HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DOLUTEGRAVIR TABLETS FOR ORAL SUSPENSION safely and effectively. See full prescribing information for DOLUTEGRAVIR TABLETS FOR ORAL SUSPENSION.

DOLUTEGRAVIR tablets for oral suspension

---------- **INDICATIONS AND USAGE** ----------
Dolutegravir tablets for oral suspension are a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients (treatment-naïve or -experienced but INSTI-naïve) aged at least 4 weeks and weighing at least 3 kg. (1)

---------- **DOSAGE AND ADMINISTRATION** ----------
- Pregnancy Testing: Perform pregnancy testing before initiation of dolutegravir in individuals of childbearing potential. (2.1, 5.3)
- May be taken without regard to food. (2.4)

Pediatric Patients: Treatment-naïve or treatment-experienced INSTI-naïve patients aged at least 4 weeks and weighing at least 3 kg. See Table 1 for complete pediatric dosing recommendations. (2.2, 2.3). Dolutegravir tablets and dolutegravir tablets for oral suspension are not bioequivalent and are not interchangeable on a milligram-per-milligram basis.

Pediatric Population Body Weight	Recommended Dose[a] Dolutegravir Tablets for Oral Suspension
3 kg to less than 6 kg	5 mg once daily (one-half tablet)
6 kg to less than 10 kg	15 mg once daily (1 and one-half tablets)
10 kg to less than 14 kg	20 mg once daily (2 tablets)
14 kg to less than 20 kg	25 mg once daily (2 and one-half tablets)
20 kg and greater	30 mg once daily (3 tablets)

[a] If certain UGT1A or CYP3A inducers are coadministered, then adjust the weight-based dose of dolutegravir to twice daily. (2.3, 7.2, 7.3)

----------**DOSAGE FORMS AND STRENGTHS** ----------
Dolutegravir tablets for oral suspension: 10 mg, functionally scored (3)
---------- **CONTRAINDICATIONS** ----------
- Previous hypersensitivity reaction to dolutegravir. (4)
- Coadministration with dofetilide. (4)

---------- **WARNINGS AND PRECAUTIONS** ----------
- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue dolutegravir tablets for oral suspension and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.1)
- Hepatotoxicity has been reported in patients receiving dolutegravir-containing regimens. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Monitoring for hepatotoxicity is recommended. (5.2)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. An alternative treatment to dolutegravir should be considered at the time of conception through the first trimester of pregnancy due to the risk of neural tube defects. Counsel adolescents and adults of childbearing potential to use effective contraception. (2.1, 5.3, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)
- Dolutegravir tablets and dolutegravir tablets for oral suspension are not interchangeable. (2.2, 5.6)

---------- **ADVERSE REACTIONS** ----------
The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving dolutegravir in any one adult trial) are insomnia, fatigue, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- **DRUG INTERACTIONS** ----------
- Refer to the full prescribing information for important drug interactions with dolutegravir. (4, 7)
- Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7.2, 7.3)
- Dolutegravir should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. When taken with food, dolutegravir and supplements containing calcium or iron can be taken at the same time. (7.3)

---------- **USE IN SPECIFIC POPULATIONS** ----------
- Pregnancy: An alternative treatment to dolutegravir should be considered at the time of conception through the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing and contraception are recommended in individuals of childbearing potential. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Dolutegravir tablets for oral suspension are indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-naïve or treatment-experienced but integrase strand inhibitor [INSTI]-naïve pediatric patients aged at least 4 weeks and weighing at least 3 kg *[see Microbiology (12.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pregnancy Testing Before Initiation

Perform pregnancy testing before initiation of dolutegravir in individuals of childbearing potential *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 General Dosing and Administration Instructions for Pediatric Patients

Do not interchange dolutegravir tablets and dolutegravir tablets for oral suspension on a milligram-per-milligram basis due to differing pharmacokinetic profiles *[see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)]*. If switching from the tablets to the tablets for oral suspension, follow the recommended dosage in Table 1. If switching from the tablets for oral suspension to the tablets, follow the recommended dosage in the label for dolutegravir tablets. See administration instructions in *Dosage and Administration (2.4)*.

2.3 Recommended Dosage in Pediatric Patients

The recommended weight-based dosage of dolutegravir tablets for oral suspension in **pediatric patients weighing at least 3 kg** (4 weeks and older, treatment-naïve or treatment-experienced but naïve to INSTI treatment) is described in Table 1.

Table 1. Recommended Dosage of Dolutegravir Tablets for Oral Suspension in Pediatric Patients 4 Weeks and Older Weighing at Least 3 kg

	Dolutegravir Tablets for Oral Suspension	
Body Weight	**Daily Dose[a]**	**Number of 10-mg Tablets**
3 kg to less than 6 kg	5 mg once daily	½ (one-half)
6 kg to less than 10 kg	15 mg once daily	1 ½ (one and one-half)
10 kg to less than 14 kg	20 mg once daily	2 (two)
14 kg to less than 20 kg	25 mg once daily	2 ½ (two and one-half)
20 kg and greater[b]	30 mg once daily	3 (three)

[a] If certain UGT1A or CYP3A inducers are coadministered, then administer dolutegravir tablets for oral suspension twice daily *[see Drug Interactions (7.2, 7.3)]*.

[b] Dosing for pediatric patients weighing 20 kg and greater may follow the adult recommendations using dolutegravir 50 mg tablets. See administration instructions in *Dosage and Administration (2.2)*.

2.4 Additional Administration Instructions

Administer dolutegravir tablets for oral suspension with or without food.

Administration Instructions for Dolutegravir Tablets for Oral Suspension: Do not chew or crush dolutegravir tablets for oral suspension. Tablets can be split for doses of ½, 1½, or 2½ tablets. Instruct patients (or instruct caregivers) to either:

- Swallow the tablets for oral suspension whole (if more than one tablet is required, swallow one tablet at a time to reduce the risk of choking), or
- Fully disperse the tablets for oral suspension in 5 mL of drinking water (if using ½ or 1½ tablets for oral suspension) or 10 mL (if using 2, 2½, or 3 tablets for oral suspension); swirl the suspension so that no lumps remain. Do not use any other drink or food to prepare the dose because there are no data regarding dispersion in any other vehicle.
- After full dispersion, give all the prepared medicine to the child. Add another 5 mL of drinking water to the cup, swirl, and give it all to the child. Repeat if any medicine remains in the cup to make sure the child gets the full dose.
- Administer the oral suspension within 30 minutes of mixing.

3 DOSAGE FORMS AND STRENGTHS

Dolutegravir Tablets for Oral Suspension are available containing dolutegravir 10 mg, equivalent to 10.52 mg of dolutegravir sodium.

- The 10 mg tablets for oral suspension are pink, film-coated, strawberry cream flavored, oval, functionally scored tablets debossed with **D** to the left of the breakline and **T** to the right of the breakline on one side of the tablet and **M** to the left of the breakline on the other side of the tablet.

