lamivudine tablets for oral suspension, is required for patients with mild hepatic impairment (Child-Pugh Score A), then the individual components should be used.

The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate (Child-Pugh Score B) or severe (ChildPugh Score C) hepatic impairment; therefore, abacavir, dolutegravir and lamivudine tablets for oral suspension are contraindicated in these patients *[see Contraindications (4.3)]*.

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 Contraindications (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.

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 and lamivudine tablets for oral suspension with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz	↓ Dolutegravir	In pediatric patients **weighing 6 to < 25 kg,** an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir, dolutegravir and lamivudine tablets for oral suspension. • 6 to < 10 kg: administer an additional 15-mg dose of dolutegravir (3 dolutegravir 5-mg tablets for oral suspension or 1½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension • 10 to < 14 kg: administer an additional 20-mg dose of dolutegravir (4 dolutegravir 5-mg tablets for oral suspension or 2 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 14 to < 20 kg: administer an additional 25-mg dose of dolutegravir (5 dolutegravir 5-mg tablets for oral suspension or 2½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 20 to < 25 kg: administer an additional 30-mg dose of dolutegravir (6 dolutegravir 5-mg tablets for oral suspension or 3 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with abacavir, dolutegravir and lamivudine tablets for oral suspension because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir Tipranavir/ritonavir	↓ Dolutegravir	In pediatric patients **weighing 6 to < 25 kg,** an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir, dolutegravir and lamivudine tablets for oral suspension. • 6 to < 10 kg: administer an additional 15-mg dose of dolutegravir (3 dolutegravir 5-mg tablets for oral suspension or 1½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 10 to < 14 kg: administer an additional 20-mg dose of dolutegravir (4 dolutegravir 5-mg tablets for oral suspension or 2 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 14 to < 20 kg: administer an additional 25-mg dose of dolutegravir (5 dolutegravir 5-mg tablets for oral suspension or 2½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 20 to < 25 kg: administer an additional 30-mg dose of dolutegravir (6 dolutegravir 5-mg tablets for oral suspension or 3 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension.
Other Agents		
Antiarrhythmic: Dofetilide	↑ Dofetilide	Coadministration is contraindicated with abacavir, dolutegravir and lamivudine tablets for oral suspension *[see Contraindications (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 and lamivudine tablets for oral suspension should be considered against the risk of seizures in these patients.
Carbamazepine	↓ Dolutegravir	In pediatric patients **weighing 6 to < 25 kg,** an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir, dolutegravir and lamivudine tablets for oral suspension. • 6 to < 10 kg: administer an additional 15-mg dose of dolutegravir (3 dolutegravir 5-mg tablets for oral suspension or 1½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 10 to < 14 kg: administer an additional 20-mg dose of dolutegravir (4 dolutegravir 5-mg tablets for oral suspension or 2 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 14 to < 20 kg: administer an additional 25-mg dose of dolutegravir (5 dolutegravir 5-mg tablets for oral suspension or 2½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 20 to < 25 kg: administer an additional 30-mg dose of dolutegravir (6 dolutegravir 5-mg tablets for oral suspension or 3 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension.
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓ Dolutegravir	Avoid coadministration with abacavir, dolutegravir and lamivudine tablets for oral suspension because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer abacavir, dolutegravir and lamivudine tablets for oral suspension 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 and lamivudine tablets for oral suspension and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, abacavir, dolutegravir and lamivudine tablets for oral suspension should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.
Metformin	↑ Metformin	Refer to the prescribing information for metformin for assessing the benefit and risk of concomitant use of abacavir, dolutegravir and lamivudine tablets for oral suspension and metformin.

Rifampin	↓ Dolutegravir	In pediatric patients **weighing 6 to < 25 kg,** an additional weight-based dose of dolutegravir should be given separated by 12 hours from abacavir, dolutegravir and lamivudine tablets for oral suspension. • 6 to < 10 kg: administer an additional 15-mg dose of dolutegravir (3 dolutegravir 5-mg tablets for oral suspension or 1½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 10 to < 14 kg: administer an additional 20-mg dose of dolutegravir (4 dolutegravir 5-mg tablets for oral suspension or 2 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 14 to < 20 kg: administer an additional 25-mg dose of dolutegravir (5 dolutegravir 5-mg tablets for oral suspension or 2½ dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension, • 20 to < 25 kg: administer an additional 30-mg dose of dolutegravir (6 dolutegravir 5-mg tablets for oral suspension or 3 dolutegravir 10-mg tablets for oral suspension), 12 hours after abacavir, dolutegravir and lamivudine tablets for oral suspension.

