

# RILPIVIRINE

EDURANT®

25 mg Film-coated Tablet

Non-nucleoside Reverse Transcriptase Inhibitor

## FORMULATION

Each film-coated tablet contains rilpivirine hydrochloride equivalent to 25 mg rilpivirine. The excipients are croscarmellose sodium, lactose monohydrate, magnesium stearate, polysorbate 20, povidone K30, silicified microcrystalline cellulose, hypromellose 2910 6 mPa.s, polyethylene glycol 3000, titanium dioxide and triacetin. The product is white to off-white, film-coated, round, biconvex tablet of 6.4 mm, debossed with “TMC” on one side and “25” on the other side.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic Properties

#### *Mechanism of Action*

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases  $\alpha$ ,  $\beta$  and  $\gamma$ .

### Pharmacodynamic effects

#### *Microbiology*

#### Antiviral Activity In Vitro

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC<sub>50</sub> value for HIV-1/IIIB of 0.73 nM (0.27 ng/mL). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC<sub>50</sub> values ranging from 2510 to 10830 nM (920 to 3970 ng/mL), treatment of HIV-2 infection with Rilpivirine (Edurant®) is not recommended in the absence of clinical data.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC<sub>50</sub> values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/mL) and group O primary isolates with EC<sub>50</sub> values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL).

Rilpivirine showed additive antiviral activity in combination with the N(t)RTIs abacavir, didanosine, emtricitabine, stavudine and tenofovir; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide; and the entry inhibitor maraviroc. Rilpivirine shows additive to synergistic antiviral activity in combination with the NRTIs lamivudine and zidovudine, and the integrase inhibitor raltegravir.

### Resistance

#### *In Cell Culture*

Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1. The most commonly observed amino acid substitutions that emerged included: L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

Resistance to rilpivirine was determined as a fold change in EC<sub>50</sub> value (FC) above the biological cut-off (BCO) of the assay.

#### *In Treatment-Naïve Subjects*

For the resistance analysis, a broader definition of virologic failure was used than in the primary efficacy analysis. In the week 48 pooled resistance analysis from the phase III trials, 62 (of a total of 72) virologic failures in the Rilpivirine (Edurant®) arm had resistance data at baseline and time of failure. In this analysis, the amino acid substitutions associated with NNRTI resistance that developed in at least 2 rilpivirine virologic failures were: V90I, K101E, E138K, E138Q, V179I, Y181C, V189I, H221Y, and F227C. The most common mutations were the same in the week 48 and week 96 analyses. In the trials, the presence of the substitutions V90I and V189I, at baseline, did not affect response. The E138K substitution emerged most frequently during rilpivirine treatment, commonly in combination with the M184I substitution.

More patients who failed virologically on Rilpivirine (Edurant®) than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance.

In the week 96 pooled resistance analysis, low rates of virologic failure, similar between the treatment arms, were observed from week 48 to week 96 (3.2% in the Rilpivirine (Edurant®) arm and 2.3% in the efavirenz arm).

Considering all of the available *in vitro* and *in vivo* data, the following amino acid substitutions, when present at baseline, are likely to affect the activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L.

### **Cross-resistance**

#### *Site-Directed NNRTI Mutant Virus*

In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96%) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V. The K103N substitution did not result in reduced susceptibility to rilpivirine by itself, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine.

#### *Recombinant Clinical Isolates*

Rilpivirine retained sensitivity (FC ≤ BCO) against 62% of 4786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

#### *Treatment-Naïve HIV-1 Infected Patients*

In the week 48 pooled analysis of the phase III trials ECHO and THRIVE, 31 of the 62 subjects with virologic failure on Rilpivirine (Edurant®) with phenotypic resistance data lost susceptibility to rilpivirine. Of these, 28 were resistant to etravirine, 27 to efavirenz, and 14 to nevirapine. These cross-resistance findings were confirmed in the week 96 pooled analyses of the phase III clinical trials.

In the week 96 pooled analyses, among virologic failures in the Rilpivirine (Edurant®) arm with baseline viral load ≤ 100000 copies/mL and with resistance to rilpivirine, there were fewer

patients with phenotypic cross-resistance than among those in the Rilpivirine (Edurant<sup>®</sup>) arm with baseline viral load > 100000 copies/mL. 3, 4 and 1 rilpivirine virologic failures with baseline viral load ≤ 100000 copies/mL and with resistance to rilpivirine (N=5) had cross-resistance to efavirenz, etravirine and nevirapine, respectively, compared to 27, 28, and 15 rilpivirine virologic failures with baseline viral load > 100000 copies/mL (N=30), respectively.

### ***Effect on QT/QTc interval and cardiac electrophysiology***

The effect of Rilpivirine (Edurant<sup>®</sup>) at the recommended dose of 25 mg q.d. on the QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady-state. Rilpivirine (Edurant<sup>®</sup>) at the recommended dose of 25 mg q.d. is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg q.d. and 300 mg q.d. of Rilpivirine (Edurant<sup>®</sup>) were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) ms, respectively. Steady-state administration of Rilpivirine (Edurant<sup>®</sup>) 75 mg q.d. and 300 mg q.d. resulted in a mean C<sub>max</sub> approximately 2.6-fold and 6.7-fold, respectively, higher than the mean steady-state C<sub>max</sub> observed with the recommended 25 mg q.d. dose of Rilpivirine (Edurant<sup>®</sup>).

### ***Clinical Studies***

#### ***Treatment-Naïve HIV-1 Infected Patients***

The evidence of efficacy of Rilpivirine (Edurant<sup>®</sup>) is based on the analyses of 96 week data from 2 randomized, double-blind, active-controlled, phase III trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE). The trials were identical in design, with the exception of the background regimen (BR). At 96 weeks, the virologic response rate [confirmed undetectable viral load (< 50 HIV-1 RNA copies/mL)] was evaluated in patients receiving Rilpivirine (Edurant<sup>®</sup>) 25 mg q.d. in addition to a BR versus patients receiving efavirenz 600 mg q.d. in addition to a BR. Similar efficacy for Rilpivirine (Edurant<sup>®</sup>) was seen in each trial demonstrating non-inferiority to efavirenz.

Antiretroviral treatment-naïve HIV-1 infected patients were enrolled who had a plasma HIV-1 RNA ≥ 5000 copies/mL and were screened for susceptibility to N(t)RTIs and for absence of specific NNRTI RAMs. In ECHO, the BR was fixed to the N(t)RTIs, tenofovir disoproxil fumarate plus emtricitabine. In THRIVE, the BR consisted of 2 investigator-selected N(t)RTIs: tenofovir disoproxil fumarate plus emtricitabine or zidovudine plus lamivudine or abacavir plus lamivudine. In ECHO, randomization was stratified by screening viral load. In THRIVE, randomization was stratified by screening viral load and by N(t)RTI BR.

This analysis included 690 patients in ECHO and 678 patients in THRIVE who had completed 96 weeks of treatment or discontinued earlier.

