

# EDURANT<sup>®</sup>

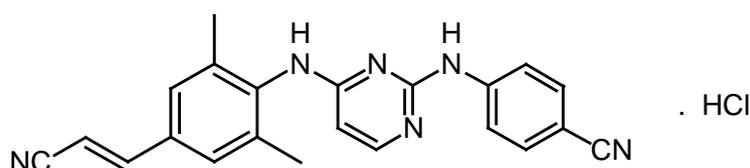
## rilpivirine

### PRODUCT INFORMATION

#### NAME OF THE MEDICINE

The chemical name of rilpivirine is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino-2-pyrimidinyl]amino]benzotrile monohydrochloride.

Rilpivirine hydrochloride has the following chemical structure:



Molecular formula: C<sub>22</sub>H<sub>18</sub>N<sub>6</sub>.HCl

Molecular weight: 402.88

CAS Registry Number: 700361-47-3

#### DESCRIPTION

Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type-1 (HIV-1).

Rilpivirine hydrochloride is a white to off-white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range, its pKa is 5.6 (pyrimidine moiety) and log P between 1-octanol and a phosphate solution (pH 7.0) is 4.86 (at 21°C).

EDURANT rilpivirine is available as 25 mg tablets. Each film-coated tablet contains rilpivirine hydrochloride equivalent to 25 mg rilpivirine. It also contains the following inactive ingredients: lactose monohydrate, croscarmellose sodium, povidone, polysorbate 20, silicified microcrystalline cellulose (a combination of microcrystalline cellulose and silicon dioxide), magnesium stearate, hypromellose, titanium dioxide, macrogol 3000 and glycerol triacetate. Each tablet contains 56 mg lactose monohydrate.

#### PHARMACOLOGY

##### Pharmacodynamics

###### 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  $\gamma$ .

### 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 2,510 to 10,830 nM (920 to 3,970 ng/ml), treatment of HIV-2 infection with rilpivirine 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 protease inhibitors: 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 patients*

For the resistance analysis, a broader definition of virologic failure was used than in the primary efficacy analysis. The definition of virologic failure used in the efficacy analysis of the Phase III studies was based on the time to loss of virologic failure (TLOVR) algorithm (see CLINICAL TRIALS section).

The broader definition of virologic failure used in the resistance analysis of the Phase III studies included patients who were defined as rebounders (had 2 consecutive viral load measurements < 50 copies/mL, followed by 2 consecutive viral load values ≥ 50 copies/mL), patients who stopped treatment while not suppressed (had 2 consecutive viral load measurements < 50 copies/mL and stopped treatment with a last observed on-treatment viral load value of ≥ 50 copies/mL) or patients who never suppressed (no confirmed viral load measurements < 50 copies/mL and an increase in viral load ≥ 0.5 log<sub>10</sub> copies/ml above the nadir, regardless of time of failure and reason for discontinuation).

In the week 48 pooled resistance analysis from the phase III trials, 62 (of a total of 72) virologic failures in the rilpivirine arm had resistance data at baseline and time of failure as compared to 28 (of a total of 39) virologic failures in the efavirenz arm. 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 the rilpivirine treatment, commonly in combination with the M184I substitution.

*More patients who failed virologically on EDURANT than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance.\**

In the week 96 pooled resistance analysis, lower rates of virologic failure were observed in the second 48 weeks than in the first 48 weeks of treatment. From the week 48 to the week 96 analysis, 24 (3.5%) and 14 (2.1%) additional virologic failures occurred in the rilpivirine and efavirenz arm, respectively. Of these virologic failures, 9 out of 24 and 4 out of 14 were in subjects with a baseline viral load < 100,000 copies/ml, respectively.

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 patients with virologic failure on rilpivirine 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 resistance analysis of the Phase III trials (ECHO and THRIVE), 42 out of 86 subjects with virologic failure on rilpivirine showed treatment-emergent resistance to rilpivirine (genotypic analysis). In these patients, phenotypic cross-resistance to other NNRTIs was noted as follows: etravirine 32/42, efavirenz 30/42, and nevirapine 16/42. In patients with a baseline viral load ≤ 100,000 copies/ml, 9 out of 27 patients with virologic failure on rilpivirine showed treatment-emergent resistance to rilpivirine (genotypic analysis), with the following frequency of phenotypic cross-resistance: etravirine 4/9, efavirenz 3/9, and nevirapine 1/9. In rilpivirine virologic failures with resistance to rilpivirine (genotypic analysis), phenotypic cross-resistance to etravirine, efavirenz, and nevirapine was observed in, respectively, 28, 27, and 15 of 30 patients with baseline viral load > 100,000 copies/mL.

### Effects on electrocardiogram

The effect of rilpivirine at the recommended dose of 25 mg q.d. on the QTcF interval was evaluated in a randomised, 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 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 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 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.

## Pharmacokinetics

The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in adult antiretroviral treatment naïve HIV 1 infected patients. Exposure to rilpivirine 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 is unknown.

