

**Brand Name:** Edurant®

**Generic Name:** rilpivirine

**Manufacturer:** Janssen-Cilag for Tibotec Therapeutics, Division of Centocor Ortho Biotech Products<sup>(1)</sup>

**Drug Class:** Antiretroviral non-nucleoside reverse transcriptase inhibitor (NNRTI)<sup>(1,2,3,4)</sup>

**Uses:** Treatment of HIV-1 infections in combination with at least 2 other antiretroviral agents<sup>(1,2,3)</sup>

**Mechanism of Action:** Blocks HIV-1 replication by non-competitively binding to reverse transcriptase and blocking RNA-dependent and DNA-dependent DNA polymerase.<sup>(1,2,3,4)</sup>

**Pharmacokinetics:**

**Absorption:** administered orally with an unknown bioavailability. Peak concentrations reached in 4-5hrs. Absorption is highest when taken with meals.<sup>(1,2,3,4)</sup>

**Distribution:** 99.7% protein bound to primarily albumin.<sup>(1,2,3,4)</sup> Distribution into other compartments besides plasma has not been determined<sup>(1,2)</sup>

**Metabolism:** hepatic oxidation by CYP 3A4<sup>(1,2,3,4)</sup> Not an inducer or an inhibitor of CYP 450 isoenzymes<sup>(2)</sup>

**Elimination:** 85% excreted in feces (25% as unchanged drug), 6% excreted in the urine (< 1% as unchanged drug). Half-life of 50hrs.<sup>(1,2,3,4)</sup>

**Efficacy:**

**Pozniak AL, Morales-Ramirez J, Katabira E, Steyn D, Lupo SH, Santoscoy M, et al. Efficacy and safety of TMC278 in antiretroviral-naïve HIV-1 patients: week 96 results of a phase IIb randomized trial. AIDS 2010; 24: 55-65.<sup>(5)</sup>**

**Design:** Multicenter, open-label, active control, randomized trial

**Description: Methods:** The trial was designed to evaluate the dose-response relationship for efficacy, tolerability and safety of three daily TMC278 doses over 96 weeks. The study was conducted in 54 centers in 14 countries. HIV-1 infected patients  $\geq$  18 years old who had never been treated with ARV drugs or therapeutic HIV-1 vaccines with genotypic sensitivity to the selected NRTIs and a plasma viral load of more than 5000 copies/mL were included. Exclusion criteria were currently active AIDS-defining illness, prior use of NNRTIs or documented genotypic evidence of NNRTI resistance. Patients were randomized to TMC278 25, 75, or 150mg daily; or an open-label control efavirenz 600mg daily. Investigators chose an NRTI backbone regimen of either zidovudine/lamivudine or tenofovir disoproxil fumarate/emtricitabine. 368 patients were treated and included in the 96 week analysis. The primary objective was to evaluate the TMC278 dose-efficacy relationship at week 48. Secondary objectives included evaluation of ARV activity over 96 weeks; safety and tolerability of TMC278; and resistance analysis of isolates from patients failing virologically. **Results:** After 48 weeks 78.9% of patients in the TMC278 group had a virologic response compared to 80.9% of patients in the efavirenz group. At week 96 73.1% of patients in the TMC278 group had a virologic response compared to 70.8% in the efavirenz group. All doses showed similar efficacy and no clear TMC278 dose-response relationships were observed. There was no statistically significant difference in the

log<sub>10</sub> reduction in viral load, or change in CD4 counts at weeks 48 and 96 between groups. In general, all TMC 278 doses were safe and well tolerated, and there was no consistent association between safety assessments and TMC278 doses. There was a lower incidence of adverse events in the TMC278 groups compared to the efavirenz group. Adverse events leading to discontinuation was lower in the TMC278 groups compared to the efavirenz group.

**Limitations:** There were several potential conflicts of interest among the authors. Several authors were employed by Tibotec, had received honoraria from Tibotec, had received grants from Tibotec, and were members of Tibotec Global Access Program Advisory Board. This was a small study that was open-label; additionally, compliance was not addressed. Because the background regimens used were a reflection of the availability in each region and the local standard of care, they were not equally used. This may have affected the study results.

**Conclusion:** The results of the study show doses of TMC278 as low as 25mg are effective in treating HIV-1 infections in treatment naïve patients when used in combination with a background regimen. This study can be used to support the use of TMC278 as an alternative option to efavirenz in treatment naïve patients with HIV-1 infections.