In the pooled analysis for ECHO and THRIVE, demographics and baseline characteristics were balanced between the Rilpivirine (Edurant<sup>®</sup>) arm and the efavirenz arm. Table 1 displays selected demographic and baseline disease characteristics of the patients in the Rilpivirine (Edurant<sup>®</sup>) and efavirenz arms.

<b>Table 1: Demographic and baseline disease characteristics of antiretroviral treatment-naïve HIV-1 infected adult subjects in the ECHO and THRIVE trials (pooled analysis)</b>		
	<b>Pooled data from the ECHO and THRIVE trials</b>	
	<b>Rilpivirine (Edurant®) + BR N=686</b>	<b>Efavirenz + BR N=682</b>
<b>Demographic characteristics</b>		
Median age, years (range)	36 (18-78)	36 (19-69)
Sex		
Male	76%	76%
Female	24%	24%
Race		
White	61%	60%
Black/African American	24%	23%
Asian	11%	14%
Other	2%	2%
Not allowed to ask per local regulations	1%	1%
<b>Baseline disease characteristics</b>		
Median baseline plasma HIV-1 RNA (range), log <sub>10</sub> copies/mL	5.0 (2-7)	5.0 (3-7)
Median baseline CD4+ cell count (range), × 10 <sup>6</sup> cells/L	249 (1-888)	260 (1-1137)
Percentage of subjects with hepatitis B/C virus co-infection	7.3%	9.5%
Percentage of patients with the following background regimens:		
tenofovir disoproxil fumarate plus emtricitabine	80.2%	80.1%
zidovudine plus lamivudine	14.7%	15.1%
abacavir plus lamivudine	5.1%	4.8%

BR=background regimen

Table 2 below shows the efficacy results at 48 weeks and at 96 weeks for patients treated with Rilpivirine (Edurant®) and patients treated with efavirenz from the pooled data from the ECHO and THRIVE trials. The response rate (confirmed undetectable viral load < 50 HIV-1 RNA copies/mL) at week 96 was comparable between the Rilpivirine (Edurant®) arm and the efavirenz arm. The incidence of virologic failure was higher in the Rilpivirine (Edurant®) arm than the efavirenz arm at week 96; however, most of the virologic failures occurred within the first 48 weeks of treatment. Discontinuations due to adverse events were higher in the efavirenz arm at week 96 than the Rilpivirine (Edurant®) arm. Most of these discontinuations occurred in the first 48 weeks of treatment.

<b>Table 2: Virologic outcome of randomized treatment in the ECHO and THRIVE trials (Pooled Analysis at Week 48 (primary) and Week 96; ITT-TLOVR*)</b>		
	<b>Outcome at Week 48</b>	<b>Outcome at Week 96</b>

%	<b>Rilpivirine (Edurant®) + BR N=686</b>	<b>Efavirenz + BR N=682</b>	<b>Rilpivirine (Edurant®) + BR N=686</b>	<b>Efavirenz + BR N=682</b>
Confirmed Undetectable Viral Load (< 50 HIV-1 RNA copies/mL) <sup>§#</sup>	84.3	82.3	77.6	77.6
Virologic Failure <sup>†</sup>	9.0	4.8	11.5	5.9
Death	0.1	0.4	0.1	0.9
Discontinued due to adverse event (AE)	2.0	6.7	3.8	7.6
Discontinued for non-AE reason <sup>¶</sup>	4.5	5.7	7.0	8.1

N=number of subjects per treatment group

\* intent-to-treat time to loss of virologic response.

§ Subjects achieved virologic response (two consecutive viral loads < 50 copies/mL and maintained it through week 48/96).

# Predicted difference of response rates (95% CI) at week 48: 1.6% (-2.2%; 5.3%) and at week 96: -0.4% (-4.6%; 3.8%); both p-values < 0.0001 (non-inferiority at 12% margin) from logistic regression model, including stratification factors and study.

† Includes subjects who were rebounder (confirmed viral load ≥ 50 copies/mL after being responder) or who were never suppressed (no confirmed viral load < 50 copies/mL, either ongoing or discontinued due to lack or loss of efficacy).

¶ e.g. lost to follow-up, non-compliance, withdrew consent.

At week 96, the mean change from baseline in CD4+ cell count was  $+228 \times 10^6$  cells/L in the Rilpivirine (Edurant®) arm and  $+219 \times 10^6$  cells/L in the efavirenz arm in the pooled analysis of the ECHO and THRIVE trials [estimated treatment difference (95% CI): 11.3 (-6.8; 29.4)].

A subgroup analysis of the virologic response (< 50 HIV-1 RNA copies/mL) at 48 and 96 weeks and virologic failure by baseline viral load, CD4 count and by background NRTIs (pooled data from the ECHO and THRIVE trials) is presented in Table 3.

<b>Table 3: Virologic response (&lt; 50 HIV-1 RNA copies/mL, ITT-TLOVR) and virologic failure by baseline viral load and by background NRTIs (Pooled Analysis at Week 48 [primary] and Week 96 from the ECHO and THRIVE trials)</b>								
	<i>Outcome at Week 48</i>				<i>Outcome at Week 96</i>			
	<b>Rilpivirine (Edurant®) + BR N=686</b>		<b>Efavirenz + BR N=682</b>		<b>Rilpivirine (Edurant®) + BR N=686</b>		<b>Efavirenz + BR N=682</b>	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
<b>Proportion of patients with HIV-1 RNA &lt; 50 copies/mL at week 48* and at week 96* by baseline plasma viral load (copies/mL)</b>								
≤ 100000	368	332 (90.2%)	330	276 (83.6%)	368	309 (84.0%)	329	263 (79.9%)
> 100000	318	246 (77.4%)	352	285 (81.0%)	318	223 (70.1%)	353	266 (75.4%)

