

Brand Name: Tivicay

Generic Name: dolutegravir

Manufacturer¹: ViiV Healthcare

Drug Class^{1,4}: Antiretroviral Agent, Integrase Inhibitor

Labeled Uses^{4,5}:

Labeled^{1,4}: In combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children aged 12 years and older and weighing at least 40 kg.

Mechanism of Action^{1,2}: Dolutegravir inhibits the catalytic activity of HIV integrase, which is an HIV encoded enzyme required for viral replication. Integrase is one of the three HIV-1 enzymes required for viral replication. Integration of HIV into cellular DNA is a multi-step process. First, the assembly of integrase in a stable complex with the viral DNA occurs. Second, the terminal dinucleotides from each end of the viral DNA are removed by endonucleolytic processing. Lastly, the viral DNA 3' ends are covalently linked to the cellular (target) DNA by strand transfer. The last two processes, which are catalytic, require integrase to be appropriately assembled on a specific viral DNA substrate. Inhibition of integrase by dolutegravir prevents the covalent insertion, or integration, of unintegrated linear HIV DNA into the host cell genome preventing the formation of the HIV provirus. The provirus is required to direct the production of progeny virus, so inhibiting integration prevents propagation of the viral infection.

Pharmacokinetics¹:

Absorption:

T _{max}	2-3 hours
V _d	17.4L
T _{1/2}	14 hours
Clearance	1.0 L/h
Protein Binding	≥98.9%
Bioavailability	Not established

Metabolism^{1,2}: Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. Metabolism occurs via UDP-glucuronosyltransferase (UGT)1A1 (major) and by the hepatic isoenzyme CYP3A (minor).

Elimination: After a single oral dose of [14C] 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 at less than one percent of the dose.

Efficacy:

Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva JF, et al.; on behalf of the extended SAILING Study Team. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naïve adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet*. 2013;382:700-708.

Study Design: Phase 3, randomized, multicenter, double-blind, active-controlled, non-inferiority design study

Description of Study: This study evaluated the safety, efficacy, and emergent resistance in antiretroviral-experienced, integrase-inhibitor-naïve adults with HIV-1 with at least two-class drug resistance. *Methods:* 719 HIV-1- infected, antiretroviral treatment-experienced adults were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator selected background regimen consisting of up to 2 agents, including at least 1 fully active agent. There were 715 subjects included in the efficacy and safety analyses (354 patients in the dolutegravir group and 361 patients in the raltegravir group). At week 48, 251 (71%) patients on dolutegravir had HIV-1 RNA less than 50 copies per mL versus 230 (64%) patients on raltegravir (adjusted difference 7.4%, 95% CI 0.7 to 14.2); superiority of dolutegravir versus raltegravir was then concluded ($p=0.03$). Significantly fewer patients had virological failure with treatment-emergent integrase-inhibitor resistance on dolutegravir (4 versus 17 patients; adjusted difference -3.7% , 95% CI -6.1 to -1.2 ; $p=0.003$). Adverse event frequencies were similar across groups; the most commonly reported events for dolutegravir versus raltegravir were diarrhea (71 [20%] versus 64 [18%] patients), upper respiratory tract infection (38 [11%] versus 29 [8%]), and headache (33 [9%] vs 31 [9%]). Safety events leading to discontinuation were infrequent in both groups (9 [3%] dolutegravir, 14 [4%] raltegravir).

Limitations: This study was funded by ViiV Healthcare, the manufacturer of dolutegravir. All operation aspects of the study, including monitoring, data collection, and statistical analysis, were managed by GlaxoSmithKline. Investigators were able to select the background therapy for both medications; this consisted of at least one fully active agent with or without a second agent, with or without full activity. Additionally, being as SAILING was designed as a double-blind, double-dummy trial another limitation is that the investigators could not assess the possible advantage of dolutegravir as a once-daily drug in this study.

Conclusions: Data from SAILING show that once-daily dolutegravir 50mg, in combination with up to two other antiretroviral drugs, is well tolerated, has higher virological efficacy, and has a higher barrier to resistance compared with twice-daily raltegravir 400mg in this treatment-experienced patient group. This is the first study to show superior virological efficacy of any retroviral drug over raltegravir. This difference was driven by fewer virological non-responders in the dolutegravir group compared with raltegravir group.

Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, et al.; SPRING-2 Study Group Once-daily dolutegravir versus raltegravir in antiretroviral-naïve adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet*. 2013;381:735-43.