4 CONTRAINDICATIONS

Dolutegravir tablets for oral suspension are contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.1)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Discontinue dolutegravir 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 dolutegravir tablets for oral suspension or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. Dolutegravir tablets for oral suspension are contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

5.2 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir tablets for oral suspension *[see Adverse Reactions (6.1)]*. 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 been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ® (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

5.3 Embryo-Fetal Toxicity

An 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 reported types of neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, an alternative treatment to dolutegravir should be considered at the time of conception through the first trimester of pregnancy *[see Use in Specific Populations (8.1)]*.

Perform pregnancy testing before initiation of dolutegravir in individuals of childbearing potential to exclude use of dolutegravir during the first trimester of pregnancy *[see Dosage and Administration (2.1)]*. Initiation of dolutegravir is not recommended in individuals actively trying to become pregnant unless there is no suitable alternative *[see Use in Specific Populations (8.1, 8.3)]*.

Counsel individuals of childbearing potential to consistently use effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

In individuals of childbearing potential currently on dolutegravir who are actively trying to become pregnant, or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing dolutegravir versus switching to another antiretroviral regimen and consider switching to an alternative regimen *[see Use in Specific Populations (8.1, 8.3)]*.

Dolutegravir 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.

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

The concomitant use of dolutegravir 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), Drug Interactions (7.3)]*:

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

For concomitant drugs for which the interaction can be mitigated, please see Table 5 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 dolutegravir tablets for oral suspension; review concomitant medications during therapy with dolutegravir tablets for oral suspension; and monitor for the adverse reactions associated with the concomitant drugs.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir 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, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

5.6 Different Formulations Are Not Interchangeable

Dolutegravir tablets and dolutegravir tablets for oral suspension are not bioequivalent and are not interchangeable on a milligram-per-milligram basis *[see Clinical Pharmacology (12.3)]*. If a pediatric patient switches from one formulation to the other, the dose must be adjusted for the new dosage formulation *[see Dosage and Administration (2.2)]*. 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 of dolutegravir.

6 ADVERSE REACTIONS

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

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.5)]*.

6.1 Clinical Trials Experience

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 practice.

Clinical Trials Experience in Adult Subjects: *Treatment-Naïve Subjects:* The safety assessment of dolutegravir in HIV-1–infected treatment-naïve subjects is based on the analyses of data from 2 international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467) and data from the international, multicenter, open-label FLAMINGO (ING114915) trial.

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir tablets 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and

lamivudine or emtricitabine/tenofovir). There were 808 subjects included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir tablets 50 mg with fixed-dose abacavir sulfate and lamivudine once daily or fixed-dose efavirenz/emtricitabine/tenofovir once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in subjects receiving dolutegravir tablets 50 mg once daily + fixed-dose abacavir sulfate and lamivudine and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir once daily.

Treatment-emergent adverse reactions of moderate to severe intensity observed in at least 2% of subjects in either treatment arm in SPRING-2 and SINGLE trials are provided in Table 2. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 2. Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

	SPRING-2		SINGLE	
System Organ Class/ Preferred Term	**Dolutegravir Tablets 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir Tablets 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)**	**Efavirenz/ Emtricitabine/ Tenofovir Once Daily (n = 419)**
Psychiatric				
Insomnia	< 1%	< 1%	3%	3%
Depression	< 1%	< 1%	1%	2%
Abnormal Dreams	< 1%	< 1%	< 1%	2%
Nervous System				
Dizziness	< 1%	< 1%	< 1%	5%
Headache	< 1%	< 1%	2%	2%
Gastrointestinal				
Nausea	1%	1%	< 1%	3%
Diarrhea	< 1%	< 1%	< 1%	2%
Skin and Subcutaneous Tissue				
Rash[a]	0	< 1%	< 1%	6%
General Disorders				
Fatigue	< 1%	< 1%	2%	2%

Ear and Labyrinth				
Vertigo	0	< 1%	0	2%

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

In addition, Grade 1 insomnia was reported by 1% and less than 1% of subjects receiving dolutegravir and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 4% for dolutegravir and fixed-dose efavirenz/emtricitabine/tenofovir, respectively. These events were not treatment limiting.

In a multicenter, open-label trial (FLAMINGO), 243 subjects received dolutegravir tablets 50 mg once daily versus 242 subjects who received darunavir 800 mg/ritonavir 100 mg once daily, both in combination with investigator-selected NRTI background regimen (either fixed-dose abacavir sulfate and lamivudine or emtricitabine/tenofovir). There were 484 subjects included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir and 6% in subjects receiving darunavir/ritonavir. The adverse reactions observed in FLAMINGO were generally consistent with those seen in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1–infected, antiretroviral treatment-experienced adults were randomized and received either dolutegravir tablets 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 rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir tablets 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent adverse reaction of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in subjects receiving dolutegravir tablets 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following adverse reactions occurred in less than 2% of treatment-naïve or treatment-experienced subjects receiving dolutegravir in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

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.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities: *Treatment-Naïve 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 are presented in Table 3. The mean change from baseline observed for selected lipid values is presented in Table 4. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

	SPRING-2		**SINGLE**	
Laboratory Parameter Preferred Term	**Dolutegravir Tablets 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir Tablets 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)**	**Efavirenz/ Emtricitabine/ Tenofovir Once Daily (n = 419)**
ALT				
Grade 2 (> 2.5-5.0 x ULN)	4%	4%	3%	5%
Grade 3 to 4 (> 5.0 x ULN)	2%	2%	1%	< 1%
AST				
Grade 2 (> 2.5-5.0 x ULN)	5%	3%	3%	4%
Grade 3 to 4 (> 5.0 x ULN)	3%	2%	1%	3%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	3%	2%	< 1%	< 1%
Grade 3 to 4 (> 2.5 x ULN)	< 1%	< 1%	< 1%	< 1%
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	2%	5%	5%	3%
Grade 3 to 4 (≥ 10.0 x ULN)	7%	4%	7%	8%
Hyperglycemia				
Grade 2 (126-250 mg/dL)	6%	6%	9%	6%
Grade 3 (> 250 mg/dL)	< 1%	2%	2%	< 1%
Lipase				
Grade 2 (> 1.5-3.0 x ULN)	7%	7%	11%	11%
Grade 3 to 4 (> 3.0 x ULN)	2%	5%	5%	4%
Total neutrophils				
Grade 2 (0.75-0.99 x 10^9)	4%	3%	4%	5%

Grade 3 to 4 (< 0.75 x 10^9)	2%	2%	3%	3%

ULN = Upper limit of normal.