### *Effect of food on absorption*

The exposure to rilpivirine was approximately 40% lower when rilpivirine 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 was taken with only a protein rich nutritional drink, exposures were 50% lower than when taken with a meal (see DOSAGE and ADMINISTRATION).

### 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. It is possible that different populations of patients have faster or slower rilpivirine metabolism because of the various isoenzymes within the CYP3A system.

### *Elimination*

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 faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.

### Additional information on special populations

#### *Paediatric population*

The pharmacokinetics of rilpivirine in paediatric patients are under investigation. Dosing recommendations for paediatric patients cannot be made due to insufficient data (see PRECAUTIONS and DOSAGE and ADMINISTRATION).

#### *Elderly*

Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years, with only 2 patients aged above 65 years) evaluated. No dose adjustment of rilpivirine is required in elderly patients. EDURANT should be used with caution in this population.

#### *Gender*

Population pharmacokinetic analysis in HIV infected patients showed no clinically relevant differences in the pharmacokinetics of rilpivirine 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.

### *Hepatic impairment*

Rilpivirine is primarily metabolised 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 mean steady-state exposure to rilpivirine was higher in patients with mild hepatic impairment (27% higher for  $C_{max}$  and 47% higher for AUC) than in healthy controls. However, rilpivirine exposure in patients with moderate hepatic impairment (5% lower for  $C_{max}$  and 5% higher for AUC) was similar to healthy controls. The mean apparent elimination half-life of rilpivirine was longer in patients with mild (81 hours versus 61 hours respectively) and moderate (91 hours versus 56 hours, respectively) hepatic impairment compared to healthy controls. No dose adjustment is required in patients with mild hepatic impairment. No dose adjustment is suggested but caution is advised in patients with moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child Pugh score C). Therefore, EDURANT is not recommended in patients with severe hepatic impairment (see PRECAUTIONS and DOSAGE AND 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.

### *Renal impairment*

The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. EDURANT has mainly been studied in patients with normal renal function. No dose adjustment is required for patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease, EDURANT should be used with caution. In patients with severe renal impairment or end stage renal disease, the combination of EDURANT with a strong CYP3A inhibitor (e.g., ritonavir boosted HIV protease inhibitor) should only be used if the benefit outweighs the risk (see DOSAGE and ADMINISTRATION). As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

## **CLINICAL TRIALS**

The evidence of efficacy of rilpivirine is based on the analyses of 96 week data from 2 randomised, double-blinded, 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)] according to the time to loss of virologic response (TLOVR) algorithm was evaluated in patients receiving rilpivirine 25 mg q.d. in addition to a BR versus patients receiving efavirenz 600 mg q.d. in addition to a BR. The TLOVR imputation algorithm was used to define confirmed virologic response i.e., two consecutive viral load values below the threshold are needed to count as a response. Non-responders or failures were defined as those patients who never responded i.e. never achieved 2 consecutive viral load values of < 50 copies/ml, or who were a rebounder (patients responded, then has two consecutive viral load values above the threshold value of 50 copies/ml), or discontinued prematurely.

Antiretroviral treatment-naïve HIV-1 infected patients were enrolled who had a plasma HIV-1 RNA  $\geq$  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, randomisation was stratified by screening viral load. In THRIVE, randomisation was stratified by screening viral load and by N(t)RTI BR.

This analysis included 690 patients in ECHO (346 on rilpivirine and 344 on efavirenz, respectively) and 678 patients in THRIVE (340 on rilpivirine and 338 on efavirenz, respectively) 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 arm and the efavirenz arm. Table 1 displays selected demographic and baseline disease characteristics of the patients in the rilpivirine and efavirenz arms. 53.3% of patients in the rilpivirine arm and 48.2% of patients in the efavirenz arm were in the  $\leq 100,000$  copies/ml baseline viral load category. The proportion of patients with baseline viral load  $> 100,000$  copies/ml was 46.7% and 51.8% in the rilpivirine arm and efavirenz arm, respectively.

<b>Table 1: Demographic and baseline disease characteristics of antiretroviral treatment-naïve HIV-1 infected adult patients in the ECHO and THRIVE trials (pooled analysis)</b>		
	<b>Pooled data from the ECHO and THRIVE trials</b>	
	<b>rilpivirine + 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 plasma HIV-1 RNA (range), copies/ml	90,450.0 (156 – 20,800,000)	104,500.0 (1,010 – 4,550,000)
Median baseline CD4+ cell count (range), x 10 <sup>6</sup> cells/l	249 (1-888)	260 (1-1137)
Percentage of patients 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 EDURANT and patients treated with efavirenz from the pooled data from the ECHO and THRIVE trials. Similar efficacy for rilpivirine was seen in each trial demonstrating non-inferiority to efavirenz, i.e. estimated treatment difference (95%CI) was -0.4 (-5.9; 5.2) and 3.5 (-1.7; 8.8) at week 48 (primary) and -3.2 (-9.4; 3.1) and 2.4 (-3.6; 8.4) at week 96, in ECHO and THRIVE respectively.

