

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EDURANT safely and effectively. See full prescribing information for EDURANT.

EDURANT (rilpivirine) [Tablets]

Initial U.S. Approval: 2011

INDICATIONS AND USAGE

EDURANT is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated:

In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients.

The following points should be considered when initiating therapy with EDURANT:

- More EDURANT treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy.
- The observed virologic failure rate in EDURANT treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz.
- More subjects treated with EDURANT developed lamivudine/emtricitabine associated resistance compared to efavirenz. (1, 12.4, 14)

DOSAGE AND ADMINISTRATION

25 mg (one 25 mg tablet) taken once daily with a meal. (2)

DOSAGE FORMS AND STRENGTHS

25 mg tablets (3)

CONTRAINDICATIONS

Co-administration of EDURANT is contraindicated with drugs where significant decreases in rilpivirine plasma concentrations may occur, which may result in loss of virologic response and possible resistance and cross-resistance. (4)

WARNINGS AND PRECAUTIONS

- Caution should be given to prescribing EDURANT with drugs that may reduce the exposure of rilpivirine. (5.1)

- Caution should be given to prescribing EDURANT with drugs with a known risk of Torsade de Pointes. (5.1)
- Depressive Disorders: Severe depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported. Immediate medical evaluation is recommended for severe depressive disorders. (5.2)
- Patients may develop redistribution/accumulation of body fat (5.3) or immune reconstitution syndrome. (5.4)

ADVERSE REACTIONS

The most common adverse drug reactions to EDURANT (incidence > 2%) of at least moderate to severe intensity (≥ Grade 2) were depression, insomnia, headache and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Tibotec Therapeutics at 1-877-REACH-TT or 1-877-732-2488 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- EDURANT should not be used in combination with NNRTIs. (7)
- Co-administration of EDURANT with drugs that induce or inhibit CYP3A4 may affect the plasma concentrations of rilpivirine. (7)
- Co-administration of EDURANT with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine. (7)
- Refer to the Full Prescribing Information for other drugs that should not be co-administered with EDURANT and for other drugs that may require a change in dose or regimen. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk. Pregnancy registry available. (8.1)
- Nursing Mothers: Mothers should not breastfeed due to the potential for HIV transmission. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: May 2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EDURANT™, in combination with other antiretroviral agents, 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 Week 48 safety and efficacy analyses from 2 randomized, double-blind, active controlled, Phase 3 trials in treatment-naïve subjects and Week 96 safety and efficacy analyses from a Phase 2b trial in treatment-naïve subjects [*see Clinical Studies (14.1)*].

The following points should be considered when initiating therapy with EDURANT:

- More EDURANT treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy [*see Clinical Studies (14.1)*].
- The observed virologic failure rate in EDURANT treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz [*see Clinical Pharmacology (12.4)*].
- More subjects treated with EDURANT developed lamivudine/emtricitabine associated resistance compared to efavirenz [*see Clinical Pharmacology (12.4)*].

2 DOSAGE AND ADMINISTRATION

The recommended dose of EDURANT is one 25 mg tablet once daily taken orally with a meal [*see Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

25 mg 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. Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of rilpivirine.

4 CONTRAINDICATIONS

EDURANT should not be co-administered with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to EDURANT or to the class of NNRTIs [*see also Drug Interactions (7) and Clinical Pharmacology (12.3)*]:

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

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

Caution should be given to prescribing EDURANT with drugs that may reduce the exposure of rilpivirine [*see Contraindications (4), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

In healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram [*see Drug Interactions (7) and Clinical Pharmacology (12.2)*]. EDURANT should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes.

5.2 Depressive Disorders

The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with EDURANT. During the Phase 3 trials (N = 1368), the incidence of depressive disorders (regardless of causality, severity) reported among EDURANT (n = 686) or efavirenz (n = 682) was 8% and 6%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both EDURANT and efavirenz. The incidence of discontinuation due to depressive disorders among EDURANT or efavirenz was 1% in each arm. Suicide attempt was reported in 2 subjects in the EDURANT arm while suicide ideation was reported in 1 subject in the EDURANT arm and in 3 subjects in the efavirenz arm. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to EDURANT, and if so, to determine whether the risks of continued therapy outweigh the benefits.