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 6).
*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 and lamivudine tablets for oral suspension 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 Contraindications (4.3)]*.

Table 6. Established and Other Potentially Significant Drug Interactions for Dolutegravir: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

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

Data from an ongoing birth outcome surveillance study has identified an increased risk of neural tube defects when dolutegravir, a component of abacavir, dolutegravir and lamivudine tablets for oral suspension, 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.

There are insufficient human data on the use of abacavir, 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.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 50 times (rats) the exposure in humans at the recommended human dose (RHD). Oral administration of abacavir to pregnant rats during organogenesis resulted in fetal malformations and other embryonic and fetal toxicities at exposures 35 times the human exposure (AUC) at the RHD. No adverse developmental effects were observed following oral administration of abacavir to pregnant rabbits during

organogenesis at exposures approximately 9 times the human exposure (AUC) at the RHD. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at a human exposure (AUC) similar to the RHD; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the RHD.

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 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 0.512.11) (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 abacavircontaining 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).

Lactation

Abacavir, dolutegravir and lamivudine are present in human milk. There is no information on the effects of abacavir, dolutegravir and lamivudine on the breastfed infant or the effects of the drug on milk production.

Fertility

There are no data on the effects of dolutegravir, abacavir or lamivudine on human male or female fertility. Animal studies indicate no effects of dolutegravir, abacavir or lamivudine on male or female fertility.

4.7 **Effects on ability to drive and use machines**

Abacavir, Dolutegravir and Lamivudine Tablets for Oral Suspension has no or negligible influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with dolutegravir.

4.8 **Undesirable effects**

The following adverse reactions are discussed in other sections of the labeling:

- Serious and sometimes fatal hypersensitivity reaction *[see Warnings and Precautions (4.4)]*.
- Exacerbations of hepatitis B *[see Warnings and Precautions (4.4)]*.
- Hepatotoxicity *[see Warnings and Precautions (4.4)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[see Warnings and Precautions (4.4)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (4.4)]*.
- Myocardial infarction *[see Warnings and Precautions (4.4)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials in Adults:

Serious and Fatal Abacavir-Associated Hypersensitivity Reactions: In clinical trials, serious and sometimes fatal hypersensitivity reactions have occurred with abacavir, a component of abacavir, dolutegravir and lamivudine tablets for oral suspension *[see Warnings and Precautions (4.4)].* These reactions have been characterized by 2 or more of the following signs or symptoms: (1) fever; (2) rash; (3) gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional symptoms (including generalized malaise, fatigue, or achiness); (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all abacavir hypersensitivity reactions include fever and/or rash as part of the syndrome.

Other signs and symptoms have included lethargy, headache, myalgia, edema, arthralgia, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, myolysis, and death have occurred in association with these hypersensitivity reactions. Physical findings have included lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and maculopapular or urticarial rash (although some patients had other types of rashes and others did not have a rash). There were reports of erythema multiforme. Laboratory abnormalities included elevated liver chemistries,

elevated creatine phosphokinase, elevated creatinine, and lymphopenia and abnormal chest x-ray findings (predominantly infiltrates, which were localized).

Serious Dolutegravir Hypersensitivity Reactions

In clinical trials, hypersensitivity reactions have occurred with dolutegravir, a component of abacavir, dolutegravir and lamivudine tablets for oral suspension *[see Warnings and Precautions (4.4)]***.** These hypersensitivity reactions have been characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury.

Additional Treatment-Emergent Adverse Drug Reactions (ADRs) with Use of Abacavir, Dolutegravir and Lamivudine: The safety assessment of abacavir, dolutegravir and lamivudine is primarily based on the analyses of data from a randomized, international, multicenter, double-blind, active-controlled trial, SINGLE (ING114467) and supported by data in treatment-experienced, INSTI-naive subjects from SAILING (ING111762) and by data from other treatment-naive trials. See full prescribing information for dolutegravir.