The response rate (confirmed undetectable viral load < 50 HIV-1 RNA copies/ml) at week 96 was comparable between the rilpivirine arm and the efavirenz arm (77.6% for both arms, estimated treatment difference [95%CI] is -0.4% [-4.6%; 3.8%] ). The incidence of virologic failure was higher in the rilpivirine arm than the efavirenz arm at week 96 (11.5% for rilpivirine and 5.9% for efavirenz) ; 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 EDURANT arm. Most of these discontinuations occurred in the first 48 weeks of treatment.

**Table 2: Virologic Outcome of Randomized Treatment in the ECHO and THRIVE Trials (Pooled Analysis at Week 48 (primary) and Week 96; ITT-TLOVR\*)**

n/N (%)	Outcome at Week 48		Outcome at Week 96	
	rilpivirine + BR N=686	efavirenz + BR N=682	rilpivirine + BR N=686	efavirenz + BR N=682
Confirmed Undetectable Viral Load (< 50 HIV-1 RNA copies/ml) §#	578/686 (84.3)	561/682 (82.3)	532/686 (77.6)	529/682 (77.6)
Virologic Failure†	62/686 (9.0)	33/682 (4.8)	(79/686) 11.5	40/682 (5.9)
Death	1/686 (0.1)	3/682 (0.4)	(1/686) 0.1	6/682 (0.9)
Discontinued due to adverse event (AE)	14/686 (2.0)	46/682 (6.7)	(26/686) 3.8	52/682 (7.6)
Discontinued for non-AE reason¶	31/686 (4.5)	39/682 (5.7)	(48/686) 7.0	55/682 (8.1)

N = number of patients per treatment group

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

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

# Estimated 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-value < 0.0001 (non-inferiority at 12% margin) from logistic regression model, including stratification factors and study.

† Includes patients 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

The mean change from baseline in CD4+ cell count was +192 x 10<sup>6</sup> cells/l in the rilpivirine arm and +176 x 10<sup>6</sup> cells/l in the efavirenz arm in the pooled analysis of the ECHO and THRIVE trials [estimated treatment difference (95% CI): 17.9 (2.1; 33.6)] at week 48. At week 96, the mean change from baseline in CD4+ cell count was +228 x 10<sup>6</sup> cells/l in the EDURANT arm (n=685) and +219 x 10<sup>6</sup> cells/l in the efavirenz arm (n=682) 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) at 48 weeks and at 96 weeks and virologic failure by baseline viral load, by baseline CD4 count, and by background NRTIs (pooled data from the ECHO and THRIVE trials)</b>								
	<b>Outcome at Week 48</b>				<b>Outcome at Week 96</b>			
	<b>EDURANT + BR N=686</b>		<b>Efavirenz + BR N=682</b>		<b>EDURANT + BR N=686</b>		<b>Efavirenz + BR N=682</b>	
	<b>N</b>	<b>n (%)</b>	<b>N</b>	<b>n (%)</b>	<b>N</b>	<b>n (%)</b>	<b>N</b>	<b>n (%)</b>
<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>								
≤ 100,000	368	332 (90.2%)	330	276 (83.6%)	368	309 (84.0%)	329	263 (79.9%)
> 100,000	318	246 (77.4%)	352	285 (81.0%)	318	223 (70.1%)	353	266 (75.4%)
<b>Virologic Failure<sup>†</sup> by baseline plasma viral load (copies/ml)</b>								
≤ 100,000	368	14 (3.8%)	330	11 (3.3%)	368	21 (5.7%)	329	12 (3.6%)
> 100,000	318	48 (15.1%)	352	22 (6.3%)	318	58 (18.2%)	353	28 (7.9%)
<b>Proportion of patients with HIV-1 RNA &lt; 50 copies/ml at week 48* and at week 96* by baseline CD4 count (x 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 (x 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%)

N=number of patients per treatment group

n=number of observations

\* Imputations according to the TLOVR algorithm.

† Includes patients 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).

At week 96, response rates (< 50 copies/ml [TLOVR]) in the pooled phase III trial population were 84.0% in the EDURANT arm and 79.9% in the efavirenz arm in patients with a baseline viral load  $\leq$  100,000 copies/ml versus 70.1% and 75.4%, respectively, in patients with a baseline viral load > 100,000 copies/ml. The proportion of virologic failures according to TLOVR in the pooled phase III trial population was 5.7% in the EDURANT arm and 3.6% in the efavirenz arm, for patients with a baseline viral load  $\leq$  100,000 copies/ml. The proportion of virologic failures was higher for patients with a baseline viral load > 100,000 copies/ml, especially in the EDURANT arm (18.2% EDURANT-treated patients vs. 7.9% efavirenz-treated patients).