Table 4. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis[a]) and SINGLE Trials (Week 144 Analysis[a])

	SPRING-2		SINGLE	
Laboratory Parameter Preferred Term	**Dolutegravir Tablets 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir Tablets 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)**	**Efavirenz/ Emtricitabine/ Tenofovir Once Daily (n = 419)**
Cholesterol (mg/dL)	8.1	10.1	24.0	26.7
HDL cholesterol (mg/dL)	2.0	2.3	5.4	7.2
LDL cholesterol (mg/dL)	5.1	6.1	16.0	14.6
Triglycerides (mg/dL)	6.7	6.6	13.6	31.9

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 30 and fixed-dose efavirenz/emtricitabine/tenofovir n = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SPRING-2: dolutegravir n = 9, raltegravir n = 13; SINGLE: dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 36, fixed-dose efavirenz/emtricitabine/tenofovir: n = 36).

Laboratory abnormalities observed in the FLAMINGO trial were generally consistent with observations in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving dolutegravir tablets were observed in 18% vs. 3% with the 50-mg once-daily dose and 13% vs. 8% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn *[see Warnings and Precautions (5.2)]*.

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 *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

Clinical Trials Experience in Pediatric Subjects: The safety and pharmacokinetics of dolutegravir tablets for oral suspension in HIV-1-infected pediatric subjects aged at least 4 weeks and weighing at least 3 kg was evaluated in the IMPAACT P1093 trial and 2 weight-band-based pharmacokinetic substudies of the ODYSSEY trial *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3)]*. Overall, the safety data in these pediatric studies were similar to those seen in adults, and there was no clinically significant difference in dolutegravir exposure *[see Clinical Pharmacology (12.3)]*.

IMPAACT P1093 is an ongoing, multicenter, open-label, non-comparative trial of HIV-1–infected pediatric subjects aged 4 weeks to less than 18 years *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3), Clinical Studies (14.3)]*.

The safety analysis based on subjects (n = 75) who received the recommended dose (determined by weight and age) through Week 24 showed that 11% of subjects experienced drug-related clinical adverse reactions. The only Grade 1 to 2 drug-related clinical adverse reaction reported by more than one subject was immune reconstitution inflammatory syndrome (IRIS) (n = 2). There were no Grade 3 or 4 drug-related adverse reactions reported. No adverse reactions led to discontinuation.

The Grade 3 or 4 laboratory abnormalities reported in more than one subject were decreased neutrophil count (n = 11), decreased blood bicarbonate (n = 4), decreased hemoglobin (n = 3), increased lipase (n = 2), and increased blood potassium (n = 2). These laboratory events were not considered to be drug-related. Median laboratory values were similar at baseline and Week 24. Changes in median serum creatinine were similar to those observed in adults.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. 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.

Hepatobiliary Disorders: Acute liver failure, hepatotoxicity.

Investigations: Weight increased.

Musculoskeletal: Arthralgia, myalgia.

Psychiatric: Anxiety.

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (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, Table 5) *[see Contraindications (4), Drug Interactions (7.3)]*.

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} greater than 50 microM) the following: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, or 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.

7.2 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 concentration and reduce the therapeutic effect of dolutegravir.

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

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 5) *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

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

7.3 Established and Other Potentially Significant Drug Interactions

Table 5 provides clinical recommendations as a result of drug interactions with dolutegravir. 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 Dosage and Administration (2), Clinical Pharmacology (12.3).]*

Table 5. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions *[see Dosage and Administration (2)]*

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓ Dolutegravir	Use of dolutegravir with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓ Dolutegravir	Increase the weight-based dose of dolutegravir to twice daily (Table 1).
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make dosing recommendations.
Protease inhibitors: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓ Dolutegravir	Increase the weight-based dose of dolutegravir to twice daily (Table 1).
Other Agents		
Dofetilide	↑ Dofetilide	Coadministration is contraindicated with dolutegravir *[see Contraindications (4)]*.
Carbamazepine[a]	↓ Dolutegravir	Increase the weight-based dose of dolutegravir to twice daily (Table 1).
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓ Dolutegravir	Avoid coadministration with dolutegravir 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 dolutegravir 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓ Dolutegravir	When taken with food, dolutegravir and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, dolutegravir should be taken

		2 hours before or 6 hours after taking supplements containing calcium or iron.
Potassium channel blocker: Dalfampridine	↑ Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with dolutegravir should be considered against the risk of seizures in these patients.
Metformin	↑ Metformin	Refer to the prescribing information for metformin for assessing the benefit and risk of concomitant use of dolutegravir and metformin.
Rifampin[a]	↓ Dolutegravir	Increase the weight-based dose of dolutegravir to twice daily (Table 1).

[a] *See Clinical Pharmacology (12.3) Table 8 or Table 9 for magnitude of interaction.*

7.4 Drugs without Clinically Significant Interactions with Dolutegravir

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: Data from a birth outcome surveillance study has identified an increased risk of neural tube defects when dolutegravir was administered at the time of conception compared with non-dolutegravir-containing antiretroviral regimens. 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. In addition, 2 of the 5 birth defects (encephalocele and iniencephaly), which have been observed with dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, an alternative treatment to dolutegravir should be considered at the time of conception through the first trimester of pregnancy. Initiation of dolutegravir is not recommended in individuals actively trying to become pregnant unless there is no suitable alternative *(see Data)*.

In individuals of childbearing potential currently on dolutegravir who are actively trying to become pregnant, or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing dolutegravir versus switching to another antiretroviral regimen and consider switching to an alternative regimen. Advise pregnant individuals of the potential risk to the embryo exposed to dolutegravir from the time of conception through the first trimester of pregnancy. A benefit-risk assessment should consider factors such as feasibility of switching,

tolerability, ability to maintain viral suppression, and risk of transmission to the infant against the risk of neural tube defects *[see Warnings and Precaution (5.3)]*.

There are insufficient human data on the use of dolutegravir 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 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of dolutegravir *(see Data)*.

Data: *Human Data:* In a birth outcome surveillance study in Botswana, there were 5 cases of neural tube defects reported out of 1,683 deliveries (0.3%) to women who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.1% (15/14,792 deliveries) in the non-dolutegravir arm and 0.08% (70/89,372 deliveries) in the HIV-uninfected arm. Five cases reported with dolutegravir included one case each of encephalocele, anencephaly, and iniencephaly, and 2 cases of myelomeningocele. In the same study, one infant out of 3,840 (0.03%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 3 infants out of 5,952 (0.05%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy.

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to 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.

Animal Data: Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on Gestation Days 6 to 17 and 6 to 18, respectively, and to rats on Gestation Day 6 to Lactation/Postpartum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/postnatal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

8.2 Lactation

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

It is not known whether dolutegravir is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir was present in milk *(see Data)*.

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

Data: *Animal Data:* Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on Lactation Day 10, with milk concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours postdose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing: Perform pregnancy testing in individuals of childbearing potential before initiation of dolutegravir *[see Dosage and Administration (2.1)]*.

In individuals of childbearing potential currently on dolutegravir who are actively trying to become pregnant, or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing dolutegravir versus switching to another antiretroviral regimen and consider switching to an alternative regimen *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Contraception: Counsel individuals of childbearing potential who are taking dolutegravir to consistently use effective contraception.