Study Design: Phase 3, randomized, double-blind, active-controlled, non-inferiority design study

Description of Study: In this study, dolutegravir was compared with HIV integrase inhibitor raltegravir, as initial treatment for adults with HIV-1. *Methods:* In SPRING-2, 822 subjects (treatment-naïve adults (aged ≥ 18 years) with HIV-1 infection and HIV-1 RNA concentration of 1,000 copies per mL or greater) were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor treatment (either abacavir sulfate and lamivudine [Epzicom] or emtricitabine/tenofovir [Truvada]). The primary efficacy endpoint was the proportion of participants with HIV-1 RNA less than 50 copies per mL at 48 weeks, with a 10% non-inferiority margin. 411 patients were randomly allocated to receive dolutegravir and 411 to receive raltegravir and received at least one dose of study drug. At 48 weeks, 361 (88%) in the dolutegravir achieved an HIV-1 RNA value of less than 50 copies per mL compared with 351 (85%) in the raltegravir group. Thus, the investigators determined that dolutegravir was at least non-inferior to raltegravir. Adverse events were similar between treatment groups. The most common adverse events were nausea (59 (14%) patients in the dolutegravir group versus 53 (13%) in the raltegravir group), headache (51 (12%) versus 48 (12%)), nasopharyngitis (46 (11%) versus 48 (12%)), and diarrhea (47(11%) in each group). Few patients had drug-related serious adverse events (3 (<1%) versus 5 (1%)) and few had adverse events leading to discontinuation (10 (2%) versus 7 (2%)) in each group.

Limitations: This study was funded by ViiV Healthcare, the manufacturer of dolutegravir. According to the investigators, other limitations include the low number of nonwhite and female patients enrolled, which is not fully representative of the HIV global epidemic. Another limitation was that the investigators could not assess the possible advantage of dolutegravir as a once-daily drug because of the double-blind, double-dummy design of the trial.

Conclusions: SPRING-2 is the first head-to-head, double blind comparison of efficacy and safety of two integrase inhibitor-based regimens for first-line antiretroviral therapy. At 48 weeks, once-daily dolutegravir 50mg was non-inferior to twice-daily raltegravir 400mg, both in combination with tenofovir/emtricitabine or abacavir/lamivudine, with 88% of patients in the dolutegravir group and 85% of those in the raltegravir group achieving plasma HIV-1 RNA concentrations of less than 50 copies per mL. The non-inferior efficacy and similar safety profile of dolutegravir compared with raltegravir means that combination treatment with once-daily dolutegravir and fixed-dose nucleoside reverse transcriptase inhibitors is an effective new option for treatment of HIV-1 in treatment naïve patients.

Eron JJ, Clotet B, Durant J, Katlama C, Kumar P, Lazzarin A, et al.; VIKING Study Group Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. *The Journal of Infectious Diseases* 2013 Mar 1;207(5):740-8

Study Design: Phase IIb, multicenter, open-label, single-arm, pilot study with 2 sequential cohorts

Description of Study: This phase IIb study assessed the activity of dolutegravir in HIV-1 infected subjects with genotypic evidence of raltegravir resistance. *Methods:* In VIKING, 2 sequential cohorts of HIV-1 infected individuals with current or historic raltegravir treatment failure and evidence of raltegravir resistance at screening were studied. The 50mg once daily dose of dolutegravir was initially selected for evaluation (cohort I); however, the viral load response of some subjects prompted protocol amendment and subsequent evaluation of dolutegravir 50mg as a twice daily regimen (cohort II). The study treatment phases for both cohorts consisted of an initial 10-day period, when dolutegravir was administered with a failing background regimen (raltegravir was discontinued prior to dolutegravir dosing), followed by a second phase (day 11 onward to 24-weeks), when dolutegravir therapy was maintained but the background therapy could be optimized according to genotypic and phenotypic tests. The primary efficacy end point was the proportion of subjects on day 11 with a plasma HIV-1 RNA load of <400 copies/mL or of >0.7 log₁₀ copies/mL below the baseline value. 27 and 24 subjects were enrolled to compose the intent-to-treat exposed populations for cohorts I and II, respectively. According to the results of this study a rapid antiviral response was observed; 96% of subjects (23 of 24) in cohort II and 78% of subjects (21 of 27) in cohort I achieved the primary efficacy end point. Thirteen subjects in cohort II and 11 subject in cohort I achieved an HIV-1 RNA level of <400 copies/mL on day 11. At week 24, 41% and 75% of subjects had an HIV-1 RNA load of <50 copies/mL in cohorts I and II, respectively. In a linear regression model accounting for differences in baseline factors and phenotypic susceptibility score of the continued failing regimen, the reduction in plasma HIV-1 RNA level at day 11 was shown to be statistically greater (P=0.017) in cohort II than in cohort I. Further integrase genotypic evolution was uncommon. Dolutegravir had a good, similar safety profile with each dosing regimen.