The incidence of emergence of N(t)RTI and NNRTI RAMs in the virologic failures (according to the resistance analysis criteria) was lower in the  $\leq$  100,000 copies/ml category than in the > 100,000 copies/ml category. This difference was observed in both treatment groups but with a lower incidence of emerging mutations in the efavirenz arm. This difference in incidence of emerging mutations between treatment groups was greater for N(t)RTI mutations. At week 48, among patients with baseline viral load  $\leq$  100,000 copies/ml (16 patients in the rilpivirine arm and 12 patients in the efavirenz arm), 7 and 6 rilpivirine virologic failures and 2 and 5 efavirenz virologic failures had emerging N(t)RTI RAMs and NNRTI RAMs, respectively. Among patients with baseline viral load > 100,000 copies/ml (46 patients in the rilpivirine arm and 16 patients in the efavirenz arm), 35 and 33 rilpivirine virologic failures and 7 and 10 efavirenz virologic failures had emerging N(t)RTI RAMs and NNRTI RAMs, respectively. The less frequent emergence of N(t)RTI and NNRTI RAMs in the  $\leq$  100,000 copies/ml category, as compared to the > 100,000 copies/ml category of both treatment groups, as well as the lower incidence of emerging N(t)RTI mutations in efavirenz virologic failures as compared to rilpivirine virologic failures were confirmed in the week 96 pooled phase III analyses..

Study TMC278-C204 was a randomised, 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 [rilpivirine doses blinded] up to 96 weeks, followed by a long-term, open label part. In the open label part of the trial, patients originally randomised to one of the 3 doses of rilpivirine were all treated with rilpivirine 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 rilpivirine 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 rilpivirine 25 mg and  $160 \times 10^6$  cells/l in patients receiving efavirenz.

Of those patients who were responders at week 96, 151/204 (74%) of patients receiving rilpivirine remained with undetectable viral load (< 50 HIV-1 RNA copies/ml) at week 240 compared to 51/63 (81%) of patients receiving efavirenz. There were no safety concerns identified in the week 240 analyses.

## INDICATIONS

EDURANT, 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 with viral load  $\leq$  100,000 copies/ml at baseline.

This indication is based on Week 48 safety and efficacy analyses from 2 randomised double-blind, controlled Phase III trials in treatment-naïve adult patients and on Week 96 safety and efficacy analyses from the Phase IIb trial TMC278-C204 in treatment-naïve adult patients (see CLINICAL TRIALS section).

## CONTRAINDICATIONS

Hypersensitivity to rilpivirine or to any of the excipients.

EDURANT 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 EDURANT (See INTERACTIONS WITH OTHER MEDICINES):

- 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*).

## PRECAUTIONS

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 to 96 weeks, patients treated with EDURANT with a baseline viral load > 100,000 HIV-1 RNA copies/ml had a greater risk of virologic failure (18.2% with EDURANT versus 7.9% efavirenz arm) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/ml (5.7% with EDURANT versus 3.6% efavirenz arm). The greater risk of virologic failure for patients in the EDURANT arm was observed in the first 48 weeks of these trials while low rates of virologic failure treatment arms were observed from week 48 to week 96 (see CLINICAL TRIALS section). Patients with a baseline viral load > 100,000 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 EDURANT than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance. This information should be taken into consideration when initiating therapy with EDURANT (see CLINICAL TRIALS section).

As with other antiretroviral medicinal products, resistance testing should guide the use of EDURANT.

### Interactions with medicinal products

Caution should be given to prescribing rilpivirine with medicinal products that may reduce the exposure of rilpivirine. For information on interactions with medicinal products (see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES).

### *Medicines that suppress gastric acid*

Use of proton pump inhibitors is contraindicated as significant decreases in EDURANT plasma concentrations may occur (see CONTRAINDICATIONS).

The combination of EDURANT and H<sub>2</sub>-receptor antagonists or antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). H<sub>2</sub>-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EDURANT and antacids should only be administered at least 2 hours before or at least 4 hours after EDURANT (see INTERACTIONS WITH OTHER MEDICINES).

#### Fat redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long term consequences of these events are currently unknown. A causal relationship has not been established (see ADVERSE EFFECTS). A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age and with drug-related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution.

#### Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including rilpivirine. 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 jirovecii* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment (see ADVERSE EFFECTS). Autoimmune disorders such as Graves' disease 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 ADVERSE EFFECTS).

#### Hepatic impairment

There is limited information regarding the use of EDURANT in patients with mild or moderate hepatic impairment, resulting in unexpected variability in the available data. EDURANT has not been studied in patients with severe hepatic impairment. Therefore, EDURANT is not recommended in patients with severe hepatic impairment (see Pharmacokinetics and DOSAGE and ADMINISTRATION). EDURANT should be used with caution in patients with moderate hepatic impairment (see Pharmacokinetics and DOSAGE and ADMINISTRATION).

#### CYP3A Metabolism

Rilpivirine is a CYP3A substrate. It is possible that different populations of patients have faster or slower rilpivirine metabolism because of the various isoenzymes within the CYP3A system.

#### **Effects on 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. 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.