8.4 Pediatric Use

The safety, pharmacokinetics, and effectiveness of dolutegravir were evaluated in 75 HIV-1–infected, treatment-naïve or treatment-experienced, INSTI-naïve pediatric and adolescent subjects aged 4 weeks to less than 18 years weighing at least 3 kg in an ongoing, open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.3)]*. 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 NRTIs compared with standard of care in HIV-1–infected pediatric subjects younger than 18 years *[see Clinical Pharmacology (12.3)]*.

Overall, the safety data in pediatric subjects from the IMPAACT P1093 trial were comparable to those observed in adults *[see Adverse Reactions (6.1)]*. The pharmacokinetic parameters of dolutegravir in pediatric subjects receiving dolutegravir tablets for oral suspension from IMPAACT P1093 and ODYSSEY were comparable to those of adults receiving 50 mg tablets once daily or twice daily *[see Clinical Pharmacology (12.3)]*. The effectiveness observed in IMPAACT P1093 is comparable to that of treatment-experienced adult subjects.

Safety and effectiveness of dolutegravir have not been established in pediatric patients aged less than 4 weeks or weighing less than 3 kg or in any pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (e.g., raltegravir, elvitegravir).

8.5 Geriatric Use

Clinical trials of dolutegravir did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of dolutegravir in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, dolutegravir is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

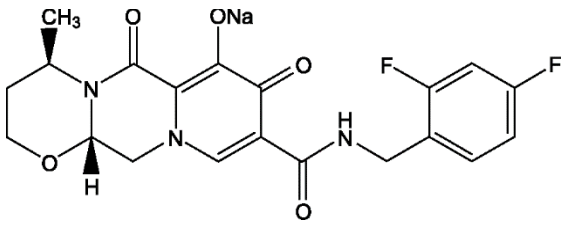
Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with those in matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment. There is inadequate information to recommend appropriate dosing of dolutegravir in patients requiring dialysis.

10 OVERDOSAGE

There is no known specific treatment for overdose with dolutegravir. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

11 DESCRIPTION

Dolutegravir tablets for oral suspension contain dolutegravir, as dolutegravir sodium, an HIV INSTI. The chemical name of dolutegravir sodium is Sodium (4R, 12aS)-N-[(2,4-Difluorobenzyl) carbamoyl]-4-methyl-6, 8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[l',2':4,5] pyrazino[2,1-b] [1,3] oxazin-7-olate. The molecular formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.37 g per mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

Each dolutegravir tablet for oral suspension contains 10 mg of dolutegravir free acid, which is equivalent to 10.52 mg dolutegravir sodium, and the following inactive ingredients: calcium sulfate dihydrate, crospovidone (Type B), mannitol, microcrystalline cellulose, povidone K29/32, silicified microcrystalline cellulose, sodium starch glycolate (Type A), sodium stearyl fumarate, strawberry cream flavor and sucralose. The tablet film-coating contains black iron oxide, hypromellose, polyethylene glycol 400, red iron oxide, titanium dioxide and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir is an HIV-1 antiretroviral agent *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects on Electrocardiogram: In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3-fold of the 50-mg tablet 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 tablets 50 mg once daily (n = 12), dolutegravir tablets 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.

12.3 Pharmacokinetics

The mean systemic exposures of dolutegravir from dolutegravir tablets for oral suspension, 10 mg, were comparable to those from two tablets of TIVICAY® PD (dolutegravir) tablets for oral suspension, 5 mg, of ViiV Healthcare, when single doses were administered to healthy subjects under fasted and fed conditions. 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. The non-linear exposure of dolutegravir following 50 mg tablets twice daily compared with 50 mg tablets once daily in HIV-1–infected subjects (Table 6) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir tablets 50 mg twice daily in clinical trials.

Table 6. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1–Infected Adults

Parameter	50 mg Tablets Once Daily Geometric Mean[a] (%CV)	50 mg Tablets Twice Daily Geometric Mean[b] (%CV)
$AUC_{(0-24)}$ (mcg•h/mL)	53.6 (27)	75.1 (35)
C_{max} (mcg/mL)	3.67 (20)	4.15 (29)
C_{min} (mcg/mL)	1.11 (46)	2.12 (47)

[a] Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.
[b] Based on population pharmacokinetic analyses using data from VIKING (ING112961) and VIKING-3.

Dolutegravir tablets and dolutegravir tablets for oral suspension are not bioequivalent. The relative bioavailability of the dolutegravir tablets for oral suspension is approximately 1.6-fold higher than dolutegravir tablets; therefore, the 2 dosage forms are not interchangeable on a milligram-per-milligram basis *[see Dosage and Administration (2.2)]*.

Absorption: 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_{24h} ranging from 1.2 to 1.5.

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegravir is a P-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established.

Effects of Food: Dolutegravir tablets for oral suspension may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir following a 50-mg dose of dolutegravir tablets. Low-, moderate-, and high-fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Distribution: Dolutegravir is highly bound (greater than or equal to 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 of dolutegravir tablets is estimated at 17.4 L based on a population pharmacokinetic analysis.

Cerebrospinal Fluid (CSF): In 12 treatment-naïve subjects on dolutegravir tablets 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng per mL to 18.3 ng per mL) 2 to 6 hours postdose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Elimination: Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population pharmacokinetic analyses.

Metabolism: Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).

Excretion: After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in 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 low (less than 1% of the dose).

Specific Populations: *Pediatric Patients:* The pharmacokinetics of dolutegravir tablets for oral suspension were evaluated in the IMPAACT P1093 trial and in 2 weight-band-based pharmacokinetic substudies from the ODYSSEY trial. Steady-state plasma exposure at doses by weight band are summarized in Table 7 *[see Clinical Studies (14.3)]*.

Mean dolutegravir $AUC_{0\text{-}24h}$ and C_{24h} in HIV-1–infected pediatric subjects were comparable to those in adults after 50 mg tablets once daily or 50 mg tablets twice daily. Mean C_{max} is higher in pediatrics, but the increase is not considered clinically significant as the safety profiles were similar in pediatric and adult subjects *[see Use in Specific Populations (8.4)]*.

Table 7. Summary of Pharmacokinetic Parameters in Pediatric HIV-1–Infected Subjects (Pooled Analyses for IMPAACT P1093 and ODYSSEY[a] Trials)

Weight Band	Dose[b] of Dolutegravir Tablets or Dolutegravir Tablets for Oral Suspension	n	Pharmacokinetic Parameter Geometric Mean (%CV)		
			C_{max} (mcg/mL)	$AUC_{0\text{-}24h}$ (mcg•h/mL)	C_{24h} (ng/mL)
3 kg to < 6 kg	Dolutegravir tablets for oral suspension 5 mg once daily	8	3.80 (34)	49.37 (49)	962 (98)
6 kg to < 10 kg	Dolutegravir tablets for oral suspension 15 mg once daily	17	5.27 (50)	57.17 (76)	706 (177)
10 kg to < 14 kg	Dolutegravir tablets for oral suspension 20 mg once daily	13	5.99 (33)	68.75 (48)	977 (100)
14 kg to < 20 kg	Dolutegravir tablets for oral suspension 25 mg once daily	19	5.97 (42)	58.97 (44)	725 (75)
20 kg to < 25 kg	Dolutegravir tablets for oral suspension 30 mg once daily	9	7.16 (26)	71.53 (26)	759 (73)
≥ 20 kg	Dolutegravir tablets	49	4.92 (40)	54.98 (43)	778 (62)

	50 mg once daily				

[a] Data from 2 weight-band-based pharmacokinetic substudies in the ODYSSEY trial.
[b] The bioavailability of dolutegravir tablets for oral suspension is ~1.6-fold that of dolutegravir tablets.