Treatment-Naive Subjects:

In SINGLE, 833 adult subjects were randomized and received at least one dose of either dolutegravir 50 mg with fixed-dose abacavir and lamivudine once daily (n = 414) or fixed-dose efavirenz/emtricitabine/tenofovir once daily (n = 419) (study treatment was blinded through Week 96 and openlabel from Week 96 through Week 144). Through 144 weeks, the rate of adverse events leading to discontinuation was 4% in subjects receiving dolutegravir + fixed-dose abacavir and lamivudine and 14% in subjects receiving efavirenz/emtricitabine/tenofovir once daily.

Treatment-emergent ADRs of moderate to severe intensity observed in at least 2% of subjects in either treatment arm of SINGLE are provided in Table 3.

Table 3. Treatment-Emergent Adverse Drug Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment- Naive Subjects in SINGLE (Week 144 Analysis**)**

Adverse Reaction	**dolutegravir + abacavir and lamivudine Once Daily (n = 414)**	**efavirenz/emtricitabine/tenofovir Once Daily (n = 419)**
Psychiatric		
Insomnia	**3%**	**3%**
Depression	**1%**	**2%**
Abnormal dreams	**< 1%**	**2%**
Nervous System		
Dizziness	**1%**	**5%**
Headache	**2%**	**2%**
Gastrointestinal		
Nausea	**< 1%**	**3%**
Diarrhea	**< 1%**	**2%**

General Disorders Fatigue	**2%**	**2%**
Skin and Subcutaneous Tissue Rash[a]	**< 1%**	**6%**
Ear and Labyrinth Vertigo	**0**	**2%**

[a] Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

Treatment-Experienced Subjects: SAILING is an international, double-blind trial in INSTI-naive, antiretroviral treatment-experienced adult subjects. Subjects were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rate of adverse events leading to discontinuation was consistent with that seen in the overall treatment-naive patient population.

The ADRs observed in the subset of subjects who received dolutegravir + abacavir and lamivudine were generally consistent with those seen in the overall treatment-naive patient population.

Less Common Adverse Reactions Observed in Clinical Trials: The following adverse reactions occurred in < 2% of treatment-naive or treatment-experienced subjects in any one trial. These events have been included because of their seriousness and/or assessment of potential causal relationship.

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.

Laboratory Abnormalities:
Treatment-Naive Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects in SINGLE are presented in Table 4. The mean change from baseline observed for selected lipid values is presented in Table 5.

Table 4. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naive Subjects in SINGLE (Week 144 Analysis)

Laboratory Abnormality	**dolutegravir + abacavir and lamivudine Once Daily (n = 414)**	**efavirenz/emtricitabine/tenofovir Once Daily (n = 419)**
ALT Grade 2 (> 2.5-5.0 x ULN) Grade 3 to 4 (> 5.0 x ULN)	 3% 1%	 5% < 1%
AST Grade 2 (> 2.5-5.0 x ULN) Grade 3 to 4 (> 5.0 x ULN)	 3% 1%	 4% 3%
Creatine kinase Grade 2 (6.0-9.9 x ULN) Grade 3 to 4 (≥ 10.0 x ULN)	 5% 7%	 3% 8%
Hyperglycemia Grade 2 (126-250 mg/dL) Grade 3 (> 250 mg/dL)	 9% 2%	 6% < 1%
Lipase	1 1	1 1

Grade 2 (> 1.5-3.0 x ULN) Grade 3 to 4 (> 3.0 ULN)	% 5 %	% 4 %
Total neutrophils Grade 2 (0.75-0.99 x 10^9) Grade 3 to 4 (< 0.75 x 10^9)	 4% 3%	 5% 3%

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, ULN = Upper limit of normal.

Table 5. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naive Subjects in SINGLE (Week 144 Analysis[a])

Lipid	dolutegravir + abacavir and lamivudine Once Daily (n = 414)	efavirenz/emtricitabine/tenofovir Once Daily (n = 419)
Cholesterol (mg/dL)	24.0	26.7
HDL cholesterol (mg/dL)	5.4	7.2
LDL cholesterol (mg/dL)	16.0	14.6
Triglycerides (mg/dL)	13.6	31.9

HDL = High-density lipoprotein, LDL = Low-density lipoprotein. [a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (dolutegravir + abacavir and lamivudine: n = 30 and efavirenz/emtricitabine/ tenofovir: n = 27). Seventy-two subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless of whether they discontinued the agent (dolutegravir + abacavir and lamivudine: n = 36 and efavirenz/emtricitabine/tenofovir: n = 36).