#### **Use in Pregnancy**

##### **Category B1**

There are no adequate and well controlled clinical or pharmacokinetic studies with rilpivirine in pregnant women. Placental transfer of rilpivirine or its metabolites from dam to fetus was demonstrated in rats. Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no clinically relevant teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 71 times higher than the exposure in humans at the recommended dose of 25 mg q.d.

EDURANT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

### **Use in Lactation**

It is not known whether rilpivirine is secreted in human milk. In nonclinical studies, rilpivirine was detected in the plasma of suckling rats following maternal dosing. 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 EDURANT.

### **Children**

Treatment with EDURANT is not recommended in paediatric patients (<18 years) due to insufficient data in this patient population.

### **Elderly**

There is limited information regarding the use of EDURANT in patients > 65 years of age (see Pharmacokinetics). No dose adjustment of EDURANT is required in elderly patients. EDURANT should be used with caution in this population (see Pharmacokinetics and DOSAGE and ADMINISTRATION).

### **Carcinogenicity**

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.).

### **Genotoxicity**

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.

## INTERACTIONS WITH OTHER MEDICINES

### Medicinal products that affect rilpivirine exposure

Rilpivirine is primarily metabolised by cytochrome P450 CYP3A, and medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-administration of EDURANT and medicinal products that induce CYP3A may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of rilpivirine. Co-administration of EDURANT and medicinal products that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

Co administration of EDURANT with medicinal products that increase gastric pH may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of rilpivirine.

### Medicinal products that are affected by the use of rilpivirine

EDURANT 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.

Established and theoretical interactions with selected antiretrovirals and non antiretroviral medicinal products are listed in Table 4 and Table 5, respectively.

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 4: 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 EDURANT 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 EDURANT (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 EDURANT 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 EDURANT.				
<b>HIV NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)</b>					
NNRTIs (delavirdine, efavirenz, etravirine, nevirapine)	It is not recommended to co-administer EDURANT with NNRTIs.				
<b>HIV PROTEASE INHIBITORS (PIs) - with co-administration of low dose ritonavir</b>					
Darunavir/ritonavir* <sup>#</sup>	800/100 mg q.d.	darunavir	↔	↔	↓ 11%
		rilpivirine	↑ 79%	↑ 130%	↑ 178%

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

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

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

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

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

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

#### CCR5 ANTAGONISTS

Maraviroc No clinically relevant drug-drug interaction is expected when EDURANT is co-administered with maraviroc.

#### HIV INTEGRASE STRAND TRANSFER INHIBITORS

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

No dose adjustment is required when EDURANT is co administered with raltegravir.

#### OTHER ANTIVIRAL AGENTS

Ribavirin No clinically relevant drug-drug interaction is expected when EDURANT is co-administered with ribavirin.

<i>Telaprevir*</i>	750 mg q8h	telaprevir	↓ 3%	↓ 5%	↓ 11%
		rilpivirine	↑ 49%	↑ 78%	↑ 93%

Concomitant use of EDURANT with telaprevir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required for either drug when EDURANT is co administered with telaprevir.

\* The interaction between 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 EDURANT assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of EDURANT 25 mg q.d.

**Table 5: 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>					
<i>Digoxin*</i>	0.5 mg singledose	digoxin	↔	↔	NA
No dose adjustment is required when EDURANT is co-administered with digoxin.					

<b>ANTIDIABETICS</b>					
<i>Metformin</i> *	850 mg single dose	metformin	↔	↔	NA
No dose adjustment is required when EDURANT is co-administered with metformin.					
<b>ANTICONVULSANTS</b>					
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	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 EDURANT.				
<b>AZOLE ANTIFUNGAL AGENTS</b>					
Ketoconazole* <sup>#</sup>	400 mg q.d.	ketoconazole	↔	↓ 24%	↓ 66%
		rilpivirine	↑ 30%	↑ 49%	↑ 76%
Fluconazole Itraconazole Posaconazole Voriconazole	Concomitant use of 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 EDURANT is co-administered with azole antifungal agents.				
<b>ANTIMYCOBACTERIALS</b>					
<i>Rifabutin</i> * <sup>#</sup>	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 EDURANT with rifabutin may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT. Throughout co-administration of EDURANT with rifabutin, the EDURANT dose should be increased from 25 mg once daily to 50 mg once daily. When rifabutin co-administration is stopped, the EDURANT dose should be decreased to 25 mg once daily.					
<i>Rifampicin</i> * <sup>#</sup>	600 mg q.d.	rifampicin	↔	↔	NA
		25-desacetyl-rifampicin	↔	↓ 9%	NA
		rilpivirine	↓ 69%	↓ 80%	↓ 89%
Rifapentine	EDURANT 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 EDURANT.				
<b>MACROLIDE ANTIBIOTICS</b>					
Clarithromycin Erythromycin Troleandomycin	Concomitant use of EDURANT with clarithromycin, erythromycin and troleandomycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.				
<b>GLUCOCORTICOIDS</b>					
Dexamethasone (systemic)	EDURANT 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 EDURANT. Alternatives should be considered, particularly for long-term use.				
<b>PROTON PUMP INHIBITORS</b>					
Omeprazole* <sup>#</sup>	20 mg q.d.	omeprazole	↓ 14%	↓ 14%	NA
		rilpivirine	↓ 40%	↓ 40%	↓ 33%

Lansoprazole Rabeprazole Pantoprazole Esomeprazole	EDURANT 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 EDURANT.
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## H<sub>2</sub>-RECEPTOR ANTAGONISTS

Famotidine* <sup>#</sup>	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 EDURANT and H <sub>2</sub> -receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (gastric pH increase). H <sub>2</sub> -receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EDURANT.				