Geriatric Patients: Population pharmacokinetic analysis indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

Patients with Hepatic Impairment: In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg tablet dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

Patients with Renal Impairment: In a trial evaluating the pharmacokinetics of a single 50-mg tablet of dolutegravir comparing 8 subjects with severe renal impairment (CrCl less than 30 mL per min) with 8 matched healthy controls, AUC, C_{max}, and C_{24} of dolutegravir were lower by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. Population pharmacokinetic analysis using data from SAILING and VIKING-3 trials indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. There is inadequate information to recommend appropriate dosing of dolutegravir in patients requiring dialysis.

HBV or HCV Co-infected Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

Gender and Race: Population analyses using pooled pharmacokinetic data from adult trials indicated gender and race had no clinically relevant effect on the exposure of dolutegravir.

Drug Interaction Studies: Drug interaction trials were performed with dolutegravir and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. The effects of dolutegravir on the exposure of coadministered drugs are summarized in Table 8 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 9.

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table 5 *[see Dosage and Administration (2.2), Drug Interactions (7.3)]*.

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

Coadministered Drug(s) and Dose(s)	**Dose of Dolutegravir Tablets**	**n**	**Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00**

			C_{max}	AUC	C_τ or C_{24}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0.94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79 to 1.15)	_
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily	50 mg once daily	24	0.88 (0.80, 0.98)	0.92 (0.85, 0.99)	NA
Metabolite (GS-331007)			1.01 (0.93, 1.10)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

[a] The number of subjects represents the maximum number of subjects that were evaluated.

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

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir Tablets	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz	50 mg	12	0.61	0.43	0.25

600 mg once daily	once daily		(0.51 to 0.73)	(0.35 to 0.54)	(0.18 to 0.34)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX®) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)

Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day®) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

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

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

[c] The number of subjects represents the maximum number of subjects that were evaluated.

12.4 Microbiology

Mechanism of Action: Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents: The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the NRTIs, abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Resistance: *Cell Culture:* 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. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Treatment-Naïve Subjects: No subject who received dolutegravir 50-mg once-daily in the treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per 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 per 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 the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), treatment-emergent integrase substitutions were observed in 6 of 28 (21%) subjects who had virologic failure and resistance data. In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M/I, Q95Q/L, V151V/I (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 subject isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E138A, G140S, and Q148H at baseline and had additional emergent INSTI-resistance substitutions T97A and E138A/T with a corresponding 148-fold reduction in dolutegravir susceptibility at failure. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140S/A, Y143R/C, Q148H/R, V151I, N155H, E157Q, and G163K/R) and raltegravir phenotypic resistance.

Cross-Resistance: *Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains:* The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). 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.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per 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 14 times higher than those in humans at the maximum recommended dose. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at the maximum recommended dose.

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

Impairment of Fertility: In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the maximum recommended dose.

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

The efficacy and safety of dolutegravir tablets or dolutegravir tablets for oral suspension were evaluated in the studies summarized in Table 10.

Table 10. Trials Conducted with Dolutegravir Tablets or Dolutegravir Tablets for Oral Suspension in HIV-1–Infected Subjects

Population	Trial	Trial Arms	Timepoint (Week)
Adults: Treatment-naïve	SPRING-2 (ING113086) (NCT01227824)	Dolutegravir Tablets + 2 NRTIs (n = 403) Raltegravir + 2 NRTIs (n = 405)	96
	SINGLE (ING114467) (NCT01263015)	Dolutegravir Tablets + Abacavir Sulfate and Lamivudine (n = 414) Efavirenz/Emtricitabine/Tenofovir (n = 419)	144
	FLAMINGO (ING114915) (NCT01449929)	Dolutegravir Tablets + NRTI BR (n = 243) Darunavir/ritonavir + NRTI BR (n = 242)	96

Treatment-experienced, INSTI-naïve	SAILING (ING111762) (NCT01231516)	Dolutegravir Tablets + BR (n = 354) Raltegravir + BR (n = 361)	48
Pediatrics: 4 weeks and older and weighing at least 3 kg without INSTI resistance	IMPAACT P1093 (NCT01302847)	Dolutegravir Tablets or Dolutegravir Tablets for Oral Suspension + BR (n = 75)	24

BR = Background regimen; CAR = Current antiretroviral regimen; OBT = Optimized background therapy.

14.2 Adult Subjects

Treatment-Naïve Subjects: In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir tablets 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual NRTI treatment (either abacavir sulfate and lamivudine or emtricitabine/tenofovir). There were 808 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 36 years, 13% female, 15% non-white, 11% had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA greater than 100,000 copies per mL, 48% had CD4+ cell count less than 350 cells per mm^3, and 39% received abacavir sulfate and lamivudine; these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir tablets 50 mg once daily with fixed-dose abacavir sulfate and lamivudine or fixed-dose efavirenz/emtricitabine/tenofovir. 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 greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) and SINGLE (Week 144 open-label phase analysis which followed the Week 96 double-blind phase) are provided in Table 11. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 11. Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96 and SINGLE at Week 144 (Snapshot Algorithm)

	SPRING-2 Week 96		**SINGLE Week 144**	
	Dolutegravir Tablets 50 mg Once Daily + 2	**Raltegravir 400 mg Twice Daily + 2 NRTIs**	**Dolutegravir Tablets 50 mg +**	**Efavirenz/ Emtricitabine/ Tenofovir Once Daily**

	NRTIs (n = 403)	(n = 405)	Abacavir Sulfate and Lamivudine Once Daily (n = 414)	(n = 419)
HIV-1 RNA < 50 copies/mL	82%	78%	71%	63%
Treatment difference[a]	4.9% (95% CI: -0.6%, 10.3%)[d]		8.3% (95% CI: 2.0%, 14.6%)[e]	
Virologic nonresponse	5%	10%	10%	7%
Data in window not < 50 copies/mL	1%	3%	4%	< 1%
Discontinued for lack of efficacy	2%	3%	3%	3%
Discontinued for other reasons while not suppressed	< 1%	3%	3%	4%
Change in ART regimen	< 1%	< 1%	0	0
No virologic data Reasons	12%	12%	18%	30%
Discontinued study/study drug due to adverse event or death[b]	2%	2%	4%	14%
Discontinued study/study drug for other reasons[c]	8%	9%	12%	13%
Missing data during window but on study	2%	< 1%	2%	3%
Proportion (%) of Subjects with HIV-1 RNA < 50 copies/mL by Baseline Category				
Plasma viral load (copies/mL)				
≤ 100,000	84%	83%	73%	64%
> 100,000	79%	63%	69%	61%
Gender				
Male	84%	79%	72%	66%
Female	70%	68%	69%	48%
Race				
White	83%	78%	72%	71%
African-American/ African Heritage/Other	77%	75%	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 86% in the raltegravir group, with a treatment difference of 2.6% and 95% CI of (-1.9%, 7.2%).