Treatment-Experienced Subjects:

Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naive trials.

Hepatitis C Virus Co-infection: In SINGLE, the pivotal Phase 3 trial, subjects with hepatitis C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal; subjects with hepatitis B co-infection were excluded. Overall, the safety profile in subjects with hepatitis C virus co-infection was similar to that observed in subjects without hepatitis C co-infection, although the rates of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) abnormalities were higher in the subgroup with hepatitis C virus co-

infection for both treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis C co-infected compared with HIV mono-infected subjects receiving abacavir, dolutegravir and lamivudine were observed in 15% and 2% (vs. 24% and 4% of subjects treated with efavirenz/emtricitabine/tenofovir) (Week 96 analysis), respectively *[see Warnings and Precautions (4.4)]*.

Changes in Serum Creatinine:

Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 144 weeks. In SINGLE, a mean change from baseline of 0.14 mg per dL (range: -0.25 mg per dL to 0.81 mg per dL) was observed after 144 weeks of treatment. Creatinine increases were similar in treatment-experienced subjects.

Abacavir and Lamivudine:

Laboratory abnormalities observed in clinical trials of abacavir (in combination with other antiretroviral treatment) were anemia, neutropenia, liver function test abnormalities, and elevations of creatine phosphokinase (CPK), blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical trials of lamivudine (in combination with other antiretroviral treatment) were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

*Clinical Trials Experience in Pediatric Subjects***:**

Abacavir, Dolutegravir and Lamivudine: The safety of abacavir, dolutegravir and lamivudine tablets for oral suspension in pediatric subjects with HIV-1 infection weighing at least 6 kg was evaluated in the IMPAACT 2019 trial. This was a multicenter, open-label, noncomparative trial of pediatric subjects with HIV-1 infection, younger than 12 years of age. Fifty-seven subjects weighing at least 6 kg to less than 40 kg were enrolled in this trial. Overall, the safety data in this pediatric study was similar to that seen in adults.

The safety analysis through Week 48 included 57 subjects weighing at least 6 kg at enrollment who received the recommended dose (determined by weight) and formulation. This analysis showed that 26% of subjects experienced clinical adverse reactions. The most common adverse reactions were classified as laboratory abnormalities and included decreased glomerular filtration rate (n = 13, 23%), increased blood creatinine (n = 10, 18%), and increased ALT (n = 3, 5%). All other adverse reactions occurred at a rate of < 2% of participants. Two subjects reported Grade 3 or 4 adverse reactions. One subject, an 8-year-old female who weighed 22 kg at baseline, experienced Grade 3 increased blood creatinine and Grade 3 decreased glomerular filtration rate. By Week 48, the glomerular filtration rate was improving, and the events did not lead to drug discontinuation. Another subject, a 7-year-old male who weighed 20 kg at baseline, experienced drug-induced liver injury with Grade 4 increased ALT and AST following 36 weeks of treatment with abacavir, dolutegravir and lamivudine tablets for oral suspension. Clinical signs or symptoms of hepatitis were not reported, and

ALT and AST values normalized after abacavir, dolutegravir and lamivudine tablets for oral suspension were discontinued.

Abacavir and Lamivudine:
The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as fixed dose abacavir and 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 pediatric subjects compared with historical data in adults.

Dolutegravir:
The safety of dolutegravir in pediatric subjects with HIV-1 infection weighing at least 6 kg was evaluated in the IMPAACT P1093 trial. Overall, the safety data in this pediatric study was similar to that seen in adults.

IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of pediatric subjects with HIV-1 infection, aged < 18 years. One hundred and fortytwo subjects weighing at least 6 kg were enrolled in this trial.

The safety analysis through Week 24 included 60 subjects weighing at least 6 kg at enrollment who received the recommended dose (determined by weight and age) and formulation. This analysis showed that 13% of subjects experienced adverse reactions. Grade 1 to 2 adverse reactions reported by more than one subject was immune reconstitution inflammatory syndrome (n = 2). There were no Grade 3 or 4 adverse reactions reported. No adverse reactions led to discontinuation.