Limitations: Both cohorts were made up of a relatively small sample size; the sequential cohort design, with some differences in baseline characteristics between cohorts and the mandate of cohort II subjects to receive >1 fully active drug in the optimized background regimen for eligibility, may limit the interpretation of comparisons at 24 weeks. There was no comparison or control group used in this investigation. Additionally, this study was supported by and numerous authors reported potential conflicts of interest with ViiV Healthcare, the manufacturer of dolutegravir.

Conclusions: VIKING is the first study to explore dolutegravir treatment of HIV-1-infected subjects who had experienced virological failure during receipt of a raltegravir-containing regimen and had genotypic evidence of raltegravir resistance. Dolutegravir 50mg twice daily with an optimized background regimen provided greater and more durable benefit than the once-daily regimen. Thus, the aggregate clinical and resistance data support the choice of 50mg twice daily as the appropriate dolutegravir dose to be further evaluated in patients with integrase inhibitor-resistant virus.

Contraindications^{4,5}: Concurrent use of dolutegravir with dofetilide is contraindicated due to the potential for increased dofetilide plasma concentrations and the risk for serious and life-threatening adverse events, such as QT prolongation and torsade de pointes (TdP). Dolutegravir inhibits the renal organic cation transporter OCT2, dofetilide is eliminated via this transporter. If coadministered, the plasma concentration of dofetilide may increase.

Precautions^{1,3}:

Autoimmune disorders: Including Graves' disease, polymyositis, and Guillain-Barré syndrome, have been reported in the setting of immune reconstitution; disorders may occur many months after initiation of therapy.

Metabolic Inducers: Concomitant use with metabolic inducers (oxcarbazepine, phenytoin, phenobarbital, carbamazepine, St. John's wort) should be avoided.

Underlying Hepatitis B or C: Increased risk for new or worsening elevated transaminases (sometimes consistent with immune reconstitution syndrome or hepatitis B reactivation, particularly if anti-hepatitis therapy was withdrawn); monitoring is recommended.

Hypersensitivity Reactions: Characterized by rash, constitutional findings, and organ dysfunction, including liver injury, have been reported; discontinue use immediately if signs or symptoms develop.

Immune Reconstitution Syndrome: This has been reported in patients treated with combination antiretroviral therapy. An inflammatory response to opportunistic infections (eg, Mycobacterium avium, cytomegalovirus, Pneumocystis jiroveci pneumonia, TB) may occur during initial phase of combination antiretroviral therapy.

Severe Renal Impairment: Dolutegravir plasma concentrations are decreased in patients with severe renal impairment and caution is advised when administering the drug to integrase strand transfer inhibitor (INSTI)-experienced patients with renal failure. Use in this patient population may result in loss of therapeutic effect and development of resistance.

Geriatric Use: Caution is advised when administering the drug to geriatric patients, due to greater frequency of decreased renal, hepatic, or cardiac function and of concomitant disease or other drug therapy. Clinical studies of dolutegravir did not include sufficient numbers of patients aged 65 years or over to determine whether they respond differently from younger patients.

Adverse Effects^{1,2,3}:

Occurring in >10% of patients

Hepatic

ALT/SGPT levels raised, hepatitis B and/or C coinfection (8% to 16%)

Occurring in >1% to <10% of patients

Dermatologic

Pruritus (<2%)

Endocrine/Metabolic

Serum cholesterol raised (8%)

Hyperglycemia, grade 2 (126-250 mg/dL) (5-7%) to grade 4 (>251 mg/dL) (1%)

Gastrointestinal

Abdominal discomfort (<2%)

Abdominal pain (adults <2%)

Diarrhea, moderate to severe (1%)

Flatulence (<2%)

Nausea, moderate to severe (up to 1%)
Upper abdominal pain (<2%)
Vomiting (<2%)

Hematologic

Neutropenia, grade 2 (2% to 3%); grade 3 to 4 (1% to 2%)

Hepatic

ALT/SGPT levels raised, grade 2 to 4 (up to 8%)
AST/SGOT level raised, grade 2 to 4 (up to 6%)
Hepatitis (less than 2%)
Increased serum lipase level, grade 3 to 4 (1% to 8%)
Serum bilirubin raised, grade 2 (up to 2%); grade 3 (up to 1%)