## ANTACIDS

Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate)	The combination of EDURANT 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 EDURANT.				
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## NARCOTIC ANALGESICS

Methadone*	60-100 mg q.d., individualised dose	R(-) methadone	↓ 14%	↓ 16%	↓ 22%
		S(+) methadone	↓ 13%	↓ 16%	↓ 21%
No dose adjustments are required when initiating co-administration of methadone with EDURANT. 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> )	EDURANT should not be used in combination with products containing St John's wort as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT.				
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## ANALGESICS

Acetaminophen* <sup>#</sup> (paracetamol)	500 mg single dose	acetaminophen ↔ rilpivirine ↔	↔ ↔	↔ ↔	NA ↑ 26%
No dose adjustment is required when EDURANT is co-administered with acetaminophen (paracetamol).					

## ESTROGEN-BASED CONTRACEPTIVES

Ethinylestradiol* Norethindrone*	0.035 mg q.d. 1 mg q.d.	ethinylestradiol norethindrone	↑ 17% ↔	↔ ↔	↔ ↔
No dose adjustment is required for the concomitant use of EDURANT and estrogen- and/or progesterone-based contraceptives.					

## HMG CO-A REDUCTASE INHIBITORS

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

Fluvastatin	No dose adjustment is required when EDURANT is co-administered with an HMG Co-A reductase inhibitor.				
Lovastatin					
Pitavastatin					
Pravastatin					
Rosuvastatin					
Simvastatin					

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

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Sildenafil**	50 mg single dose	sildenafil	↔	↔	NA
		rilpivirine	↔	↔	↔
Vardenafil	No dose adjustment is required when EDURANT is co-administered with a PDE-5 inhibitor.				
Tadalafil					

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\* The interaction between rilpivirine 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 EDURANT assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg q.d.

† This interaction study has been performed with a dose higher than the recommended dose for EDURANT.

#### QT prolonging drugs

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and other medicinal products that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, suprathreshold doses of rilpivirine (75 mg q.d. and 300 mg q.d.) have been shown to prolong the QTc interval of the electrocardiogram (see Pharmacodynamics). EDURANT at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. EDURANT should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

## Effect on Ability to Drive or Operate Machinery

EDURANT has no or negligible influence on the ability to drive and use machines.

## ADVERSE EFFECTS

### Adverse Effects from Clinical Trials

The safety assessment is based on the 96 week 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 EDURANT (25 mg q.d.) (see CLINICAL TRIALS section). The median duration of exposure for patients in the EDURANT and efavirenz arms was 104.3 and 104.1 weeks, respectively. Most adverse drug reactions (ADRs) occurred in the first 48 weeks of treatment.

In the phase III controlled trials ECHO and THRIVE to 96 weeks, the most frequently reported ADRs ( $\geq 2\%$ ) that were at least grade 2 in severity were depression, headache, insomnia, transaminases increased and rash (see table 6 for the complete list of ADRs).

The majority of the ADRs reported during treatment with EDURANT 25 mg once daily were grade 1 to 2 in severity. Grade 3 or 4 ADRs were reported in 3.6% and 5.9% of the EDURANT and efavirenz treated patients, respectively. The most common (reported in more than 1 patient in the EDURANT arm) grade 3 or 4 ADRs were transaminases increased (1.6% in the EDURANT 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 EDURANT arm discontinued treatment due to ADRs compared to 4.0% of patients in the efavirenz arm. In the EDURANT arm, all ADRs leading to discontinuation had an incidence  $< 0.5\%$ . In the efavirenz arm, the most common ADRs leading to discontinuation were rash (1.5%), transaminases increased (0.7%), depression (0.6%) and abnormal dreams (0.6%).

The most common ADRs were identified in the system organ classes (SOC) of nervous system disorders (25.7% in the EDURANT arm and 42.8% in the efavirenz arm), psychiatric disorders (23.6% in the EDURANT arm and 26.4% in the efavirenz arm) and gastrointestinal disorders (24.1% in the EDURANT arm and 22.1% in the efavirenz arm). The difference between EDURANT and the efavirenz arms observed in the SOC nervous system disorders was mainly due to the difference in dizziness experienced by patients.

ADRs of at least moderate intensity ( $\geq$  grade 2) reported in adult patients treated with EDURANT are summarised in Table 6. The ADRs are listed by system organ class (SOC) and frequency. Selected treatment emergent laboratory abnormalities, considered as ADRs, are included in Table 7.