> 100000 to ≤ 500000	249	198 (79.5%)	270	223 (82.6%)	249	178 (71.5%)	270	205 (75.9%)
> 500000	69	48 (69.6%)	82	62 (75.6%)	69	45 (65.2%)	83	61 (73.5%)
<b>Virologic failure<sup>†</sup> by baseline plasma viral load (copies/mL)</b>								
≤ 100000	368	14 (3.8%)	330	11 (3.3%)	368	21 (5.7%)	329	12 (3.6%)
> 100000	318	48 (15.1%)	352	22 (6.3%)	318	58 (18.2%)	353	28 (7.9%)
> 100000 to ≤ 500000	249	33 (13.3%)	270	13 (4.8%)	249	43 (17.3%)	270	18 (6.7%)
> 500000	69	15 (21.7%)	82	9 (11.0%)	69	15 (21.7%)	83	10 (12.0%)
<b>Proportion of patients with HIV-1 RNA &lt; 50 copies/mL at week 48* and at week 96* by baseline CD4 count (× 10<sup>6</sup> cells/L)</b>								
< 50	34	20 (58.8%)	36	29 (80.6%)	34	19 (55.9%)	36	25 (69.4%)
≥ 50-< 200	194	156 (80.4%)	175	143 (81.7%)	194	138 (71.1%)	175	131 (74.9%)
≥ 200-< 350	313	272 (86.9%)	307	253 (82.4%)	313	252 (80.5%)	307	244 (79.5%)
≥ 350	144	130 (90.3%)	164	136 (82.9%)	144	123 (85.4%)	164	129 (78.7%)
<b>Virologic Failure<sup>†</sup> by baseline CD4 count (× 10<sup>6</sup> cells/L)</b>								
< 50	34	6 (17.6%)	36	1 (2.8%)	34	6 (17.6%)	36	4 (11.1%)
≥ 50-< 200	194	27 (13.9%)	175	14 (8.0%)	194	37 (19.1%)	175	14 (8.0%)
≥ 200-< 350	313	21 (6.7%)	307	14 (4.6%)	313	26 (8.3%)	307	15 (4.9%)
≥ 350	144	8 (5.6%)	164	4 (2.4%)	144	10 (6.9%)	164	7 (4.3%)
<b>Proportion of patients with HIV-1 RNA &lt; 50 copies/mL at week 48* and at week 96* by background N(t)RTI</b>								
tenofovir disoproxil fumarate plus emtricitabine	550	459 (83.5%)	546	450 (82.4%)	550	423 (76.9%)	546	422 (77.3%)
zidovudine plus lamivudine	101	88 (87.1%)	103	83 (80.6%)	101	82 (81.2%)	103	79 (76.7%)
abacavir plus lamivudine	35	31 (88.6%)	33	28 (84.8%)	35	27 (77.1%)	33	28 (84.8%)

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N=number of subjects per treatment group

n=number of observations

\* Imputations according to the TLOVR algorithm.

† Includes subjects who were rebounder (confirmed viral load  $\geq 50$  copies/mL after being responder) or who were never suppressed (no confirmed viral load  $< 50$  copies/mL, either ongoing or discontinued due to lack or loss of efficacy).

Study TMC278-C204 was a randomized, active-controlled, phase IIb trial in antiretroviral treatment-naïve HIV-1 infected adult patients consisting of 2 parts: an initial partially blinded dose-finding part [Ralpivirine (Edurant<sup>®</sup>) doses blinded] up to 96 weeks, followed by a long-term, open label part. In the open label part of the trial, patients originally randomized to one of the 3 doses of Ralpivirine (Edurant<sup>®</sup>) were all treated with Ralpivirine (Edurant<sup>®</sup>) 25 mg once daily in addition to a BR, once the dose for the phase III studies was selected. Patients in the control arm received efavirenz 600 mg once daily in addition to a BR in both parts of the study. The BR consisted of 2 investigator-selected N(t)RTIs: zidovudine plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine.

Study TMC278-C204 enrolled 368 HIV-1 infected treatment-naïve adult patients who had a plasma HIV-1 RNA  $\geq 5000$  copies/mL, previously received  $\leq 2$  weeks of treatment with an N(t)RTI or protease inhibitor, had no prior use of NNRTIs, and were screened for susceptibility to N(t)RTI and for absence of specific NNRTI RAMs.

At 96 weeks, the proportion of patients with  $< 50$  HIV-1 RNA copies/mL receiving Ralpivirine (Edurant<sup>®</sup>) 25 mg (N=93) compared to patients receiving efavirenz (N=89) was 76% and 71%, respectively. The mean increase from baseline in CD4+ counts was  $146 \times 10^6$  cells/L in patients receiving Ralpivirine (Edurant<sup>®</sup>) 25 mg and  $160 \times 10^6$  cells/L in patients receiving efavirenz.

Of those patients who were responders at week 96, 74% of patients receiving Ralpivirine (Edurant<sup>®</sup>) remained with undetectable viral load ( $< 50$  HIV-1 RNA copies/mL) at week 240 compared to 81% of patients receiving efavirenz. There were no safety concerns identified in the week 240 analyses.

### *Pregnancy*

Ralpivirine in combination with a background regimen was evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to ralpivirine as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks). Virologic response was preserved throughout the trial period. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. Ralpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of ralpivirine in HIV-1 infected adults.

### **Pharmacokinetic Properties**

The pharmacokinetic properties of ralpivirine have been evaluated in adult healthy subjects and in adult antiretroviral treatment-naïve HIV-1 infected patients. Exposure to ralpivirine was generally lower in HIV-1 infected patients than in healthy subjects.

### *Absorption*

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours. The absolute bioavailability of Rilpivirine (Edurant<sup>®</sup>) is unknown.

### ***Effect of Food on Absorption***

The exposure to rilpivirine was approximately 40% lower when Rilpivirine (Edurant<sup>®</sup>) was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high-fat high-caloric meal (928 kcal). When Rilpivirine (Edurant<sup>®</sup>) was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal.

### ***Distribution***

Rilpivirine is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

### ***Metabolism***

*In vitro* experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system.

### ***Excretion***

The terminal elimination half-life of rilpivirine is approximately 45 hours. After single dose oral administration of <sup>14</sup>C-rilpivirine, on average 85% and 6.1% of the radioactivity could be 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.

### ***Special Populations***

#### ***Pediatrics (17 years of age and younger)***

The pharmacokinetics of rilpivirine in pediatric patients are under investigation. Dosing recommendations for pediatric patients cannot be made due to insufficient data (see ***Dosage and Method of Administration***).

#### ***Elderly (65 years of age and older)***

Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years) evaluated. No dose adjustment of Rilpivirine (Edurant<sup>®</sup>) is required in elderly patients (see ***Dosage and Method of Administration***).

#### ***Renal Impairment***

The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. Therefore, the impact of renal impairment on rilpivirine elimination is expected to be minimal. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis (see ***Dosage and Method of Administration***).

#### ***Hepatic Impairment***

Rilpivirine is primarily metabolized and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. No dose adjustment is required in patients with



mild or moderate hepatic impairment. Rilpivirine (Edurant®) has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see ***Dosage and Method of Administration***).

#### *Hepatitis B and/or Hepatitis C Virus Co-Infection*

Population pharmacokinetic analysis indicated that hepatitis B and/or C virus co-infection had no clinically relevant effect on the exposure to rilpivirine.

#### *Pregnancy and Postpartum*

The exposure to total rilpivirine after intake of rilpivirine 25 mg once daily as part of an antiretroviral regimen was lower during pregnancy (similar for the 2<sup>nd</sup> and 3<sup>rd</sup> trimester) compared with postpartum (see Table 4). The decrease in unbound (i.e., active) rilpivirine pharmacokinetic parameters during pregnancy compared to postpartum was less pronounced than for total rilpivirine.