[e] 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 group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

SPRING-2: Virologic outcomes were also comparable across baseline characteristics including CD4+ cell count, age, and use of fixed-dose abacavir sulfate and lamivudine or emtricitabine/tenofovir as NRTI background regimen. The median change in CD4+ cell counts from baseline was 276 cells per mm^3 in the group receiving dolutegravir and 264 cells per mm^3 for the raltegravir group at 96 weeks.

There was no treatment-emergent resistance to dolutegravir or to the NRTI background.

SINGLE: 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 + fixed-dose abacavir sulfate and lamivudine and 332 cells per mm^3 for the efavirenz/emtricitabine/tenofovir 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).

There was no treatment-emergent resistance to dolutegravir, abacavir, or lamivudine.

FLAMINGO: In FLAMINGO, 485 subjects were randomized and received at least 1 dose of either dolutegravir tablets 50 mg once daily (n = 243) or darunavir + ritonavir 800 mg/100 mg once daily (n = 242), both in combination with investigator-selected NRTI background regimen (either fixed-dose abacavir and lamivudine or fixed-dose emtricitabine/tenofovir disoproxil fumarate). There were 484 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 34 years, 15% female, 28% non-white, 10% had hepatitis B and/or C virus co-infection, 3% were CDC Class C (AIDS), 25% had HIV-1 RNA greater than 100,000 copies per mL, and 35% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups. Overall response rates by Snapshot algorithm through Week 96 were 80% for dolutegravir and 68% for darunavir/ritonavir. The proportion of subjects who were non-responders (HIV-1 RNA greater than or equal to 50 copies per mL) at Week 96 was 8% and 12% in the arms receiving dolutegravir and darunavir + ritonavir, respectively; no virologic data were available for 12% and 21% for subjects treated with dolutegravir and darunavir + ritonavir, respectively. The adjusted overall response rate difference in proportion and 95% CI was 12.4% (4.7%, 20.2%). No treatment-emergent primary resistance substitutions were observed in either treatment group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In the international, multicenter, double-blind trial (SAILING), 719 HIV-1–infected, antiretroviral treatment-experienced adults were randomized and received either dolutegravir tablets 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least 1 fully active agent. There were 715 subjects

included in the efficacy and safety analyses. At baseline, the median age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C virus co-infection, 46% were CDC Class C (AIDS), 20% had HIV-1 RNA greater than 100,000 copies per mL, and 72% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups. All subjects had at least 2-class antiretroviral treatment resistance, and 49% of subjects had at least 3-class antiretroviral treatment resistance at baseline. Week 48 outcomes for SAILING are shown in Table 12.

Table 12. Virologic Outcomes of Randomized Treatment in SAILING at 48 Weeks (Snapshot Algorithm)

	Dolutegravir Tablets 50 mg Once Daily + BR[a] (n = 354)	**Raltegravir 400 mg Twice Daily + BR[a] (n = 361)**
HIV-1 RNA < 50 copies/mL	71%	64%
Adjusted[b] treatment difference	7.4% (95% CI: 0.7%, 14.2%)	
Virologic nonresponse	20%	28%
No virologic data Reasons	9%	9%
Discontinued study/study drug due to adverse event or death	3%	4%
Discontinued study/study drug for other reasons[c]	5%	4%
Missing data during window but on study	2%	1%
Proportion (%) with HIV-1 RNA < 50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤ 50,000 copies/mL	75%	71%
> 50,000 copies/mL	62%	47%
Background regimen		
No darunavir use	67%	60%
Darunavir use with primary PI substitutions	85%	67%
Darunavir use without primary PI substitutions	69%	70%
Gender		
Male	70%	66%
Female	74%	60%
Race		
White	75%	71%
African-American/African Heritage/Other	67%	57%

[a] BR = Background regimen. Background regimen was restricted to less than or equal to 2 antiretroviral treatments with at least 1 fully active agent.

[b] Adjusted for pre-specified stratification factors.

[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Treatment differences were maintained across the baseline characteristics including CD4+ cell count and age.

The mean changes in CD4+ cell counts from baseline were 162 cells per mm^3 in the group receiving dolutegravir and 153 cells per mm^3 in the raltegravir group.

14.3 Pediatric Subjects

IMPAACT P1093 is an ongoing Phase 1/2, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of dolutegravir tablets or dolutegravir tablets for oral suspension in combination treatment regimens in HIV-1–infected infants, children, and adolescents aged at least 4 weeks to 18 years. Subjects were stratified by 5 age cohorts: Cohort 1, aged 12 to less than 18 years; Cohort 2A, aged 6 to less than 12 years; Cohort 3, aged 2 to less than 6 years; Cohort 4, aged 6 months to less than 2 years; and Cohort 5, aged 4 weeks to less than 6 months. Seventy-five subjects received the recommended dose (determined by weight and age) of dolutegravir tablets or dolutegravir tablets for oral suspension *[see Dosage and Administration (2.2, 2.3)]*.

These 75 subjects had a median age of 27 months (range: 1 to 214), were 59% female, and 68% were black or African American. At baseline, mean plasma HIV-1 RNA was 4.4 $\log_{10}$ copies per mL, median CD4+ cell count was 1,225 cells per mm^3 (range: 1 to 8,255), and median CD4+% was 23% (range: 0.3% to 49%). Overall, 33% had baseline plasma HIV-1 RNA greater than 50,000 copies per mL and 12% had a CDC HIV clinical classification of category C. The majority (80%) of subjects were treatment-experienced, but all were INSTI-naïve. Most subjects had previously used at least 1 NNRTI (44%) or 1 PI (76%).

Virologic outcomes from IMPAACT P1093 include subjects who received either dolutegravir tablets or dolutegravir tablets for oral suspension as per the dosing recommendations for their weight band and who had reached Week 24 (n = 58) or Week 48 (n = 42). At Week 24, 62% of subjects achieved HIV-1 RNA less than 50 copies per mL and 86% achieved HIV-1 RNA less than 400 copies per mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 24 was 105 cells per mm^3 (5%). At Week 48, 69% of subjects achieved HIV-1 RNA less than 50 copies per mL and 79% achieved HIV-1 RNA less than 400 copies per mL (Snapshot algorithm). The median CD4 count (percent) increase from baseline to Week 48 was 141 cells per mm^3 (7%).

