Selected Properties of Rilpivirine

Other names	Edurant®, TMC-278 Combination formulation: • Complera®: Emtricitabine/rilpivirine/tenofovir (marketed as Eviplera® in Europe)
Manufacturer	Janssen Inc. (rilpivirine); Gilead Sciences Canada (Complera®)
Pharmacology/Mechanism of Action	A di-aryl-pyrimidine (DAPY) derivative NNRTI. The inherent molecular flexibility of rilpivirine relative to other NNRTIs permits the compound to retain its binding affinity to the reverse transcriptase in spite of the binding site changes induced by the presence of common NNRTI resistance mutations.
Activity	Shows high intrinsic activity against both wild-type HIV-1 and against HIV strains harboring resistance inducing mutations. Rilpivirine exhibits potent *in vitro* anti-HIV activity with an EC50 against wild-type HIV-1 of 0.5 nM, and little or no loss of activity (<5-fold reduction in susceptibility) against HIV-1 variants having key NNRTI resistance mutations. In extensive testing of more than 1500 clinical HIV-1 isolates, all exhibiting resistance to at least one currently marketed NNRTI, the EC50 of rilpivirine was below 100 nM for 95% of the isolates. In addition, the development of resistance was only seen *in vitro* when the rilpivirine concentration was very low (10 nM).
Resistance - genotypic	In mutation selection experiments using a concentration of 10 nM, virus breakthrough was observed on day 10; viruses selected contained up to eight mutations including L100I, V106I, Y181C and M230I, with a fold-change of 4.[De Bethune, 2005]
Resistance - phenotypic	In the pooled resistance analysis from the Phase 3 Studies C209 and C215 in treatment-naïve subjects, emerging NNRTI substitutions in the rilpivirine virologic failures included V90I, K101E/P/T, E138K/G, V179I/L, Y181I/C, V189I, H221Y, F227C/L and M230L, which were associated with a rilpivirine phenotypic fold change range of 2.6 - 621. The E138K substitution emerged most frequently on rilpivirine treatment commonly in combination with the M184I substitution.
Cross-Resistance	Cross-resistance has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I and Y181V conferred 52-fold, 15-fold and 12-fold decreased susceptibility to rilpivirine, respectively. The combination of E138K and M184I showed 6.7-fold reduced susceptibility to rilpivirine compared to 2.8-fold for E138K alone. The K103N substitution did not show reduced susceptibility to rilpivirine. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave decreased susceptibility to rilpivirine (fold change range of 3.7 - 554) in 38% and 66% of mutants, respectively.
Oral Bioavailability	Absolute bioavailability is unknown.

Effect of Food	The effect of different types of food on the bioavailability of single dose rilpivirine 75 mg tablet was examined in 20 healthy subjects. **Fasting conditions:** rilpivirine Cmax ↓ 46%, AUC ↓ 43% compared to standard breakfast (21 g fat, 533 kcal). **Protein rich nutritional drink (8 g fat, 300 kcal):** similar exposures to fasting conditions (Cmax & AUC ↓ 50% compared to standard breakfast). **High Fat Breakfast (56 g fat, 928 kcal):** rilpivirine Cmax ↓ 8%, AUC ↓ 8% compared to standard breakfast. **Recommendations**: Give rilpivirine with food (standard or high fat meal). Do not give rilpivirine on an empty stomach or with a protein rich nutritional drink.[Crauwels, 2008] The impact of food on rilpivirine absorption when administered as the single tablet regimen Complera® (emtricitabine/ rilpivirine/tenofovir) in healthy subjects (n=24) was examined. When administered as a single-tablet regimen (Complera®), food has a modest effect on rilpivirine pharmacokinetics, with no relevant differences between a light meal (390 kcal, 12 g fat) versus a standard meal (540 kcal, 21 g fat). Complera® may be administered with a light or standard meal.[Ramanathan et al, 2012]
Protein Binding	99.7%
Vd	
Tmax	4 hours
serum T ½	Terminal half-life of 50 hours
Drug Concentrations	In a single-dose study in healthy volunteers who received a fixed-dose tablet of emtricitabine 200 mg/rilpivirine 25 mg/tenofovir 300 mg versus the individual components, mean rilpivirine Cmax was 116 vs. 99.8 ng/mL and AUCinf was 3410 vs. 2900 ng.h/mL, respectively.[Mathias et al. 2010] Population pharmacokinetic estimates of rilpivirine 25 mg once daily in antiretroviral treatment-naïve HIV-1-infected subjects (pooled data from phase 3 trials to week 48): AUC 2204 ng.h/mL, Cmin 74 ng/mL Rilpivirine 25 mg daily with a meal in HIV-infected adolescents (between ages 13-17) resulted in exposures comparable to adults.[Crauwels et al. 2014] Hepatitis B and/or C virus co-infection, gender, and race have no clinically relevant effect on the exposure to rilpivirine. Following a single 600 mg IM injection of long-acting (LA) rilpivirine in HIV-negative subjects, rilpivirine concentrations persisted in plasma for more than 84 days postdose. In females, rilpivirine cervicovaginal fluid and tissue concentrations