**Cohen CJ, Andrade-Villanueva J, Clotet B, Fourie J, Johnson MA, Ruxrungtham K, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naïve adults infected with HIV-1 (THRIVE): a phase 3, randomized, non-inferiority trial. Lancet 2001; 378(9787):229-37.<sup>(6)</sup>**

**Study Design:** randomized, double-blind, double-dummy, active-controlled, multicenter trial

**Description:Methods:** This was a 48 week, in 98 centers in 21 countries. Patients  $\geq 18$  years who were naïve to antiretroviral therapy, had a plasma viral load of 5000 copies/mL or more, and had viral sensitivity to the background N(t)RTIs were included in the study. Patients with HIV-2 infections, documented presence of at least one of 39 NNRTI resistance-associated mutations, active clinically significant disease, renal impairment and pregnancy/breastfeeding were excluded. Patients were randomly assigned to receive 25mg rilpivirine once daily or efavirenz 600mg once daily in addition to an investigator selected background N(t)RTI regimen, which included tenofovir-disoproxil-fumarate plus emtricitabine, zidovudine plus lamivudine, or abacavir plus lamivudine. The primary outcome was non-inferiority with a 12% margin of rilpivirine to efavirenz in terms of percentage of all patients who had a confirmed virological response at 48 weeks. Secondary outcomes included non-inferiority with a 10% margin and superiority, antiviral activity in time, changes in CD4 cell count, safety, HIV genotypic and phenotypic characteristics (in virological failures), and adherence. **Results:** Rilpivirine was found to be non-inferior to efavirenz at the 12% and the 10% margin. Viral load  $< 50$  copies/mL in the rilpivirine group and the efavirenz group was 291/340 (86%) and 276/338 (82%) respectively [95% CI 3.9% -1.6 to 9.5]. There was no significant difference in virological failure or changes in CD4 counts between groups. Adherence was self-reported by patients, and was found to be similar between treatment groups. The safety analysis showed adverse events to be generally mild to moderate (grade 1 or 2). The adverse events were found to be statistically less common in the rilpivirine group than the efavirenz group. The mean change in fasting lipid panels was found to be significantly lower in the rilpivirine group.

**Limitations:** The study had several potentials of bias due to affiliations of the authors, funding by Tibotec which is the manufacturer of rilpivirine, and extensive involvement of the study sponsor with the design, conduct, and analysis of the trial and the study results. Unblinding was not assessed in the trial, and was likely due to the known and unique side-effect profile of efavirenz. Adherence was self-monitored, and data was not available for all patients. The trial is also limited because it was not powered to assess efficacy in various subsets of patients.

**Conclusion:** The results of this study show rilpivirine to be non-inferior to efavirenz in the treatment of HIV-1 infections in treatment naïve patients, and to have a statistically less side effects. The results give strong support of the use of rilpivirine as a treatment option in treatment naïve patients with HIV-1 infections in combination with a background regimen.

**Molina JM, Cahn P, Grinsztejn B, Lazzarin A, Mills A, Saag M, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment –naïve adults infected with HIV-1 (ECHO): a phase 3 randomized double-blind active-controlled trial. Lancet. 2011; 378(9787): 238-46<sup>(7)</sup>**

**Design:** This was a randomized, double-blind, double-dummy, active-controlled trial.

**Description: Methods:** This trial was conducted at 112 sites in 21 countries. Main inclusion criteria were HIV-1 infected patients  $\geq 18$  years who were antiretroviral treatment naïve, had a plasma viral load of  $\geq 5000$  copies per mL, and viral sensitivity to tenofovir-disoproxil-fumarate and emtricitabine. Exclusion criteria were HIV-2 infection, documented evidence of at least one NNRTI resistance-associated mutation, any active clinically significant disease, renal impairment, and pregnancy/breastfeeding. Patients were randomly assigned to receive either daily 25mg rilpivirine or daily 600mg efavirenz, both given in combination with a fixed dose background regimen of 300mg tenofovir-disoproxil-fumarate and 20mg emtricitabine. The primary objective was to show non-inferiority of rilpivirine to efavirenz in terms of the percentage of patients with confirmed response at week 48, with a non-inferiority margin of 12%. The secondary endpoints included non-inferiority at 10% margin, superiority, durability of antiviral activity, changes in CD4 cell count, safety, HIV genotypic and phenotypic characteristics, and adherence. At week 48, 83% of patients from both groups had confirmed response with a percent difference of 0.1 (95% -5.5 to 5.7). Rilpivirine was non-inferior to efavirenz at the 12% and 10% margin. CD4 cell counts were similar in both treatment groups. Superiority was not established in this study. Rilpivirine had a lower dropout rate due to adverse events compared to efavirenz; however, it had a higher number of dropouts due to virological failure. Rilpivirine was associated with smaller increases in lipids compared to efavirenz.