5.3 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.

5.4 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including EDURANT. 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.

6 ADVERSE REACTIONS

The following adverse drug reaction (ADR) is discussed in greater detail in other sections of the package insert:

- Depressive Disorders [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

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 pooled data from 1368 patients in the Phase 3 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 once daily) [see *Clinical Studies* (14.1)]. The median duration of exposure for patients in the EDURANT arm and efavirenz arm was 55.7 and 55.6 weeks, respectively. The proportion of subjects who discontinued treatment with EDURANT or efavirenz due to ADR, regardless of severity, was 2% and 4%, respectively. The most common ADRs leading to discontinuation were psychiatric disorders: 10 (1%) subjects in the EDURANT arm and 15 (2%) subjects in the efavirenz arm. Rash led to discontinuation in 1 (0.1%) subject in the EDURANT arm and 10 (1.5%) subjects in the efavirenz arm.

Common Adverse Drug Reactions

Clinical ADRs of at least moderate intensity (\geq Grade 2) reported in at least 2% of adult subjects are presented in Table 1. Selected treatment-emergent laboratory abnormalities are included in Table 2.

Table 1: Selected Treatment-Emergent Adverse Drug Reactions of at least Moderate Intensity* (Grades 2-4) Occurring in at Least 2% of Antiretroviral Treatment-Naïve HIV-1 Infected Adult Subjects-(Week 48 analysis)		
System Organ Class, Preferred Term, %	Pooled Data from the TMC278-C209 and TMC278-C215 Trials	
	EDURANT + BR N=686	Efavirenz + BR N=682
Gastrointestinal Disorders		
Nausea	1%	3%
Abdominal pain	1%	2%
Vomiting	1%	2%
General Disorders and Administration Site Conditions		
Fatigue	1%	2%
Nervous System Disorders		
Headache	3%	3%
Dizziness	1%	7%
Psychiatric Disorders		
Depressive disorders [†]	4%	3%
Insomnia	3%	3%
Abnormal dreams	1%	4%
Skin and Subcutaneous Tissue Disorders		
Rash	3%	11%
N=total number of subjects per treatment group, BR=background regimen		
* Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).		
[†] includes adverse drug reactions reported as depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicide ideation		

There were no additional ADR terms identified in adult subjects in the Phase 2b TMC278-C204 trial through 192 weeks. The incidence of adverse events in the Phase 2b TMC278-C204 trial was similar to the Phase 3 trials.

Less Common Adverse Drug Reactions

Treatment-emergent ADRs of at least moderate intensity (\geq Grade 2) occurring in less than 2% of antiretroviral treatment-naïve subjects receiving EDURANT are listed below by Body System. Some of these events have been included because of investigator's assessment of potential causal relationship and were considered serious or have been reported in more than 1 subject treated with EDURANT.

Gastrointestinal Disorders: diarrhea, abdominal discomfort

Hepatobiliary Disorders: cholecystitis, cholelithiasis

Metabolism and Nutrition Disorders: decreased appetite

Nervous System: somnolence

Psychiatric Disorder: sleep disorders, anxiety

Renal and Urinary Disorders: glomerulonephritis membranous, glomerulonephritis mesangioproliferative

Laboratory Abnormalities in Treatment-Naïve Subjects

The percentage of subjects treated with EDURANT or efavirenz in the Phase 3 trials with selected treatment-emergent clinical laboratory abnormalities (Grades 1 to 4), representing worst Grade toxicity are shown in Table 2.