	approximated that in plasma. In males, rilpivirine concentrations in rectal tissue approximated that in plasma, while concentrations in rectal fluid were lower.[Else et al. HIVPK 2012, #O_12] In a post-hoc analysis, absorption of rilpivirine-LA was influenced by BMI, with higher BMI associated with lower vaginal tract rilpivirine concentrations.[Else et al. HIVPK 2013, O_01] In eight HIV-infected males virologically suppressed on tenofovir/FTC and nevirapine who were switched to tenofovir/FTC and rilpivirine for 60 days, paired plasma and semen samples were obtained on day 59. Mean rilpivirine concentrations were 4.9 ng/mL in seminal plasma and 51.7 ng/mL in plasma, with a seminal plasma:plasma ratio of 0.10 (0.05-0.21). Seminal plasma and plasma rilpivirine concentrations were above published EC50 and EC90 values for wildtype virus (0.27 and 1.35 ng/mL, respectively) in all patients.[Watson et al. 2013]
Minimum target trough concentrations (for wildtype virus)	
CSF (% of serum)	In HIV-infected, virologically suppressed males on stable tenofovir/FTC/nevirapine N=12) who switched to tenofovir/FTC/ rilpivirine for 60 days, rilpivirine concentrations in lumbar puncture and plasma samples were assessed. The overall rilpivirine CSF concentration was 0.81 ng/mL (95% CI 0.68-0.96), representing a mean CSF:plasma ratio of 1.2% (95% CI 1.0 to 1.5%). No rilpivirine CSF concentrations were below the EC50 of 0.27 ng/mL.[Mora-Peris et al. HIV PK 2013, PP_04]
Metabolism	Metabolized primarily by CYP3A4, as well as CYP2C19, 1A2, 2C8/9/10 (minor).
Excretion	After single dose oral administration, 85% and 6.1% retrieved in feces and urine, respectively. In feces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.
Dosing – Adult	Edurant® (rilpivirine 25 mg) : 25 mg once daily with a meal in treatment-naïve adult patients with HIV-1 RNA less than or equal to 100,000 copies/mL. The following points should be considered when initiating therapy with rilpivirine: • More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy • The observed virologic failure rate in rilpivirine treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz • More subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz

	Complera® (emtricitabine 200 mg/rilpivirine 25 mg/tenofovir 300 mg): one tablet daily with a meal in treatment-naïve adult patients with HIV-1 RNA less than or equal to 100,000 copies/mL. Complera® as switch therapy in patients currently virologically suppressed (<50 copies/mL) and who meet the following criteria: • no history of virological failure • virologically suppressed (<50 copies/mL) for at least 6 months prior to switch • on their 1st or 2nd ARV regimen prior to switch • no current or past history of resistance to any of the 3 components of Complera®
Dosing – Pediatric	Safety and effectiveness in pediatric patients have not been established.
Special instructions for pediatric patients	
Adjust in Liver Dysfunction	No dose adjustment of rilpivirine is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). In a study comparing 8 subjects with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment.
Adjust in Renal Failure/Dialysis	Rilpivirine exposure is similar in HIV-1 infected subjects with mild renal impairment relative to HIV-1 infected subjects with normal renal function. No dose adjustment is required in patients with mild or moderate renal impairment. However, in patients with severe renal impairment or end-stage renal disease, rilpivirine should be used with caution and with increased monitoring for adverse effects, as rilpivirine concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. Do not administer Complera® (emtricitabine/rilpivirine/tenofovir) in patients with creatinine clearance below 50 mL per minute. In 750 patients on rilpivirine with tenofovir/emtricitabine (naïve or switch), average eGFR decreased 7.72 mL/min/1.73 m2 in switch patients and decreased 13.40 mL/min/1.73m2 in naïve patients. Changes likely reflect rilpivirine's inhibitory effect on tubular secretion of creatinine, rather than an actual change in