Musculoskeletal

Myositis (<2%)

Neurologic

Headache (2%)
Insomnia, grade 1 (1% to 7%); grade 2 (1% to 3%)

Renal

Increased creatinine kinase levels, grade 2 (1% to 3%); grade 3 to 4 (3% to 4%)
Renal impairment (\leq 2%)

Other

Fatigue (\leq 2%)

Drug Interactions^{1,2,3}:

Co-administration with drugs that are eliminated by the organic cation transporter OCT2. Dolutegravir inhibits the renal OCT2 transporter, and the plasma concentration of drugs that are eliminated by this mechanism are enhanced

Dofetilide, metformin

Furthermore, concurrent use of dolutegravir with dofetilide is contraindicated due of the potential for serious and life-threatening adverse events, such as QT prolongation and torsade de pointes (TdP).

Co-administration with drugs that cause decreased dolutegravir plasma concentrations through induction of CYP3A

Vemurafenib, topiramate, quinine, primidone, pioglitazone, perampanel, griseofulvin, felbamate, enzalutamide, clobazam, bosentan, bexarotene, armodafinil, modafinil, aprepitant/fosprepitant, alcohol, St. John's Wort (*hypericum perforatum*), carbamazepine, phenobarbital, phenytoin, oxcarbazepine, nevirapine, ritonavir, rifampin, etravirine, efavirenz or efavirenz-containing products (e.g., efavirenz; emtricitabine; tenofovir)

Furthermore, coadministration of dolutegravir with etravirine should be avoided, unless also administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir. When administered with etravirine (a CYP3A4 inducer), the plasma concentration of dolutegravir (a

CYP3A4 substrate) is significantly reduced; however, this effect is diminished by the presence of one of the above mentioned protease inhibitors.

Administer dolutegravir 2 hours before or 6 hours after taking orally administered Iron or calcium salts, cation-containing laxatives or antacids, sucralafate, buffered medications (aspirin, aluminum hydroxide, calcium carbonate, magnesium hydroxide). The chemical structure of these medications contain polyvalent cations which can bind dolutegravir in the GI tract. Taking these drugs simultaneously may result in reduced bioavailability of dolutegravir.

Dosing/Administration^{1,2}:

Adults who are treatment-naïve or treatment-experienced but integrase strand transfer inhibitor (INSTI)-naïve:

50mg by mouth once daily

During coadministration with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin, the recommended dose is increased to 50mg by mouth twice daily.

Adults who are INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance:

50mg by mouth twice daily

Children (≥ 12 years and ≥ 40 kg) who are treatment-naïve or treatment-experienced but integrase strand transfer inhibitor (INSTI)-naïve:

50mg by mouth once daily

During coadministration with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin, the recommended dose is increased to 50mg by mouth twice daily.

Elderly:

The maximum recommended dose for use in the elderly population is 100mg/day PO.

Renal impairment

No dosage adjustment is necessary for patients with mild to moderate renal impairment. In patients with severe renal impairment, no dosage adjustment is necessary for those who are integrase strand transfer inhibitor (INSTI)-naïve, though caution is advised if administering to INSTI-experienced patients.

Hepatic impairment

No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh A or B). Use is not recommended in patients with severe hepatic impairment (Child-Pugh C), as studies have not been conducted in this population.

Use in Special Circumstances:

Overdosage¹: Limited experience with single higher doses (up to 250 mg in healthy subjects) revealed no specific symptoms or signs apart from those listed as adverse reactions. There is no known specific treatment for overdose with TIVICAY. 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.

Conclusion:

Dolutegravir is an effective once-daily HIV integrase inhibitor with potent antiviral activity and a favorable safety profile. It has limited cross-resistance to older generations of integrase inhibitors, raltegravir and elvitegravir in vitro, making it an increasingly viable treatment alternative in many individuals with raltegravir resistance at screening. However, due to the progressive nature of HIV, use of dolutegravir should cautiously be reserved, except when clinically mandated, as a secondary treatment option to raltegravir in order to preserve its lack of cross-resistance in the general patient population. Dolutegravir's most common side effects include insomnia and headache. Serious adverse effects include hypersensitivity reactions and abnormal liver function among those coinfecting with HIV and hepatitis B or C. With its tolerability, limited cross resistance with older generations of integrase inhibitors, and effectiveness in managing HIV-1, dolutegravir appears to be another clinically useful integrase inhibitor in the management of HIV-1. It is FDA approved for use in both treatment-naïve as well as treatment-experienced individuals with HIV, including those who have already taken raltegravir.

Recommended References:

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