<b>Table 6: ADRs of at least moderate intensity (<math>\geq</math> grade 2) reported in antiretroviral treatment-naïve HIV-1 infected adult patients treated with rilpivirine</b>		
<b>System Organ Class (SOC) Adverse drug reaction, %</b>	<b>Pooled data from the week 96 analysis of the phase III ECHO and THRIVE trials</b>	
	<b>rilpivirine + BR N=686</b>	<b>efavirenz + BR N=682</b>
<b>Skin and subcutaneous tissue disorders</b>	<b>2.3%</b>	<b>9.5%</b>
Rash*#	2.3%	9.5%
<b>Psychiatric disorders</b>	<b>9.3%</b>	<b>9.7%</b>
Depression	4.1%	3.2%
Insomnia	3.5%	3.5%
Abnormal dreams*†	1.6%	4.0%
Sleep disorders	1.3%	0.9%
Depressed mood	0.4%	0.3%
<b>Nervous system disorders</b>	<b>4.5%</b>	<b>10.7%</b>
Headache*	3.5%	3.8%
Dizziness*#	1.0%	6.7%
Somnolence	0.7%	1.3%
<b>Gastrointestinal disorders</b>	<b>3.8%</b>	<b>5.6%</b>
Abdominal pain	2.0%	1.9%
Nausea*	1.3%	2.8%
Vomiting	1.0%	2.1%
Abdominal discomfort	0.4%	0.1%
<b>Metabolism and nutrition disorders</b>	<b>1.2%</b>	<b>0.6%</b>
Decreased appetite	1.2%	0.6%
<b>General disorders and administration site conditions</b>	<b>1.6%</b>	<b>2.1%</b>
Fatigue	1.6%	2.1%
<b>Investigations</b>	<b>2.8%</b>	<b>4.0%</b>
Transaminases increased	2.8%	4.0%

BR=background regimen; CI=confidence interval

N=total number of patients per treatment group; ND=not determined.

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

† p-value < 0.01

# p-value < 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), considered as ADRs, reported in EDURANT-treated patients are shown in Table 7.

<b>Table 7: Selected treatment emergent laboratory abnormalities (grade 3 or grade 4) observed in antiretroviral treatment-naïve HIV-1 infected adult patients</b>			
Laboratory parameter abnormality, n/N (%)	DAIDS toxicity range	Pooled data from the week 96 analysis of the phase III ECHO and THRIVE trials	
		rilpivirine + BR N=686	efavirenz + BR N=682
<b>HEMATOLOGY</b>			
Decreased hemoglobin	< 4.5 mmol/L < 74 g/L	1/685 (0.1%)	4/669 (0.6%)
Decreased platelet count	< 49999/mm <sup>3</sup> < 49999 x 10 <sup>9</sup> /L	1/684 (0.1%)	2/667 (0.3%)
Decreased white blood cell count	< 1499/mm <sup>3</sup> < 1.499 10 <sup>9</sup> /L	8/685 (1.2%)	7/669 (1.0%)
<b>BIOCHEMISTRY</b>			
Increased creatinine	> 1.8 x ULN	1/685 (0.1%)	1/670 (0.1%)
Increased AST	> 5.0 x ULN	16/685 (2.3%)	22/669 (3.3%)
Increased ALT	> 5.0 x ULN	11/685 (1.6%)	25/670 (3.7%)
Increased bilirubin	> 2.5 x ULN	5/685 (0.7%)	2/670 (0.3%)
Increased pancreatic amylase	> 2 x ULN	26/685 (3.8%)	32/670 (4.8%)
Increased lipase	> 3 x ULN	6/685 (0.9%)	11/670 (1.6%)
Increased total cholesterol (fasted)*	> 7.77 mmol/L > 300 mg/dl	1/685 (0.1%)	22/669 (3.3%)
Increased LDL cholesterol (fasted)*	≥ 4.91 mmol/L ≥ 191 mg/dl	10/685 (1.5%)	35/666 (5.3%)
Increased Triglycerides (fasted)*	≥ 8.49 mmol/L ≥ 751 mg/dl	4/685 (0.6%)	22/669 (3.3%)

BR=background regimen; ULN=upper limit of normal

N=number of patients 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 patients with results for the analyte.

### Adrenal Function

In the pooled phase III trials, at Week 96, the overall mean change from baseline in basal cortisol was -19.1 nmol/L in the EDURANT group, and -0.6 nmol/L in the efavirenz group. At Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the EDURANT group (+18.4 ± 8.36 nmol/L) than in the efavirenz group (+54.1 ± 7.24 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 96 were within the normal range (>248nmol/L for basal and >500 nmol/L for stimulated values respectively). Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency.