	GFR.[Roelofsen et al. 2013]
Toxicity	Most common adverse drug reactions to rilpivirine (incidence greater than or equal to 2%, Grades 2-4) are depression, insomnia, headache and rash. The effect of rilpivirine on the QTc interval of the ECG was evaluated in two Phase I studies in healthy adult volunteers. Rilpivirine 75mg qd and 300mg qd prolonged the QTc interval in a dose- and plasma-concentration-dependent manner. The maximum mean QTc interval prolongation (baseline- and placebo-adjusted) was 10.7 (90% CI 6.1, 15.3) msec in the 75 mg q.d. treatment arm and 23.3 (90% CI 18.0, 28.7) msec at 4.5 h post-dosing in the 300 mg q.d. arm. In a double-blind, placebo-controlled thorough QT trial in HIV-negative volunteers, no significant effect on QTcF interval was observed with rilpivirine 25mg daily or EFV 600mg daily. There was no effect of rilpivirine 25mg qd on heart rate or QTcB interval.[Vanveggel et al. EACS 2009] Rilpivirine should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes. Severe depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported. Immediate medical evaluation is recommended for severe depressive disorders. Hepatic adverse events have been reported in patients receiving a rilpivirine containing regimen. Patients with underlying hepatitis B or C, or marked elevations in serum liver biochemistries prior to treatment may be at increased risk for worsening or development of serum liver biochemistries elevations with use of rilpivirine. A few cases of hepatic toxicity have been reported in patients receiving a rilpivirine containing regimen who had no pre-existing hepatic disease or other identifiable risk factors.
Pregnancy & Lactation	Pregnancy category B. Rilpivirine did not show teratogenic potential in rat and rabbit models at exposures 13- to 80-times higher than those seen in HIV-1-infected patients receiving rilpivirine 25mg daily at steady-state.[Desmidt et al. EACS 2009]. Use during pregnancy only if the potential benefit justifies the potential risk.
Drug Interactions	Metabolized primarily by CYP3A4, as well as CYP2C19, 1A2, 2C8/9/10 (minor). Moderate inducer of CYP2C19, slight inducer of CYP1A2, 2B6 and 3A4. No effect on CYP2E1 activity.[Van Heeswijk, 2007] Rilpivirine at a dose of 25 mg q.d. is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes.[Crauwels, 2009] Rilpivirine is a weak substrate for the influx transporter OCT1 *in*

	vitro, but this is unlikely to have clinical significance. Rilpivirine is not a substrate for Pgp, OATP1A2, OATP1B1, OATP1B3, OAT1 or OAT3 *in vitro*. Rilpivirine inhibited both OCT1 and OATP1B1 *in vitro*, but inhibition was weak and unlikely to be relevant at RPV concentrations seen in patients.[Moss et al. CROI 2012] Rilpivirine plasma concentrations may be decreased if coadministered with CYP3A inducers or drugs that increase gastric pH, possibly resulting in loss of viral response and development of resistance. Rilpivirine is contraindicated with the following drugs: • Anticonvulsants (carbamazepine, oxcarbazepine, Phenobarbital, phenytoin) • Rifamycins (rifabutin, rifampin, rifapentine) • proton pump inhibitors (e.g., esomeprazole, dexlansoprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) • systemic dexamethasone (more than a single dose) • St John's wort (*Hypericum perforatum*) Rilpivirine plasma concentrations may be increased if coadministered with CYP3A inhibitors. Caution should be given to prescribing with drugs that may reduce the exposure of rilpivirine.
Baseline Assessment	
Routine Labs	Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with COMPLERA is recommended in patients with underlying hepatic disease such as hepatitis B or C, or in patients with marked elevations in serum liver biochemistries prior to treatment initiation. Serum liver biochemistries monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors.
Dosage Forms	Edurant®: 25 mg white, film-coated, round tablet, DIN 02370603. **Combination formulation:** • Complera®: Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir DF 300 mg tablet, DIN 02374129.
Storage	Store tablets in the original bottle in order to protect from light. Store at 25°C (77°F), with excursions permitted to 15°-30°C (59°-86°F).

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