Table 2: Selected Treatment-Emergent Changes in Laboratory Parameters (Grades 1 to 4) Observed in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects			
Laboratory Parameter Abnormality, (%)	DAIDS Toxicity Range	Pooled Data from the TMC278-C209 and TMC278-C215 Trials	
		EDURANT + BR N=686	Efavirenz + BR N=682
BIOCHEMISTRY			
Increased Creatinine			
Grade 1	≥ 1.1- ≤ 1.3 x ULN	5%	<1%
Grade 2	> 1.3- ≤ 1.8 x ULN	<1%	<1%
Grade 3	> 1.8- ≤ 3.4 x ULN	0	0
Grade 4	> 3.4 x ULN	0	<1%
Increased AST			
Grade 1	≥ 1.25- ≤ 2.5 x ULN	12%	16%
Grade 2	> 2.5- ≤ 5.0 x ULN	3%	6%
Grade 3	> 5.0- ≤ 10.0 x ULN	2%	2%
Grade 4	> 10.0 x ULN	<1%	<1%
Increased ALT			
Grade 1	≥ 1.25- ≤ 2.5 x ULN	15%	18%
Grade 2	> 2.5-≤ 5.0 x ULN	4%	6%
Grade 3	> 5.0- ≤ 10.0 x ULN	<1%	2%
Grade 4	> 10.0 x ULN	<1%	1%
Increased Total Bilirubin			
Grade 1	≥ 1.1-≤ 1.5 x ULN	5%	<1%
Grade 2	> 1.5-≤ 2.5 x ULN	2%	<1%
Grade 3	> 2.5-≤ 5.0 x ULN	<1%	<1%
Grade 4	> 5.0 x ULN	0	0
Increased Total Cholesterol (fasted)			
Grade 1	5.18-6.19 mmol/L 200-239 mg/dL	14%	28%
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	5%	16%
Grade 3	> 7.77 mmol/L > 300 mg/dL	<1%	2%
Increased LDL Cholesterol (fasted)			
Grade 1	3.37-4.12 mmol/L 130-159 mg/dL	12%	23%

Laboratory Parameter Abnormality, (%)	DAIDS Toxicity Range	Pooled Data from the TMC278-C209 and TMC278-C215 Trials	
		EDURANT + BR N=686	Efavirenz + BR N=682
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	5%	11%
Grade 3	> 4.91 mmol/L > 191 mg/dL	<1%	4%
Increased Triglycerides (fasted)			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	2%	2%
Grade 3	8.49-13.56 mmol/L 751-1,200 mg/dL	< 1%	2%
Grade 4	> 13.56 mmol/L > 1,200 mg/dL	0	< 1%
BR = background regimen; ULN = upper limit of normal N = number of subjects per treatment group Note: Percentages were calculated versus the number of subjects in ITT.			

Adrenal Function

In the pooled Phase 3 trials, at Week 48, the overall mean change from baseline in basal cortisol showed a decrease of -13.1 nmol/L in the EDURANT group, and an increase of +9.0 nmol/L in the efavirenz group. At Week 48, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the EDURANT group (+16.5 ± 6.14 nmol/L) than in the efavirenz group (+58.1 ± 6.66 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 48 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency.

Serum Creatinine

Increases in serum creatinine occurred within the first four weeks of treatment and remained stable through 48 weeks. A mean change of 0.09 mg/dL (range: -0.20 mg/dL to 0.62 mg/dL) was observed after 48 weeks of treatment. In subjects who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects 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 3.

Table 3: Lipid Values, Mean Change from Baseline*								
	Pooled data from the TMC278-C209 and TMC278-C215 trials							
	EDURANT + BR				Efavirenz + BR			
	N	Baseline	Week 48		N	Baseline	Week 48	
Mean (95% CI)	Mean (mg/dL)	Mean (mg/dL)	Mean Change[†] (mg/dL)		Mean (mg/dL)	Mean (mg/dL)	Mean Change[†] (mg/dL)	
Total Cholesterol (fasted)	584	161	163	2	549	160	187	27
HDL-cholesterol (fasted)	582	41	45	4	548	40	50	10
LDL-cholesterol (fasted)	580	96	95	-1	547	95	109	15
Triglycerides (fasted)	584	121	115	-6	549	131	140	9

N = number of subjects per treatment group
* Excludes subjects who received lipid lowering agents during the treatment period
[†] The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values

Subjects co-infected with hepatitis B and/or hepatitis C virus

In subjects co-infected with hepatitis B or C virus receiving EDURANT, the incidence of hepatic enzyme elevation was higher than in subjects receiving EDURANT who were not co-infected. This observation was the same in the efavirenz arm. The pharmacokinetic exposure of rilpivirine in co-infected subjects was comparable to that in subjects without co-infection.