In women receiving rilpivirine 25 mg once daily during the 2<sup>nd</sup> trimester of pregnancy, mean intra-individual values for total rilpivirine C<sub>max</sub>, AUC<sub>24h</sub> and C<sub>min</sub> values were, respectively, 21%, 29% and 35% lower as compared to postpartum; during the 3<sup>rd</sup> trimester of pregnancy, C<sub>max</sub>, AUC<sub>24h</sub> and C<sub>min</sub> values were, respectively, 20%, 31% and 42% lower as compared to postpartum.

**Table 4: Pharmacokinetic Results of Total Rilpivirine After Administration of Rilpivirine 25 mg Once Daily as Part of an Antiretroviral Regimen, During the 2<sup>nd</sup> Trimester of Pregnancy, the 3<sup>rd</sup> Trimester of Pregnancy and Postpartum**

Pharmacokinetics of total rilpivirine (mean ± SD, t <sub>max</sub> : median [range])	Postpartum (6-12 Weeks) (n=11)	2 <sup>nd</sup> Trimester of pregnancy (n=15)	3 <sup>rd</sup> Trimester of pregnancy (n=13)
C <sub>min</sub> , ng/mL	84.0 ± 58.8	54.3 ± 25.8	52.9 ± 24.4
C <sub>max</sub> , ng/mL	167 ± 101	121 ± 45.9	123 ± 47.5
t <sub>max</sub> , h	4.00 (2.03-25.08)	4.00 (1.00-9.00)	4.00 (2.00-24.93)
AUC <sub>24h</sub> , ng.h/mL	2714 ± 1535	1792 ± 711	1762 ± 662

#### *Other populations*

##### Gender

No clinically relevant differences in the pharmacokinetics of rilpivirine have been observed between men and women.

##### Race

Population pharmacokinetic analysis of rilpivirine in HIV infected patients indicated that race had no clinically relevant effect on the exposure to rilpivirine.

## **NON-CLINICAL INFORMATION**

### **Carcinogenicity and Mutagenicity**

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of rilpivirine did not cause a statistically significant increase in

the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats are considered to be rodent-specific, associated with liver enzyme induction. A similar mechanism does not exist in humans; hence, these tumors are not relevant for humans. The follicular cell findings are considered to be rat-specific, associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg q.d.).

Rilpivirine has tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocyte and *in vitro* clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. Rilpivirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

### **Toxicology**

Animal toxicology studies have been conducted with rilpivirine in mice, rats, rabbits, dogs and cynomolgus monkeys. The target organs and systems of toxicity were the adrenal cortex and the associated steroid biosynthesis (mouse, rat, dog, cynomolgus monkey), the reproductive organs (female mouse, male and female dog), the liver (mouse, rat, dog), the thyroid and pituitary gland (rat), the kidney (mouse, dog), the hematopoietic system (mouse, rat, dog), and the coagulation system (rat).

### **Reproductive Toxicology and Fertility**

In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day, a dose of rilpivirine that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg q.d. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg q.d. In a pre- and postnatal development assessment in rats, rilpivirine had no effect on development of offspring during lactation or post-weaning when the mothers were dosed up to 400 mg/kg/day.

### **THERAPEUTIC INDICATIONS**

Rilpivirine (Edurant<sup>®</sup>), in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients.

This indication is based on safety and efficacy analyses through 96 weeks from 2 randomized, double-blind, controlled, phase III trials in treatment-naïve patients (see *Pharmacological Properties - Clinical Studies*).

### **DOSAGE AND METHOD OF ADMINISTRATION**

Rilpivirine (Edurant<sup>®</sup>) must always be given in combination with other antiretroviral medicinal products.

#### ***Dosage - Adults***

The recommended dose of Rilpivirine (Edurant<sup>®</sup>) is one 25 mg tablet once daily taken orally with a meal (see ***Pharmacological Properties - Pharmacokinetic Properties***).

#### ***Dose Adjustment***

For patients concomitantly receiving rifabutin, the Rilpivirine (Edurant<sup>®</sup>) dose should be increased to 50 mg (two tablets of 25 mg each) once daily, taken with a meal. When rifabutin co-administration is stopped, the Rilpivirine (Edurant<sup>®</sup>) dose should be decreased to 25 mg once daily, taken with a meal (see ***Interactions with Other Medicinal Products and Other Forms of Interaction***).

#### ***Pregnancy and Postpartum***

The recommended dose of Rilpivirine (Edurant<sup>®</sup>) in pregnant patients is one 25 mg tablet once daily taken orally with a meal. Lower exposures of rilpivirine were observed during pregnancy, therefore viral load should be monitored closely (see ***Pregnancy, Breastfeeding and Fertility and Pharmacokinetic Properties-Special Populations – Pregnancy and Postpartum***).

#### ***Missed dose(s)***

If the patient misses a dose of Rilpivirine (Edurant<sup>®</sup>) within 12 hours of the time it is usually taken, the patient should take Rilpivirine (Edurant<sup>®</sup>) with a meal as soon as possible and then take the next dose of Rilpivirine (Edurant<sup>®</sup>) at the regularly scheduled time. If a patient misses a dose of Rilpivirine (Edurant<sup>®</sup>) by more than 12 hours, the patient should not take the missed dose, but resume the usual dosing schedule.

#### ***Special populations***

##### ***Pediatrics (17 years of age and younger)***

The safety and efficacy of Rilpivirine (Edurant<sup>®</sup>) in adolescents and children are under investigation (see ***Pharmacokinetic properties***). Treatment with Rilpivirine (Edurant<sup>®</sup>) is not recommended in these populations.

##### ***Elderly (65 years of age and older)***

No dose adjustment of Rilpivirine (Edurant<sup>®</sup>) is required in elderly patients (see ***Pharmacokinetic Properties***).

##### ***Renal Impairment***

No dose adjustment of Rilpivirine (Edurant<sup>®</sup>) is required in patients with renal impairment (see ***Pharmacokinetic Properties***).

##### ***Hepatic Impairment***

No dose adjustment of Rilpivirine (Edurant<sup>®</sup>) is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). Rilpivirine (Edurant<sup>®</sup>) has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see ***Pharmacokinetic Properties***).

## **CONTRAINDICATIONS**

Hypersensitivity to rilpivirine or to any of the excipients.

Rilpivirine (Edurant<sup>®</sup>) should not be co-administered with the following medicinal products, as significant decreases in rilpivirine plasma concentrations may occur (due to CYP3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of Rilpivirine (Edurant<sup>®</sup>) (see ***Interactions with Other Medicinal Products and Other Forms of Interaction***):

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampicin, rifapentine
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole
- the glucocorticoid systemic dexamethasone, except as a single dose treatment
- St John’s wort (*Hypericum perforatum*).

## **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**

### ***Transmission of HIV***

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood or sexual contact. Appropriate precautions to prevent the transmission of HIV should continue to be employed.