**Limitations:** The study had potentials of bias due to affiliations of the authors, funding by Tibotec which is the manufacturer of rilpivirine, and extensive involvement of the study sponsor with the design, conduct, and analysis of the trial and the study results. Unblinding was not assessed in the trial, and was likely due to the known and unique side-effect profile of efavirenz. Adherence was self-monitored, and data was not available for all patients. The trial is also limited because it was not powered to assess efficacy in various subsets of patients.

**Conclusion:** This study showed rilpivirine to be non-inferior to efavirenz in the treatment of HIV-1 infected adults who are treatment naïve. Although rilpivirine was associated with a higher virological failure rate compared to efavirenz, it was shown to have a better safety and tolerability profile. Over all, this study can be used to support the use of rilpivirine as a

treatment option in treatment naïve patients with HIV-1 infections in combination with a background regimen.

**Contraindications:** Concomitant use with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, dexamethasone (more than one dose) and St. John's wort.<sup>(1,3,4)</sup>

**Precautions:**<sup>(1,3,4)</sup>

- May cause depressive disorders such as depression, depressed mood, dysphoria, mood changes, negative thoughts, suicide attempts, or suicidal ideation
- May cause fat redistribution
- May cause immune reconstitution syndrome

**Adverse Effects:**<sup>(1,2,3,4)</sup>

- **Psychiatric:** depressive disorders (8%), insomnia (3%), abnormal dreams (1%), anxiety (<2%), suicidal ideations/attempts (0.4%)
- **Neurologic:** headache (3%), fatigue (1%), dizziness (1%), drowsiness (< 2%)
- **Gastrointestinal:** Nausea (1%), vomiting (1%), abdominal pain and discomfort (1%), diarrhea (< 2%), cholecystitis (< 2%), cholelithiasis (< 2%), and decreased appetite (< 2%)
- **Hepatic:** elevated AST 2.5- 5 x ULN (3%), >5-10 x ULN (2%), > 10 x UNL (<1%); elevated ALT >2.5-5 x UNL (4%), >5->10 x ULN (1%); elevated total bilirubin 1.1-1.5 x UNL (5%), > 2.5 x UNL (<1%)
- **Renal:** elevated serum creatinine of 1.1-1.3 x UNL (5%); >1.3-1.8 (<1%) glomerulonephritis membranous and glomerulonephritis mesangioproliferative (<2%)
- **Endocrine/Metabolic:** increased LDL 130-190mg/dL (17%), > 191mg/dL (<1%), increased total cholesterol 200-239mg/dL(14%), 240-300mg/dL(5%), >300mg/dL(<1%); Increased triglycerides 500-750mg/dL(2%), 751-1200mg/dL(< 1%)
- **Dermatologic:** unspecific rash 3%

**Drug Interactions:**<sup>(1,2,3,4)</sup>

- The following drugs are potent inducers of CYP3A4 and may result in decreased rilpivirine serum concentrations. Concomitant use is contraindicated due to potential for treatment failure and/or NNRTI resistance.
  - carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, dexamethasone (more than one dose) and St. John's wort
- The following drugs are inhibitors of the CYP 3A4 system. Close clinical monitoring is advised with co-administration of the following drugs and rilpivirine due to increased potential for rilpivirine related adverse events. No dosing adjustment for rilpivirine is recommended
  - HIV-antivirals: ritonavir, darunavir/ritonavir, lopinavir/ritonavir, other boosted PIs (atazanavir/ritonavir, fosamprenavir/ritonavir, squinavir/ritonavir, tipranavir/ritonavir), unboosted PIs (atazanavir, fosamprenavir, indinavir, nelfinavir)
  - Azole antifungals: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
  - Macrolides: clarithromycin, erythromycin. When possible use azithromycin
  - aldesleukin IL-2, amiodarone, aprepitant and fosaprepitant, basiliximab, bosentan, bromocriptine, chloramphenicol, conivaptan, danazol, dasatinib, delavirdine, diltiazem, dronedarone, ethinyl estradiol, fluoxetine, fluvoxamine, grapefruit juice, imatinib, isoniazid, lapatinib, miconazole, mifepristone, nefazodone, nifedipine, octreotide,

quinine, dalfopristine; quinupristin, ranolazine, rifaximin, tamoxifen, verapamil, zafirlukast, boceprevir, telaprevir