The Grade 3 or 4 laboratory abnormalities reported in more than one subject weighing at least 6 kg at enrollment were decreased neutrophil count (n = 5), decreased blood bicarbonate (n = 3), increased lipase (n = 2), and increased blood potassium (n = 2). These laboratory events were not considered to be drug related. Changes in median serum creatinine were similar to those observed in adults.
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 and lamivudine tablets for oral suspension. 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

Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

Digestive
Stomatitis.

Gastrointestinal
Pancreatitis, vomiting, flatulence, abdominal pain, upper abdominal pain, abdominal distension, abdominal discomfort, gastro-oesophageal reflux disease, dyspepsia

General disorders
Weakness asthenia, fever, malaise

Hepatobiliary Disorders
Acute liver failure, liver transplant *[see Warnings and Precautions (4.4)]***.**

Hypersensitivity
Sensitization reactions (including anaphylaxis), urticaria *[see Warnings and Precautions (4.4).*

Investigations
Weight increased, Raised creatine kinase (creatine phosphokinase, CPK)

Metabolism and Nutrition Disorders
Hyperlactemia.
Musculoskeletal
CPK elevation, muscle weakness,
myalgia, rhabdomyolysis.
Nervous
Paresthesia, peripheral
neuropathy, seizures.
Psychiatric
Anxiety.
Respiratory
Abnormal breath sounds/wheezing.
Skin
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.

4.9 **Overdose**

There is no known specific treatment for overdose with abacavir, dolutegravir and lamivudine tablets for oral suspension. 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**

Abacavir, dolutegravir and lamivudine tablets for oral suspension are a fixed-dose combination of the HIV-1 antiretroviral agents abacavir, dolutegravir, and lamivudine

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 (CBVTP), 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.

5.2 **Pharmacokinetic properties**

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 7. Dolutegravir Steady state Pharmacokinetic Parameter Estimates in HIV 1−Infected Adults min

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 (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

Food is unlikely to have a clinically meaningful effect on systemic exposure of abacavir, lamivudine, and dolutegravir following the administration of abacavir, dolutegravir and lamivudine tablets for oral suspension.

Pediatric Patients: The pharmacokinetics of abacavir, dolutegravir and lamivudine tablets for oral suspension (abacavir, dolutegravir, and lamivudine) and their individual components have been evaluated in pediatric subjects.

Abacavir, Dolutegravir and Lamivudine: The pharmacokinetics of abacavir, dolutegravir and lamivudine tablets for oral suspension and abacavir, dolutegravir and lamivudine tablets were evaluated in the IMPAACT 2019 trial. Steady-state plasma exposure at doses by weight band are summarized in Table 8. Overall, exposures of abacavir, dolutegravir and lamivudine at the recommended doses for abacavir, dolutegravir and lamivudine tablets for oral suspension and abacavir, dolutegravir and lamivudine tablets are within the observed exposure ranges at the recommended doses of individual products in adults and pediatrics. Refer to the prescribing information for EPIVIR, TIVICAY, and ZIAGEN for pharmacokinetic information on lamivudine, dolutegravir, and abacavir, respectively, in pediatric patients.

Table 8. Summary of Pharmacokinetic Parameters in Pediatric HIV-1–Infected Subjects (IMPAACT 2019 Trial)

Drug	Weight Band	Dose[a] of single entities in abacavir, dolutegravir and lamivudine tablets or abacavir, dolutegravir and lamivudine tablets for oral suspension	n	Pharmacokinetic Parameter Geometric Mean (%CV)		
				Cmax (mcg/mL)	$AUC_{0\text{-}24}$h (mcg·h/mL)	C24h (ng/mL)

Abacavir	6 to < 10 kg	180 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	7.30 (20)	17.7 (34)	3 (128)
	10 to < 14 kg	240 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	8.36 (44)	19.8 (51)	5 (127)
	14 to < 20 kg	300 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	6.26 (31)	15.1 (40)	3 (108)
	20 to < 25 kg	360 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	6.65 (28)	17.4 (19)	4 (85)
	≥ 25 to < 40 kg	600 mg once daily abacavir, dolutegravir and lamivudine tablets	7	9.04 (22)	25.7 (15)	11 (229)
Dolutegravir	6 to < 10 kg	15 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	7.40 (28)	75.9 (34)	910 (68)
	10 to < 14 kg	20 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	8.85 (21)	91.0 (36)	1220 (77)
	14 to < 20 kg	25 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	7.04 (17)	71.4 (23)	790 (44)
	20 to < 25 kg	30 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	7.29 (17)	84.4 (26)	1350 (95)
	≥ 25 to < 40 kg	50 mg once daily abacavir, dolutegravir and lamivudine tablets	7	6.25 (21)	71.8 (14)	980 (28)
Lamivudine	6 to < 10 kg	90 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	2.29 (40)	10.7 (46)	55 (39)
	10 to < 14 kg	120 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	3.55 (19)	14.2 (24)	46 (48)
	14 to < 20 kg	150 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	2.92 (23)	13.0 (16)	58 (37)
	20 to < 25 kg	180 mg once daily abacavir, dolutegravir and lamivudine tablets for oral suspension	7	2.99 (32)	14.5 (17)	60 (18)