7 DRUG INTERACTIONS

[See also *Contraindications (4)* and *Clinical Pharmacology (12.3)*.]

Rilpivirine is primarily metabolized by cytochrome P450 (CYP)3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-administration of EDURANT and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. Co-administration of EDURANT and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Co-administration of EDURANT with drugs that increase gastric pH may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs.

EDURANT at a dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of drugs metabolized by CYP enzymes.

Table 4 shows the established and other potentially significant drug interactions based on which alterations in dose or regimen of EDURANT and/or co-administered drug may be recommended. Drugs that are not recommended for co-administration with EDURANT are also included in Table 4.

Table 4: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [See <i>Clinical Pharmacology</i> (12.3)]		
Concomitant Drug Class: Drug Name	Effect on Concentration of Rilpivirine or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine* [†]	↔ rilpivirine ↔ didanosine	No dose adjustment is required when EDURANT is co-administered with didanosine. Didanosine is to 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).
HIV-Antiviral Agents: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
NNRTI (delavirdine) Other NNRTIs (efavirenz, etravirine, nevirapine)	↑ rilpivirine ↔ delavirdine ↓ rilpivirine ↔ other NNRTIs	It is not recommended to co-administer EDURANT with delavirdine and other NNRTIs.
HIV-Antiviral Agents: Protease Inhibitors (PIs)-Boosted (i.e., with co-administration of low-dose ritonavir) or Unboosted (i.e., without co-administration of low-dose ritonavir)		
darunavir/ritonavir* [†]	↑ rilpivirine ↔ boosted darunavir	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* [†]	↑ rilpivirine ↔ boosted lopinavir	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)	↑ rilpivirine ↔ boosted PI	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.
unboosted PIs (atazanavir, fosamprenavir, indinavir, nelfinavir)	↑ rilpivirine ↔ unboosted PI	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.
Other Agents		
Antacids: antacids (e.g., aluminum or magnesium hydroxide, calcium carbonate)	↔ rilpivirine (antacids taken at least 2 hours before or at least 4 hours after rilpivirine)	The combination of EDURANT and antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). Antacids should only be administered either at least 2 hours before or at least 4 hours after EDURANT.

	↓ rilpivirine (concomitant intake)	
Azole Antifungal Agents: fluconazole itraconazole ketoconazole* [†] posaconazole voriconazole	↑ rilpivirine ↓ ketoconazole	Concomitant use of EDURANT with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No rilpivirine dose adjustment is required when EDURANT is co-administered with azole antifungal agents. Clinically monitor for breakthrough fungal infections when azole antifungals are co-administered with EDURANT.
H₂-Receptor Antagonists: cimetidine famotidine* [†] nizatidine ranitidine	↔ rilpivirine (famotidine taken 12 hours before rilpivirine or 4 hours after rilpivirine) ↓ rilpivirine (famotidine taken 2 hours before rilpivirine)	The combination of EDURANT and H ₂ -receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). H ₂ -receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EDURANT.
Macrolide antibiotics: clarithromycin, erythromycin, troleandomycin	↑ rilpivirine ↔ 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.
Narcotic Analgesics: methadone*	↓ R(-) methadone ↓ S(+) methadone	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.
<p>↑ = increase, ↓ = decrease, ↔ = no change * The interaction between EDURANT 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 EDURANT 25 mg once daily.</p>		

In addition to the drugs included in Table 4, the interaction between EDURANT and the following drugs was evaluated in clinical studies and no dose adjustment is needed for either drug [see *Clinical Pharmacology (12.3)*]: acetaminophen, atorvastatin, chlorzoxazone, ethinylestradiol, norethindrone, sildenafil and tenofovir disoproxil fumarate. No clinically relevant drug-drug interaction is expected when EDURANT is co-administered with maraviroc, raltegravir, ribavirin or the NRTIs abacavir, emtricitabine, lamivudine, stavudine and zidovudine.

QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and drugs that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram [see *Clinical Pharmacology (12.2)*]. EDURANT should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

No adequate and well-controlled or pharmacokinetic studies of EDURANT use in pregnant women have been conducted. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with rilpivirine during pregnancy and lactation, there were no toxicologically significant effects on developmental endpoints. 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 once daily. EDURANT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to EDURANT, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats and their offspring indicate that rilpivirine was present in rat milk. It is not known whether rilpivirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving EDURANT.**

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of EDURANT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of EDURANT in elderly patients reflecting the greater frequency of decreased renal and hepatic function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

No dose adjustment of EDURANT is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. EDURANT has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) [*see Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. However, in patients with severe renal impairment or end-stage renal disease, rilpivirine should be used with caution and with increased monitoring for adverse effects, as rilpivirine concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis [*see Clinical Pharmacology (12.3)*].

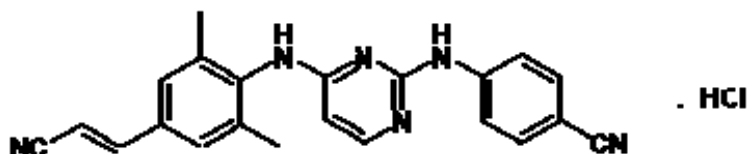
10 OVERDOSAGE

There is no specific antidote for overdose with EDURANT. Human experience of overdose with EDURANT is limited. Treatment of overdose with 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. If indicated, elimination of unabsorbed active substance may be achieved by gastric lavage. Administration of activated charcoal may also 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.

11 DESCRIPTION

EDURANT (rilpivirine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). EDURANT is available as a white to off-white, film-coated, round, biconvex, 6.4 mm tablet for oral administration. Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of rilpivirine.

The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6 \cdot HCl$ and its molecular weight is 402.88. Rilpivirine hydrochloride has the following structural formula:



Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

Each EDURANT tablet also contains the inactive ingredients croscarmellose sodium, magnesium stearate, lactose monohydrate, povidone K30, polysorbate 20 and silicified microcrystalline cellulose. The tablet coating contains hypromellose 2910 6 mPa.s, lactose monohydrate, PEG 3000, titanium dioxide and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rilpivirine is an antiviral drug [*see Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

Effects on Electrocardiogram

The effect of EDURANT at the recommended dose of 25 mg once daily 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. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction was 4.8 (8.2) milliseconds (i.e., below the threshold of clinical concern).

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of EDURANT 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) milliseconds, respectively. Steady-state administration of EDURANT 75 mg once daily and 300 mg once daily resulted in a mean steady-state C_{max} approximately 2.6-fold and 6.7-fold, respectively, higher than the mean C_{max} observed with the recommended 25 mg once daily dose of EDURANT [*see Warnings and Precautions (5.1)*].

12.3 Pharmacokinetics

Pharmacokinetics in Adults

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

Table 5: Population Pharmacokinetic Estimates of Rilpivirine 25 mg once daily in Antiretroviral Treatment-Naïve HIV-1-Infected Subjects (Pooled Data from Phase 3 Trials through Week 48)	
Parameter	Rilpivirine 25 mg once daily N = 679
AUC _{24h} (ng•h/mL)	
Mean ± Standard Deviation	2397 ± 1032
Median (Range)	2204 (482 - 8601)
C _{0h} (ng/mL)	
Mean ± Standard Deviation	80 ± 37
Median (Range)	74 (1 - 300)

Absorption and Bioavailability

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours. The absolute bioavailability of EDURANT is unknown.