- The following drugs are inducers of the CYP 3A4 system. Close clinical monitoring is advised with co-administration of the following drugs and rilpivirine due treatment failure of rilpivirine
  - aminoglutethimide, barbiturates, bexarotene, bosentan, efavirenz, etravirine, flutamide, griseofulvin, modafinil, nafcillin, nevirapine, pioglitazone, primidone, topiramate,
- Caution is advised when administering rilpivirine with other drugs that may prolong the QT or PR interval such as the following:
  - arsenic trioxide, chloroquine, chlorpromazine, citalopram, class IA antiarrhythmics (disopyramide, procainamide, quinidine), class III antiarrhythmics (amiodarone, bretylium, dofetilide, ibutilide, sotalol), droperidol, haloperidol, pentamidine, pimozide, propafenone, thioridazine, ziprasidone, alfuzosin, amoxapine, apomorphine, artemether; lumefantrine, asenapine, beta-agonists, ofloxacin, ciprofloxacin, clozapine, cyclobenzaprine, dolasetron, eribulin, flecainide, gemifloxacin, halogenated anesthetics, iloperidone, levofloxacin, local anesthetics, magnesium sulfate, potassium sulfate, sodium sulfate, maprotiline, mefloquine, moxifloxacin, nilotinib, norfloxacin, olanzapine, ondansetron, paliperidone, palonosetron, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, quetiapine, risperidone, sunitinib, tacrolimus, telavancin, tetrabenazine, vardenafil, venlafaxine, vorinostat
- Didanosine should be dosed at least 2 hours before or at least 4 hours after rilpivirine
- Coadministration of rilpivirine and medications that increase gastric pH such as H<sub>2</sub> receptor antagonists and antacids may significantly decrease the absorption and plasma concentration of rilpivirine. Avoid use of antacids and H<sub>2</sub> receptor antagonists for at least 12 hours before and at least 4 hours after rilpivirine

**Dosing/Administration:** one 25mg tablet taken orally with meals once daily<sup>(1,3)</sup> taken in combination with other antiretroviral<sup>(2,4)</sup>

#### Use in special populations:

- **Pregnancy:** Category B<sup>(1,2,3,4)</sup>
  - Antiretroviral Pregnancy Registry in place to monitor maternal-fetal outcomes<sup>(1,2,3,4)</sup>
- **Breastfeeding:** It is not known whether rilpivirine is excreted in the breast milk; however, to avoid transmission of HIV to the infant, mothers should not breastfeed.<sup>(1,2,3,4)</sup>
- **Children and adolescents:** Safety and efficacy has not been established<sup>(1,2,3,4)</sup>
- **Elderly:** Clinical trials did not include a large number of patients over the age of 65 to determine how that patient population would respond. It is generally recommended that caution be used when administering rilpivirine to elderly patients due to greater frequency of renal and hepatic impairment as well as concomitant disease states and drug therapies.<sup>(1)</sup>
- **Renal impairment:** No dosing adjustments are required in mild to moderate renal impairment. Close monitoring is recommended in severe impairment and end-stage renal disease due to potentially increased rilpivirine plasma concentrations. Because rilpivirine is highly protein bound, it is unlikely to be removed by hemodialysis or peritoneal dialysis<sup>(1,2,3,4)</sup>
- **Hepatic impairment:** No dosing adjustments are required in mild or moderate hepatic impairment (Child-Pugh Class A and B). Rilpivirine has not been studied in severe hepatic impairment.<sup>(1,2,3,4)</sup>

**Conclusion:** Rilpivirine is an effective treatment for HIV-1 infections in treatment naïve patients; furthermore, it has a promising safety profile. It is important to note that the ECHO trial showed rilpivirine to have a higher rate of virological failure compared to efavirenz. Rilpivirine is pregnancy category B; therefore, would be a good option for use in women who are pregnant, or of childbearing age not using contraceptive methods. The cost of Edurant<sup>®</sup> (rilpivirine) is approximately \$720 for a 30 day supply compared to Sustiva<sup>®</sup> (efavirenz) which is approximately \$643 for a 30 day supply. The total cost would be heavily determined by the additional background regimen used. Because rilpivirine is a newly approved agent, more studies are needed to further investigate virological failure rates, non-inferiority compared to other HIV-1 treatment options, and effectiveness when used with other background regimens in order for fully understand its place in current HIV-1 treatment.

**References:**

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