### ***Virologic failure and development of resistance***

In the pooled analysis from the Phase III trials through 96 weeks, patients treated with Rilpivirine (Edurant<sup>®</sup>) with a baseline viral load > 100000 HIV-1 RNA copies/mL had a greater risk of virologic failure compared to patients with a baseline viral load ≤ 100000 HIV-1 RNA copies/mL. The greater risk of virologic failure for patients in the Rilpivirine (Edurant<sup>®</sup>) arm was observed in the first 48 weeks of these trials while low rates of virologic failure, similar between the treatment arms, were observed from week 48 to week 96 (see ***Pharmacodynamic Properties***). Patients with a baseline viral load > 100000 HIV-1 RNA copies/mL who experienced virologic failure exhibited a higher rate of treatment emergent resistance to the NNRTI class. More patients who failed virologically on Rilpivirine (Edurant<sup>®</sup>) than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance (see ***Pharmacodynamic Properties***). This information should be taken into consideration when initiating therapy with Rilpivirine (Edurant<sup>®</sup>).

### ***Interactions with Medicinal Products***

Caution should be given to prescribing Rilpivirine (Edurant<sup>®</sup>) with medicinal products that may reduce the exposure of rilpivirine.

For information on interactions with medicinal products, see ***Interactions With Other Medicinal Products and Other Forms of Interaction***.

### ***Immune Reconstitution Inflammatory Syndrome***

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including Rilpivirine (Edurant<sup>®</sup>). During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders such as Graves’ disease and autoimmune hepatitis have also been reported to occur in the setting of immune reconstitution inflammatory syndrome; however, the time to onset is more variable, and these events can occur many months after initiation of treatment (see ***Undesirable Effects***).

## **INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**

### ***Medicinal Products that Affect Rilpivirine Exposure***

Rilpivirine is primarily metabolized by cytochrome P450 (CYP)3A, and medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see **Pharmacokinetic Properties**). Co-administration of Rilpivirine (Edurant<sup>®</sup>) and medicinal products that induce CYP3A may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of Rilpivirine (Edurant<sup>®</sup>). Co-administration of Rilpivirine (Edurant<sup>®</sup>) and medicinal products that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

Co-administration of Rilpivirine (Edurant<sup>®</sup>) with medicinal products that increase gastric pH may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of Rilpivirine (Edurant<sup>®</sup>).

### **Medicinal Products that are Affected by the Use of Rilpivirine**

Rilpivirine (Edurant<sup>®</sup>) at a dose of 25 mg q.d. is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes.

Established and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed below in Table 5 and Table 6, respectively.

### **Interaction Table**

Interactions between rilpivirine and co-administered medicinal products are listed in the tables below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, not applicable as “NA”, once daily as “q.d.” and twice daily as “b.i.d.”).

**Table 5: Drug interactions – Rilpivirine co-administered with antiretroviral and antiviral medicinal products**

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C <sub>max</sub>	AUC	C <sub>min</sub>
<b>HIV NUCLEOSIDE OR NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs/N[t]RTIs)</b>					
Didanosine* <sup>#</sup>	400 mg q.d.	didanosine	↔	↑ 12%	NA
		rilpivirine	↔	↔	↔
No dose adjustment is required when Rilpivirine (Edurant <sup>®</sup> ) is co-administered with didanosine. Didanosine should be administered on an empty stomach and at least two hours before or at least four hours after Rilpivirine (Edurant <sup>®</sup> ) (which should be administered with a meal).					
Tenofovir disoproxil fumarate* <sup>#</sup>	300 mg q.d.	tenofovir	↑ 19%	↑ 23%	↑ 24%
		rilpivirine	↔	↔	↔
No dose adjustment is required when Rilpivirine (Edurant <sup>®</sup> ) is co-administered with tenofovir disoproxil fumarate.					
Other NRTIs (abacavir, emtricitabine, lamivudine, stavudine and zidovudine)	Based on the different elimination routes for rilpivirine and these other NRTIs, no clinically relevant drug-drug interactions are expected between these medicinal products and Rilpivirine (Edurant <sup>®</sup> ).				
<b>HIV NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)</b>					

NNRTIs (delavirdine, efavirenz, etravirine, nevirapine) It is not recommended to co-administer Rilpivirine (Edurant<sup>®</sup>) with NNRTIs.

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### HIV PROTEASE INHIBITORS (PIs) - with co-administration of low dose ritonavir

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Darunavir/ritonavir* <sup>#</sup>	800/100 mg q.d.	darunavir	↔	↔	↓ 11%
		rilpivirine	↑ 79%	↑ 130%	↑ 178%

Concomitant use of Rilpivirine (Edurant<sup>®</sup>) with darunavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when Rilpivirine (Edurant<sup>®</sup>) is co-administered with darunavir/ritonavir.

Lopinavir/ritonavir (soft gel capsules)* <sup>#</sup>	400/100 mg b.i.d.	lopinavir	↔	↔	↓ 11%
		rilpivirine	↑ 29%	↑ 52%	↑ 74%

Concomitant use of Rilpivirine (Edurant<sup>®</sup>) with lopinavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when Rilpivirine (Edurant<sup>®</sup>) is co-administered with lopinavir/ritonavir.

Other boosted PIs (atazanavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir, tipranavir/ritonavir) Concomitant use of Rilpivirine (Edurant<sup>®</sup>) with boosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Rilpivirine (Edurant<sup>®</sup>) is not expected to affect the plasma concentrations of co-administered PIs.

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### HIV PROTEASE INHIBITORS (PIs) - without co-administration of low dose ritonavir

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Unboosted PIs (atazanavir, fosamprenavir, indinavir, nelfinavir) Concomitant use of Rilpivirine (Edurant<sup>®</sup>) with unboosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Rilpivirine (Edurant<sup>®</sup>) is not expected to affect the plasma concentrations of co-administered PIs.

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### CCR5 ANTAGONISTS

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Maraviroc No clinically relevant drug-drug interaction is expected when Rilpivirine (Edurant<sup>®</sup>) is co-administered with maraviroc.

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### HIV INTEGRASE STRAND TRANSFER INHIBITORS

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Raltegravir*	400 mg b.i.d.	raltegravir	↑ 10%	↑ 9%	↑ 27%
		rilpivirine	↔	↔	↔

No dose adjustment is required when Rilpivirine (Edurant<sup>®</sup>) is co-administered with raltegravir.

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### OTHER ANTIVIRAL AGENTS

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Ribavirin No clinically relevant drug-drug interaction is expected when Rilpivirine (Edurant<sup>®</sup>) is co-administered with ribavirin.

Simeprevir*	150 mg once daily	simeprevir	↑ 10%	↔	↔
		Rilpivirine	↔	↔	↑ 25%

No dose adjustment is required for either drug when Rilpivirine (Edurant<sup>®</sup>) is co-administered with simeprevir.

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\* The interaction between Rilpivirine (Edurant®) and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.

# This interaction study has been performed with a dose higher than the recommended dose for Rilpivirine (Edurant®) assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of Rilpivirine (Edurant®) 25 mg q.d.