16 HOW SUPPLIED/STORAGE AND HANDLING

Dolutegravir Tablets for Oral Suspension, 10 mg, are pink, film-coated, strawberry cream flavored, oval, functionally scored tablets debossed with **D** to the left of the breakline and **T** to the right of the breakline on one side of the tablet and **M** to the left of the breakline on the other side of the tablet. They are available as follows:

NDC 65015-353-14
bottles of 30 tablets with desiccant and non-child-resistant caps.

NDC 65015-353-17

bottles of 60 tablets with desiccant and non-child-resistant caps.

NDC 65015-353-18
bottles of 90 tablets with desiccant and non-child-resistant caps.

Store dolutegravir tablets for oral suspension below 30°C (86°F).

Store and dispense the 10 mg tablets for oral suspension in the original bottle, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant. Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions: Dolutegravir tablets for oral suspension may interact with other drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Drug Interactions (7)]*.

Hypersensitivity Reactions: Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking dolutegravir tablets for oral suspension and other suspect agents, and seek medical attention if they develop a rash associated with any of the following symptoms, as it may be a sign of a more serious reaction such as severe hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters or peeling of the skin; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue, or mouth; breathing difficulty; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes, dark or tea-colored urine, pale-colored stools or bowel movements, nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on the right side below the ribs) *[see Warnings and Precautions (5.1)]*.

Hepatotoxicity: Inform patients that hepatotoxicity has been reported with dolutegravir *[see Warnings and Precautions (5.2)]*. Advise patients that laboratory monitoring for hepatoxicity during therapy with dolutegravir tablets for oral suspension is recommended, especially for patients with liver disease, such as hepatitis B or C.

Embryo-Fetal Toxicity: Advise individuals of childbearing potential to consider an alternative treatment to dolutegravir at the time of conception through the first trimester of pregnancy. Advise individuals of childbearing potential to contact their healthcare provider if they plan to become pregnant, become pregnant, or if pregnancy is suspected during treatment with dolutegravir *[see Warnings and Precaution (5.3), Use in Specific Populations (8.1, 8.3)]*.

Counsel individuals of childbearing potential taking dolutegravir to consistently use effective contraception *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

Immune Reconstitution Syndrome: Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection as inflammation from previous infection may

occur soon after combination antiretroviral therapy, including when dolutegravir tablets for oral suspension are started *[see Warnings and Precautions (5.5)]*.

Different Formulations Are Not Bioequivalent: Advise patients that dolutegravir tablets and dolutegravir tablets for oral suspension are not bioequivalent and are not interchangeable on a milligram-per-milligram basis. Advise patients or their care provider that patients switching from one formulation to the other must adjust the dose for the new dosage formulation *[see Dosage and Administration (2.2) and Warnings and Precautions (5.6)]*.

Lactation: Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Administration Instructions: To avoid a dosing error from using the wrong formulation of dolutegravir, strongly advise patients and caregivers to visually inspect the tablets to verify the correct formulation each time the prescription is filled *[see Dosage and Administration (2), Warnings and Precautions (5.6), How Supplied/Storage and Handling (16)]*.

Inform patients and caregivers that dolutegravir tablets for oral suspension may be swallowed whole or dispersed in drinking water and should not be chewed or crushed. The amount of water needed to disperse the tablet will depend on the dose (number of tablets prescribed) *[see Dosage and Administration (2.4)]*.

Instruct patients and caregivers that if a dose of dolutegravir tablets for oral suspension is missed, to take it as soon as they remember. Advise patients and caregivers not to double the next dose or take more than the prescribed dose *[see Dosage and Administration (2)]*.

Storage: Instruct patients and caregivers to store the dolutegravir 10-mg tablets for oral suspension in the original package, keep the bottle tightly closed, and protect from moisture. Do not remove desiccant *[see How Supplied/Storage and Handling (16)]*.

Patient Information

Dolutegravir Tablets for Oral Suspension

(doe″ loo teg′ ra vir)

What are dolutegravir tablets for oral suspension?

Dolutegravir tablets for oral suspension are a prescription medicine that is used to treat Human Immunodeficiency Virus-1 (HIV-1) infection together with other HIV-1 medicines in children, aged at least 4 weeks and weighing at least 6.6 pounds (3 kg), who have not received HIV-1 medicines in the past or to replace their current HIV-1 medicines when their healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

It is not known if dolutegravir tablets for oral suspension are safe and effective in children who are less than 4 weeks of age and weigh less than 6.6 pounds (3 kg) or in children who have received certain types of medicine for HIV-1 infection.

Do not take dolutegravir tablets for oral suspension if you:

- have ever had an allergic reaction to a medicine that contains dolutegravir.
- take dofetilide.

Before you take dolutegravir tablets for oral suspension, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had liver problems, including hepatitis B or C infection.
- are pregnant or plan to become pregnant. Dolutegravir tablets for oral suspension may harm your unborn baby.
  - Your healthcare provider may prescribe a different medicine than dolutegravir tablets for oral suspension if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy.
  - If you can become pregnant, your healthcare provider will perform a pregnancy test before you start treatment with dolutegravir tablets for oral suspension.
  - If you can become pregnant, you should consistently use effective birth control (contraception) during treatment with dolutegravir tablets for oral suspension.
  - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with dolutegravir tablets for oral suspension.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take dolutegravir tablets for oral suspension.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - It is not known if dolutegravir can pass to your baby in your breast milk.

  Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with dolutegravir tablets for oral suspension. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with dolutegravir tablets for oral suspension.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take dolutegravir tablets for oral suspension with other medicines.

How should I take dolutegravir tablets for oral suspension?

- **Take dolutegravir tablets for oral suspension exactly as your healthcare provider tells you to take them.**
- Take dolutegravir tablets for oral suspension with or without food.
- Dolutegravir tablets for oral suspension may be swallowed whole or dispersed in drinking water and should not be chewed or crushed. Tablets can be split for doses of ½, 1½, or 2½ tablets.
- Swallow the tablets for oral suspension whole (if more than one tablet is required, swallow one tablet at a time to reduce the risk of choking), or
- For children who cannot swallow tablets:
  - Mix the dolutegravir tablets for oral suspension in 5 mL (one teaspoonful) of drinking water (if using ½ or 1½ tablets for oral suspension) or 10 mL (two teaspoonfuls) of drinking water (if using 2, 2½, or 3 tablets for oral suspension).
  - Swirl the suspension so that no lumps remain.
  - After completely mixed give all the prepared medicine to the child.
  - Add another 5 mL (one teaspoonful) of drinking water to the cup, swirl, and give it all to the child. Repeat if any medicine remains in the cup to make sure the child gets the full dose.
  - Do not use any other drink or food to prepare the dose.
  - Give the oral suspension to the child within 30 minutes of mixing.
- **Dolutegravir tablets are not the same as dolutegravir tablets for oral suspension and cannot be substituted for each other. Check to make sure you receive the correct form of dolutegravir each time you or your child's prescription is filled to avoid using the wrong medicine.**
- Do not change your dose, switch medicines or stop taking dolutegravir tablets for oral suspension without talking with your healthcare provider.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, dolutegravir tablets for oral suspension should be taken at least 2 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with dolutegravir tablets for oral suspension:
  - If you take dolutegravir tablets for oral suspension with food, you may take these supplements at the same time that you take dolutegravir tablets for oral suspension.