	≥ 25 to < 40 kg	300 mg once daily abacavir, dolutegravir and lamivudine tablets	7	4.15 (29)	21.7 (26)	84 (35)

%CV, coefficient of variation expressed as a percentage.

[a] The relative dolutegravir bioavailability of abacavir, dolutegravir and lamivudine tablets for oral suspension is ~1.7-fold that of abacavir, dolutegravir and lamivudine tablets.

Geriatric Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir. The pharmacokinetics of abacavir or lamivudine have not been studied in subjects older than 65 years.

Male and Female Patients

There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (dolutegravir, abacavir, or lamivudine) based on the available information that was analyzed for each of the individual components.

Racial Groups

There are no significant or clinically relevant racial differences in pharmacokinetics of the individual components (dolutegravir, abacavir, or lamivudine) based on the available information that was analyzed for each of the individual components

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 and Reproductive Toxicology

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).

Abacavir, dolutegravir and lamivudine crossed the placenta in animal studies.

Abacavir was toxic to the developing embryo and fetus in rats, but not in rabbits. These findings included decreased fetal body weight, fetal oedema, increased skeletal variations or malformations, early intra-uterine deaths and stillbirths. No conclusion can be drawn about the teratogenic potential of abacavir because of this embryo-fetal toxicity.

Dolutegravir did not affect male or female fertility in rats at doses up to 24 times the 50 mg twice daily human clinical exposure based on AUC. Oral administration of dolutegravir to pregnant rats at doses up to 27 times the 50 mg twice daily human clinical exposure based on AUC from days 6 to 17 of gestation did not cause maternal toxicity, developmental toxicity or teratogenicity.

Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, reduced urine or faeces, suppressed bodyweight gain) was observed at 1000 mg/kg.

In a juvenile toxicity study in rats, there were two pre-weaning deaths at dolutegravir dose of 75 mg/kg daily. Over the pre-weaning period, mean bodyweight gain was decreased and the decrease persisted throughout the study for females during the post-weaning period. The systemic exposure at this dose (based on AUC) to dolutegravir was about 17 to 20-fold higher than in humans at the recommended paediatric exposure. No new target organs were identified in juveniles compared to adults. In the rat prenatal and postnatal development study, bodyweight decreased in the developing offspring during lactation at a maternally toxic dose (about 27 times human exposure at the maximum recommended dose).

Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryo lethality at systemic exposure similar to the recommended clinical dose. A similar effect was not seen in rats even at very high systemic exposure.

A fertility study in rats has shown that abacavir and lamivudine had no effect on male or female fertility.

6. Pharmaceutical Particulars

6.1 List of Excipients

Tablet Core:
Acesulfame potassium, crospovidone, ferric oxide, mannitol, microcrystalline cellulose, povidone, silicified microcrystalline cellulose, sodium starch glycolate, sodium stearyl fumarate, strawberry cream flavor permaseal [contains maltodextrin, modified starch, propylene glycol] and sucralose.

Film-coating:
Iron oxide black, iron oxide red, polyethyelene glycol, polyvinyl alcohol-part hydrolyzed, talc and titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Store below 30°C.

6.5 Nature and Content of container

HDPE container of 90's & 180's

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 Authorization Holder

AUROBINDO PHARMA LIMITED
APL Healthcare Limited,
Unit-IV, Plot No.16, APIIC Multi Products SEZ,
Menakuru Village, Naidupeta Mandal,
Tirupati District,
Andhra Pradesh, INDIA

8. Marketing Authorization Number

CTD 12342

9. Date of first authorization/renewal of the authorization

16/01/2025

10. Date of revision of the text

11/05/2025