**Table 6: Drug interactions – Rilpivirine co-administered with non-antiretroviral medicinal products**

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C <sub>max</sub>	AUC	C <sub>min</sub>
<b>ANTIARRHYTHMICS</b>					
Digoxin*	0.5 mg single dose	digoxin	↔	↔	NA
No dose adjustment is required when Rilpivirine (Edurant®) is co-administered with digoxin.					
<b>ANTIDIABETICS</b>					
Metformin*	850 mg single dose	metformin	↔	↔	NA
No dose adjustment is required when Rilpivirine (Edurant®) is co-administered with metformin.					
<b>ANTICONVULSANTS</b>					
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Rilpivirine (Edurant®) should not be used in combination with these anticonvulsants as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of Rilpivirine (Edurant®).				
<b>AZOLE ANTIFUNGAL AGENTS</b>					
Ketoconazole*#	400 mg q.d.	ketoconazole rilpivirine	↔ ↑ 30%	↓ 24% ↑ 49%	↓ 66% ↑ 76%
Fluconazole Itraconazole Posaconazole Voriconazole	Concomitant use of Rilpivirine (Edurant®) with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when Rilpivirine (Edurant®) is co-administered with azole antifungal agents.				
<b>ANTIMYCOBACTERIALS</b>					
Rifabutin*	300 mg q.d. <sup>†</sup>	rifabutin 25- <i>O</i> -desacetyl- rifabutin	↔ ↔	↔ ↔	↔ ↔
	300 mg q.d.	rilpivirine (25 mg q.d.)	↓ 31%	↓ 42%	↓ 48%
	300 mg q.d.	rilpivirine (50 mg q.d.)	↑ 43%	↑ 16%	↔
(as compared to 25 mg q.d. rilpivirine alone)					

Concomitant use of Rilpivirine (Edurant<sup>®</sup>) with rifabutin may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of Rilpivirine (Edurant<sup>®</sup>). Throughout co-administration of Rilpivirine (Edurant<sup>®</sup>) with rifabutin, the Rilpivirine (Edurant<sup>®</sup>) dose should be increased from 25 mg once daily to 50 mg once daily. When rifabutin co-administration is stopped, the Rilpivirine (Edurant<sup>®</sup>) dose should be decreased to 25 mg once daily.

Rifampicin*#	600 mg q.d.	rifampicin	↔	↔	NA
		25-desacetyl-rifampicin	↔	↓9%	NA
		rilpivirine	↓ 69%	↓ 80%	↓ 89%
Rifapentine	Rilpivirine (Edurant <sup>®</sup> ) should not be used in combination with rifampicin or rifapentine as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of Rilpivirine (Edurant <sup>®</sup> ).				

### MACROLIDE ANTIBIOTICS

Clarithromycin Erythromycin	Concomitant use of Rilpivirine (Edurant <sup>®</sup> ) with clarithromycin or erythromycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.				
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### GLUCOCORTICOIDS

Dexamethasone (systemic)	Rilpivirine (Edurant <sup>®</sup> ) should not be used in combination with systemic dexamethasone as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of Rilpivirine (Edurant <sup>®</sup> ). Alternatives should be considered, particularly for long-term use.				
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### PROTON PUMP INHIBITORS

Omeprazole*#	20 mg q.d.	omeprazole	↓ 14%	↓ 14%	NA
		rilpivirine	↓ 40%	↓ 40%	↓ 33%
Lansoprazole Rabeprazole Pantoprazole Esomeprazole	Rilpivirine (Edurant <sup>®</sup> ) should not be used in combination with proton pump inhibitors as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). This may result in loss of therapeutic effect of Rilpivirine (Edurant <sup>®</sup> ).				

### H<sub>2</sub>-RECEPTOR ANTAGONISTS

Famotidine*#	40 mg single dose taken 12 hours before rilpivirine	rilpivirine	↔	↓ 9%	NA
	40 mg single dose taken 2 hours before rilpivirine	rilpivirine	↓ 85%	↓ 76%	NA
	40 mg single dose taken 4 hours after rilpivirine	rilpivirine	↑ 21%	↑ 13%	NA



Cimetidine Nizatidine Ranitidine	The combination of Rilpivirine (Edurant <sup>®</sup> ) and H2-receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). H2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after Rilpivirine (Edurant <sup>®</sup> ).
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**ANTACIDS**

Antacids (e.g., aluminum or magnesium hydroxide, calcium carbonate)	The combination of Rilpivirine (Edurant <sup>®</sup> ) and antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). Antacids should only be administered either at least 2 hours before or at least 4 hours after Rilpivirine (Edurant <sup>®</sup> ).
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**NARCOTIC ANALGESICS**

Methadone*	60-100 mg q.d., individualized dose	R(-) methadone	↓ 14%	↓ 16%	↓ 22%
		S(+) methadone	↓ 13%	↓ 16%	↓ 21%

No dose adjustments are required when initiating co-administration of methadone with Rilpivirine (Edurant<sup>®</sup>). However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.

**HERBAL PRODUCTS**

St John's wort ( <i>Hypericum perforatum</i> )	Rilpivirine (Edurant <sup>®</sup> ) should not be used in combination with products containing St John's wort ( <i>Hypericum perforatum</i> ) as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of Rilpivirine (Edurant <sup>®</sup> ).
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**ANALGESICS**

Acetaminophen*# (paracetamol)	500 mg single dose	acetaminophen	↔	↔	NA
		rilpivirine	↔	↔	↑ 26%

No dose adjustment is required when Rilpivirine (Edurant<sup>®</sup>) is co-administered with acetaminophen (paracetamol).

**ESTROGEN-BASED CONTRACEPTIVES**

Ethinylestradiol*	0.035 mg q.d.	ethinylestradiol	↑ 17%	↔	↔
Norethindrone*	1 mg q.d.	norethindrone	↔	↔	↔

No dose adjustment is required for the concomitant use of Rilpivirine (Edurant<sup>®</sup>) and estrogen- and/or progesterone-based contraceptives.

**HMG CO-A REDUCTASE INHIBITORS**

Atorvastatin*#	40 mg q.d.	atorvastatin	↑ 35%	↔	↓ 15%
		rilpivirine	↓ 9%	↔	↔

No dose adjustment is required when Rilpivirine (Edurant<sup>®</sup>) is co-administered with an HMG Co-A reductase inhibitor.

Fluvastatin  
Lovastatin  
Pitavastatin  
Pravastatin  
Rosuvastatin  
Simvastatin

**PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITOR**

Sildenafil*#	50 mg single dose	sildenafil	↔	↔	NA
		rilpivirine	↔	↔	↔
Vardenafil	No dose adjustment is required when Rilpivirine (Edurant <sup>®</sup> ) is				
Tadalafil	co-administered with a PDE-5 inhibitor.				