### Serum Creatinine

In the pooled phase III trials, serum creatinine increased minimally over 96 weeks of treatment with EDURANT. In the overall population, small mean increases from baseline in serum creatinine values were observed at the first on treatment assessment (week 2) for the rilpivirine-treated patients, which remained relatively stable until week 24 when further mean increases from baseline were observed until Week 96 (ranging from 5.3 mmol/L at week 2 to a maximum mean increase from baseline of 9.7 mmol/L at Week 96). For efavirenz-treated patients, serum creatinine values fluctuated around baseline up to Week 48 with a maximum mean increase from baseline of 3.5 mmol/L at Week 96. In patients who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in patients with normal renal function. These changes are not considered to be clinically relevant and no subject discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

### Serum lipids

Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are presented in Table 8. The mean changes from baseline were smaller in the EDURANT arm versus the efavirenz arm. The impact of such findings has not been demonstrated.

<b>Table 8: Lipid values, mean change from baseline<sup>#</sup></b>								
<b>Pooled data from the week 96 analysis of the phase III ECHO and THRIVE Trials</b>								
<b>rilpivirine + BR</b>					<b>efavirenz + BR</b>			
	<b>N</b>	<b>Baseline</b>	<b>Week 96</b>		<b>N</b>	<b>Baseline</b>	<b>Week 96</b>	
Mean		<b>Mean (mmol/L)</b>	<b>Mean (mmol/L)</b>	<b>Mean change* (mmol/L)</b>		<b>Mean (mmol/L)</b>	<b>Mean (mmol/L)</b>	<b>Mean change* (mmol/L)</b>
Total cholesterol (fasted) <sup>†</sup>	546	4.2	4.3	0.1	507	4.1	4.8	0.7
HDL-cholesterol (fasted) <sup>†</sup>	545	1.1	1.2	0.1	505	1.0	1.3	0.3
LDL-cholesterol (fasted) <sup>†</sup>	543	2.5	2.5	0.0	503	2.5	2.8	0.4
Triglycerides (fasted) <sup>†</sup>	546	1.4	1.3	-0.1	507	1.5	1.6	0.1

N=number of patients 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

# Excludes subjects who received lipid lowering agents during the treatment period

### Lipodystrophy

Combination antiretroviral therapy (CART) has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see PRECAUTIONS).

### 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) (see PRECAUTIONS). Autoimmune disorders such as Graves' disease have also been reported in the context of immune reconstitution inflammatory syndrome (see PRECAUTIONS).

### 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 EDURANT, the incidence of hepatic enzyme elevation was higher than in patients receiving EDURANT 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.

## **DOSAGE AND ADMINISTRATION**

EDURANT must always be given in combination with other antiretroviral medicinal products.

### Adults

The recommended dose of EDURANT is one 25 mg tablet once daily taken orally with a meal (see Pharmacokinetics).

### Elderly

There is limited information regarding the use of EDURANT in patients > 65 years of age (see Pharmacokinetics and PRECAUTIONS). No dose adjustment of EDURANT is required in elderly patients (see Pharmacokinetics). EDURANT should be used with caution in this population (see Pharmacokinetics and PRECAUTIONS).

### Paediatric Population

The safety and efficacy of EDURANT in adolescents and children are under investigation (see Pharmacokinetics). No data are available patients <18 years of age. Treatment with EDURANT is not recommended in these populations.

### Dose adjustment

*For patients concomitantly receiving rifabutin, the EDURANT 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 EDURANT dose should be decreased to 25 mg once daily, taken with a meal (see INTERACTIONS WITH OTHER MEDICINES).\**

### Hepatic impairment

No dose adjustment of EDURANT is required in patients with mild or moderate hepatic impairment (Child Pugh score A or B). EDURANT has not been studied in patients with severe hepatic impairment (Child Pugh score C). Therefore, EDURANT is not recommended in patients with severe hepatic impairment. EDURANT should be used with caution in patients with moderate hepatic impairment (see Pharmacokinetics and PRECAUTIONS).

### Renal impairment

Rilpivirine has mainly been studied in patients with normal renal function. No dose adjustment of EDURANT is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, EDURANT should be used with caution. In patients with severe renal impairment or end-stage renal disease, the combination of EDURANT with a strong CYP3A inhibitor (e.g., ritonavir-boosted HIV protease inhibitor) should only be used if the benefit outweighs the risk (see Pharmacokinetics).

### Timing of dosing

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

## OVERDOSAGE

There is no specific antidote for overdose with EDURANT. Human experience of overdose with rilpivirine is limited. Treatment of overdose with rilpivirine 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. Administration of activated charcoal may be used to aid in removal of unabsorbed active substance. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

## PRESENTATION AND STORAGE CONDITIONS

EDURANT 25 mg tablets are 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.

EDURANT tablets are provided in a high density polyethylene (HDPE) bottle with a polypropylene (PP) child resistant closure and induction seal liner. One bottle contains 30 tablets.

Store below 30°C. Store in the original bottle. Protect from light.

## NAME AND ADDRESS OF SPONSOR

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Tibotec, a division of JANSSEN-CILAG Pty Ltd

## POISON SCHEDULE OF THE DRUG

Prescription Only Medicine

**Date of inclusion on the ARTG:** 23 December 2011

**Date of most recent amendment:** 16 December 2014

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Please note change(s) presented as *\*italicised text* in Product Information.