- If you do not take dolutegravir tablets for oral suspension with food, take dolutegravir tablets for oral suspension at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of dolutegravir tablets for oral suspension.
- If you miss a dose of dolutegravir tablets for oral suspension, take it as soon as you remember. Do not take 2 doses at the same time or take more than your prescribed dose.
- Stay under the care of a healthcare provider during treatment with dolutegravir tablets for oral suspension.
- Do not run out of dolutegravir tablets for oral suspension. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too many dolutegravir tablets for oral suspension, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of dolutegravir tablets for oral suspension?

- **Dolutegravir tablets for oral suspension can cause serious side effects, including**:
- **Allergic reactions**. Call your healthcare provider right away if you develop a rash with dolutegravir tablets for oral suspension. **Stop taking dolutegravir tablets for oral suspension and get medical help right away if you develop a rash with any of the following signs or symptoms:**
  - fever
  - generally ill feeling
  - tiredness
  - muscle or joint aches
  - blisters or sores in mouth
  - blisters or peeling of the skin
  - redness or swelling of the eyes
  - swelling of the mouth, face, lips, or tongue
  - problems breathing

- **Liver problems.** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with dolutegravir tablets for oral suspension. Liver problems, including liver failure, have also happened in people without a history of liver disease or other risk factors. Your healthcare provider may do blood tests to check your liver. **Call your healthcare provider right away if you develop any of the following signs or symptoms of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - nausea or vomiting
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking dolutegravir tablets for oral suspension.
- **The most common side effects of dolutegravir tablets for oral suspension include:**
  - trouble sleeping
  - tiredness
  - headache

These are not all the possible side effects of dolutegravir tablets for oral suspension. **Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

How should I store dolutegravir tablets for oral suspension?

- Store dolutegravir tablets for oral suspension below 30°C (86°F) in the original bottle. Keep the bottle tightly closed and protected from moisture. The bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

Keep dolutegravir tablets for oral suspension and all medicines out of the reach of children.

General information about the safe and effective use of dolutegravir tablets for oral suspension.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use dolutegravir tablets for oral suspension for a condition for which they were not prescribed. Do not give dolutegravir tablets for oral suspension to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about dolutegravir tablets for oral suspension that is written for health professionals. For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in dolutegravir tablets for oral suspension?

Active ingredient: dolutegravir.
Inactive ingredients: calcium sulfate dihydrate, crospovidone (Type B), mannitol, microcrystalline cellulose, povidone K29/32, silicified microcrystalline cellulose, sodium starch glycolate (Type A), sodium stearyl fumarate, strawberry cream flavor and sucralose. The tablet film-coating contains black iron oxide, hypromellose, polyethylene glycol 400, red iron oxide, titanium dioxide and yellow iron oxide.

Manufactured by: Mylan Laboratories Limited, Hyderabad – 500 096, India

This Patient Information has been approved by the U.S. Food and Drug Administration.

Mylan®

Manufactured by:
Mylan Laboratories Limited
Hyderabad — 500 096, India

Revised: 10/2020

750XXXXX MXI:DOLUOS:RX3

Mylan®

1.14.1.1 DRAFT CARTON AND/OR CONTAINER LABELS

10 MG – BOTTLES OF 30 TABLETS

Each film-coated tablet contains dolutegravir 10 mg, equivalent to 10.52 mg of dolutegravir sodium.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store below 30°C (86°F).

Manufactured by:
Mylan Laboratories Limited
Hyderabad – 500 096, India

NDC 65015-353-14

Dolutegravir

Tablets for Oral Suspension

10 mg

Dolutegravir Tablets for Oral Suspension and Dolutegravir Tablets are not interchangeable.

Do not chew or crush tablet for oral suspension, but can be split on the breakline.

30 Tablets **Rx only**

Mylan.com

Mylan

UPC Version A Barcode Here.
(N3) 65015-353-14 (6)

Store and dispense in the original bottle, protect from moisture and keep the bottle tightly closed. Do not remove desiccant.

Code No.: MP/DRUGS/25/1/2014

Mylan Laboratories Limited
ITF Barcode Label Code
750XXXXX

[Varnish free area for Variable Data Coding (i.e., Lot and Exp.)]

Mylan®

1.14.1.1 DRAFT CARTON AND/OR CONTAINER LABELS

10 MG – BOTTLES OF 60 TABLETS

Each film-coated tablet contains dolutegravir 10 mg, equivalent to 10.52 mg of dolutegravir sodium.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store below 30°C (86°F).

Manufactured by:
Mylan Laboratories Limited
Hyderabad – 500 096, India

NDC 65015-353-17

Dolutegravir

Tablets for Oral Suspension

10 mg

Dolutegravir Tablets for Oral Suspension and Dolutegravir Tablets are not interchangeable.

Do not chew or crush tablet for oral suspension, but can be split on the breakline.

60 Tablets **Rx only**

Mylan.com

Mylan

UPC Version A Barcode Here.
(N3) 65015-353-17 (7)

Store and dispense in the original bottle, protect from moisture and keep the bottle tightly closed. Do not remove desiccant.

Code No.: MP/DRUGS/25/1/2014

Mylan Laboratories Limited
ITF Barcode Label Code
750XXXXX

[Varnish free area for Variable Data Coding (i.e., Lot and Exp.)]

Mylan®

1.14.1.1 DRAFT CARTON AND/OR CONTAINER LABELS

10 MG – BOTTLES OF 90 TABLETS

Each film-coated tablet contains dolutegravir 10 mg, equivalent to 10.52 mg of dolutegravir sodium.

Usual Dosage: See accompanying prescribing information.

Keep this and all medication out of the reach of children.

Store below 30°C (86°F).

Manufactured by:
Mylan Laboratories Limited
Hyderabad – 500 096, India

NDC 65015-353-18

Dolutegravir

Tablets for Oral Suspension

10 mg

Dolutegravir Tablets for Oral Suspension and Dolutegravir Tablets are not interchangeable.

Do not chew or crush tablet for oral suspension, but can be split on the breakline.

90 Tablets **Rx only**

Mylan.com

Mylan

UPC Version A Barcode Here.
(N3) 65015-353-18 (4)

Store and dispense in the original bottle, protect from moisture and keep the bottle tightly closed. Do not remove desiccant.

Code No.: MP/DRUGS/25/1/2014

Mylan Laboratories Limited
ITF Barcode Label Code
750XXXXX

[Varnish free area for Variable Data Coding (i.e., Lot and Exp.)]