\* The interaction between Rilpivirine (Edurant<sup>®</sup>) and the drug was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

# This interaction study has been performed with a dose higher than the recommended dose for Rilpivirine (Edurant<sup>®</sup>) assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of Rilpivirine (Edurant<sup>®</sup>) 25 mg q.d.

† This interaction study has been performed with a dose higher than the recommended dose for Rilpivirine (Edurant<sup>®</sup>).

***QT-Prolonging Drugs***

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicinal products that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg q.d. and 300 mg q.d.) have been shown to prolong the QTc interval of the electrocardiogram (see ***Pharmacodynamic Properties***). Rilpivirine (Edurant<sup>®</sup>) should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

**PREGNANCY, BREAST-FEEDING AND FERTILITY*****Contraception in Males and Females***

A trial to investigate the effect of Rilpivirine (Edurant<sup>®</sup>) when co-administered with oral contraceptives demonstrated that Rilpivirine (Edurant<sup>®</sup>) is unlikely to decrease the effectiveness of oral contraceptives. Rilpivirine (Edurant<sup>®</sup>) and estrogen- and/or progesterone-based contraceptives can be used together without dose adjustments (see ***Interactions with Other Medicinal Products and Other Forms of Interaction***).

***Pregnancy***

There are no well controlled clinical or pharmacokinetic studies with Rilpivirine (Edurant<sup>®</sup>) in pregnant women. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function (see ***Non-Clinical Information***). There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg q.d. (see ***Non-Clinical Information***).

To monitor maternal-fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established (<http://www.apregistry.com>). This is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products. For rilpivirine, sufficient first trimester exposures are available to allow detection of at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

Rilpivirine in combination with a background regimen was evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to rilpivirine as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks).

Virologic response was preserved throughout the trial period. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of rilpivirine in HIV-1 infected adults (see ***Pharmacokinetic Properties-Special Populations – Pregnancy and Postpartum***).

Rilpivirine (Edurant<sup>®</sup>) should be used during pregnancy only if the potential benefit justifies the potential risk.

### ***Breast-Feeding***

It is not known whether rilpivirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving Rilpivirine (Edurant<sup>®</sup>).

### ***Fertility***

No human data on the effect of rilpivirine on fertility are available. In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day, a dose of rilpivirine that showed maternal toxicity (see ***Non-Clinical Information***). This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg q.d.

## **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

Rilpivirine (Edurant<sup>®</sup>) has no or negligible influence on the ability to drive and use machines.

## **UNDESIRABLE EFFECTS**

### ***Adverse Reactions from Clinical Trials***

Throughout this section, adverse reactions are reported. Adverse reactions (ARs) are adverse events that were considered to be reasonably associated with the use of Rilpivirine (Edurant<sup>®</sup>) based on the comprehensive assessment of the available adverse event information. A causal relationship with Rilpivirine (Edurant<sup>®</sup>) cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety assessment is based on the week 96 pooled data from 1368 patients in the Phase III controlled trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in antiretroviral treatment-naïve HIV-1 infected adult patients, 686 of whom received Rilpivirine (Edurant<sup>®</sup>) (25 mg q.d.) (see ***Pharmacodynamic Properties***). The median duration of exposure for patients in the Rilpivirine (Edurant<sup>®</sup>) and efavirenz arms was 104.3 and 104.1 weeks, respectively. Most ARs occurred in the first 48 weeks of treatment.

In the Phase III controlled trials ECHO and THRIVE through 96 weeks, the most frequently reported adverse reactions (ARs) (> 2%) to Rilpivirine (Edurant<sup>®</sup>) that were at least grade 2 in severity were depression, headache, insomnia, transaminases increased and rash (see table 7 for the complete list of ARs).

The majority of the ARs reported during treatment with Rilpivirine (Edurant<sup>®</sup>) 25 mg once daily were grade 1 to 2 in severity. Grade 3 or 4 ARs were reported in 3.6% and 5.9% of the

Rilpivirine (Edurant<sup>®</sup>) and efavirenz treated patients, respectively. The most common (reported in more than 1 patient in the Rilpivirine (Edurant<sup>®</sup>) arm) grade 3 or 4 ARs were transaminases increased (1.6% in the Rilpivirine (Edurant<sup>®</sup>) arm and 2.9% in the efavirenz arm), depression (0.7% and 0.7%, respectively), abdominal pain (0.4% and 0.1%, respectively), dizziness (0.3% and 0.4%, respectively) and rash (0.3% and 0.6%, respectively). 1.7% of patients in the Rilpivirine (Edurant<sup>®</sup>) arm discontinued treatment due to ARs compared to 4.0% of patients in the efavirenz arm. In the Rilpivirine (Edurant<sup>®</sup>) arm, all ARs leading to discontinuation had an incidence < 0.5%. In the efavirenz arm, the most common ARs leading to discontinuation were rash (1.5%), transaminases increased (0.7%), depression (0.6%) and abnormal dreams (0.6%).

ARs of at least moderate intensity ( $\geq$  grade 2) reported in adult patients treated with Rilpivirine (Edurant<sup>®</sup>) are summarized in table 7. The ADRs are listed by system organ class (SOC) and frequency.

<b>Table 7: ARs of at least moderate intensity (<math>\geq</math> grade 2) reported in antiretroviral treatment-naïve HIV-1 infected adult patients treated with Rilpivirine (Edurant<sup>®</sup>)</b>			
<b>System Organ Class (SOC) Adverse reaction, %</b>	<b>Pooled data from the Week 96 analysis of the Phase III ECHO and THRIVE trials</b>		
	<b>Rilpivirine (Edurant<sup>®</sup>) + BR N=686</b>	<b>Efavirenz + BR N=682</b>	<b>Treatment Difference (95%CI)</b>
<b>Metabolism and nutrition disorders</b>			
Decreased appetite	1.2%	0.6%	0.6 (-0.4; 1.6)
<b>Psychiatric disorders</b>			
Depression	4.1%	3.2%	0.9 (-1.1; 2.8)
Insomnia	3.5%	3.5%	0 (-2.0; 1.9)
Abnormal dreams* <sup>†</sup>	1.6%	4.0%	-2.4 (-4.1; -0.6)
Sleep disorders	1.3%	0.9%	0.4 (-0.7; 1.5)
Depressed mood	0.4%	0.3%	0.1 (-0.5; 0.8)
<b>Nervous system disorders</b>			
Headache*	3.5%	3.8%	-0.3 (-2.3; 1.7)
Dizziness* <sup>#</sup>	1.0%	6.7%	-5.7 (-7.7; -3.7)
Somnolence	0.7%	1.3%	-0.6 (-1.7; 0.5)
<b>Gastrointestinal disorders</b>			
Abdominal pain	2.0%	1.9%	0.1 (-1.3; 1.6)
Nausea*	1.3%	2.8%	-1.5 (-3.0; 0)
Vomiting	1.0%	2.1%	-1.0 (-2.3; 0.3)
Abdominal discomfort	0.4%	0.1%	0.3 (-0.3; 0.9)
<b>Skin and subcutaneous tissue disorders</b>			
Rash* <sup>#</sup>	2.3%	9.5%	-7.2 (-9.7; -4.7)
<b>General disorders and administration site conditions</b>			
Fatigue	1.6%	2.1%	-0.4 (-1.9; 1.0)
<b>Investigations</b>			
Transaminases increased	2.8%	4.0%	-1.2 (-3.1; 0.7)

BR=background regimen; CI=confidence interval

N=total number of subjects per treatment group

\* Treatment comparison was pre-specified for these ARs (Fisher's Exact Test)

† p-value &lt; 0.01

# p-value &lt; 0.0001

No new ADR terms were identified in adult patients in the Phase III ECHO and THRIVE trials between 48 weeks and 96 weeks nor in the Phase IIb TMC278-C204 trial through 240 weeks.

### Laboratory Abnormalities

Selected treatment emergent clinical laboratory abnormalities (grade 3 or grade 4), reported in Rilpivirine (Edurant<sup>®</sup>)-treated patients, are shown in Table 8.

<b>Table 8: Selected treatment emergent laboratory abnormalities (grade 3 or grade 4) observed in antiretroviral treatment-naïve HIV-1 infected adult patients</b>			
<b>Laboratory parameter abnormality, %</b>	<b>DAIDS toxicity range</b>	<b>Pooled data from the week 96 analysis of the Phase III ECHO and THRIVE trials</b>	
		<b>Rilpivirine (Edurant<sup>®</sup>) + BR N=686</b>	<b>Efavirenz + BR N=682</b>
<b>HEMATOLOGY</b>			
Decreased hemoglobin	< 4.5 mmol/L < 7.4 g/dL	0.1%	0.6%
Decreased platelet count	< 49999/mm <sup>3</sup> < 49999 × 10 <sup>9</sup> /L	0.1%	0.3%
Decreased white blood cell count	< 1499/mm <sup>3</sup> < 1.499 giga/L	1.2%	1.0%
<b>BIOCHEMISTRY</b>			
Increased creatinine	> 1.8 × ULN	0.1%	0.1%
Increased AST	> 5.0 × ULN	2.3%	3.3%
Increased ALT	> 5.0 × ULN	1.6%	3.7%
Increased bilirubin	> 2.5 × ULN	0.7%	0.3%
Increased pancreatic amylase	> 2 × ULN	3.8%	4.8%
Increased lipase	> 3 × ULN	0.9%	1.6%
Increased total cholesterol (fasted)*	> 7.77 mmol/L > 300 mg/dL	0.1%	3.3%
Increased LDL cholesterol (fasted)*	≥ 4.91 mmol/L ≥ 191 mg/dL	1.5%	5.3%
Increased triglycerides (fasted)*	≥ 8.49 mmol/L ≥ 751 mg/dL	0.6%	3.3%

BR=background regimen; ULN=upper limit of normal

N=number of subjects per treatment group

\*  $p \leq 0.001$  according to Fisher's Exact test (difference in grade 3 plus 4 abnormalities between the two treatment groups).

Note: Percentages were calculated for the number of subjects with results for the analyte.

Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are presented in Table 9. The mean changes from baseline were smaller in the Rilpivirine (Edurant<sup>®</sup>) arm versus the efavirenz arm. The impact of such findings has not been demonstrated.

<b>Table 9: Lipid values, mean change from baseline</b>						
<b>Pooled data from the week 96 analysis of the Phase III ECHO and THRIVE trials</b>						
	<b>Rilpivirine (Edurant<sup>®</sup>) + BR N=686</b>			<b>Efavirenz + BR N=682</b>		
	<b>Baseline</b>	<b>Week 96</b>		<b>Baseline</b>	<b>Week 96</b>	
<b>Mean (95% CI)</b>	<b>Mean (mg/dL)</b>	<b>Mean (mg/dL)</b>	<b>Mean change* (mg/dL)</b>	<b>Mean (mg/dL)</b>	<b>Mean (mg/dL)</b>	<b>Mean change* (mg/dL)</b>
Total cholesterol (fasted) <sup>†</sup>	161	167	5	161	190	28
HDL-cholesterol (fasted) <sup>†</sup>	41	46	4	40	51	11
LDL-cholesterol (fasted) <sup>†</sup>	96	98	1	96	110	14
Triglycerides (fasted) <sup>†</sup>	124	117	-7	133	148	12

N=number of subjects per treatment group.

\* The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and week 96 values.

† p-value < 0.001, Wilcoxon rank-sum test for treatment comparison of change from baseline.

### *Immune Reconstitution Inflammatory Syndrome*

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reconstitution inflammatory syndrome). Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported in the context of immune reconstitution inflammatory syndrome (see **Special Warnings and Special Precautions for Use**).

### *Additional Information on Special Populations*

#### *Patients Co-Infected With Hepatitis B and/or Hepatitis C Virus*

In patients co-infected with hepatitis B or C virus receiving Rilpivirine (Edurant<sup>®</sup>), the incidence of hepatic enzyme elevation was higher than in patients receiving Rilpivirine (Edurant<sup>®</sup>) who were not co-infected. This observation was the same in the efavirenz arm. The pharmacokinetic exposure of rilpivirine in co-infected patients was comparable to that in patients without co-infection.

## **OVERDOSE**

There is no specific antidote for overdose with Rilpivirine (Edurant®). Human experience of overdose with Rilpivirine (Edurant®) is limited. Treatment of overdose with Rilpivirine (Edurant®) consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

## **INCOMPATIBILITIES**

Not applicable.

## **STORAGE CONDITIONS**

Store at temperatures not exceeding 30°C.  
Store in the original bottle in order to protect from light.  
Keep out of the sight and reach of children.

## **NATURE AND CONTENTS OF CONTAINER**

75 mL high density polyethylene (HDPE) bottle with a polypropylene (PP) child resistant closure and induction seal liner. Each carton contains one bottle of 30 film-coated tablets.

## **AVAILABILITY**

HDPE Plastic Bottle x 30's (1 bottle in a box)

## **INSTRUCTIONS FOR USE AND HANDLING**

No special requirements.

## **INSTRUCTIONS FOR DISPOSAL**

Any unused product or waste material should be disposed of in accordance with local requirements.

## **CAUTION**

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Patients must seek medical attention immediately at the first sign of any adverse drug reaction. For suspected adverse drug reaction, report to the FDA: [www.fda.gov.ph](http://www.fda.gov/ph).

Questions or comments? Email us at [Janssendrugsafety\\_Phil@its.jnj.com](mailto:Janssendrugsafety_Phil@its.jnj.com).

## **REGISTRATION NUMBER**

DR-XY43314

## **DATE OF FIRST AUTHORIZATION**

14 March 2014

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*Revision date: 22 August 2022 (based on CCDS v013, 23 August 2021)*