Effects of Food on Oral Absorption

The exposure to rilpivirine was approximately 40% lower when EDURANT was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high-fat high-caloric meal (928 kcal). When EDURANT 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.

Elimination

The terminal elimination half-life of rilpivirine is approximately 50 hours. After single dose oral administration of ¹⁴C-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

Hepatic Impairment

Rilpivirine is primarily metabolized and eliminated by the liver. In a study comparing 8 subjects with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment. EDURANT has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) [*see Use in Specific Populations (8.6)*].

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

Population pharmacokinetic analysis indicated that rilpivirine exposure was similar in HIV-1 infected subjects with mild renal impairment relative to HIV-1 infected subjects with normal renal function. No dose adjustment is required in patients with mild renal impairment. There is limited or no information regarding the pharmacokinetics of rilpivirine in patients with moderate or severe renal impairment or in patients with end-stage renal disease, and rilpivirine concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction. The potential impact is not expected to be of clinical relevance for HIV-1-infected subjects with moderate renal impairment, and no dose adjustment is required in these patients. Rilpivirine should be used with caution and with increased monitoring for adverse effects in patients with severe renal impairment or end-stage renal disease. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis [*see Use in Specific Populations (8.7)*].

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.

Pediatric Patients

The pharmacokinetics and dosing recommendations of rilpivirine in pediatric patients have not been established [*see Use in Specific Populations (8.4)*].

Drug Interactions

[*See also Contraindications (4) and Drug Interactions (7).*]

Rilpivirine is primarily metabolized by cytochrome P450 (CYP)3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-administration of EDURANT and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance. Co-administration of EDURANT and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Co-administration of EDURANT with drugs that increase gastric pH may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine and to the class of NNRTIs.

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.

Drug interaction studies were performed with EDURANT and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. The effects of co-administration of other drugs on the C_{max} , AUC, and C_{min} values of rilpivirine are summarized in Table 6 (effect of other drugs on EDURANT). The effect of co-administration of EDURANT on the C_{max} , AUC, and C_{min} values of other drugs are summarized in Table 7 (effect of EDURANT on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 6: Drug Interactions: Pharmacokinetic Parameters for <u>Rilpivirine</u> in the Presence of Co-administered Drugs						
Co-administered Drug	Dose/Schedule		N	Mean Ratio of <u>Rilpivirine</u> Pharmacokinetic Parameters With/Without Co-administered Drug (90% CI); No Effect = 1.00		
	Co-administered Drug	Rilpivirine		C _{max}	AUC	C _{min}
Co-Administration With Protease Inhibitors (PIs)						
Darunavir/ ritonavir	800/100 mg q.d.	150 mg q.d. [†]	14	1.79 (1.56-2.06)	2.30 (1.98-2.67)	2.78 (2.39-3.24)
Lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	150 mg q.d. [†]	15	1.29 (1.18-1.40)	1.52 (1.36-1.70)	1.74 (1.46-2.08)
Co-Administration With Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[<u>t</u>]RTIs)						
Didanosine	400 mg q.d. delayed release capsules taken 2 hours before rilpivirine	150 mg q.d. [†]	21	1.00 (0.90-1.10)	1.00 (0.95-1.06)	1.00 (0.92-1.09)
Tenofovir disoproxil fumarate	300 mg q.d.	150 mg q.d. [†]	16	0.96 (0.81-1.13)	1.01 (0.87-1.18)	0.99 (0.83-1.16)
Co-Administration With Drugs other than Antiretrovirals						
Acetaminophen	500 mg single dose	150 mg q.d. [†]	16	1.09 (1.01-1.18)	1.16 (1.10-1.22)	1.26 (1.16-1.38)
Atorvastatin	40 mg q.d.	150 mg q.d. [†]	16	0.91 (0.79-1.06)	0.90 (0.81-0.99)	0.90 (0.84-0.96)
Chlorzoxazone	500 mg single dose	150 mg q.d. [†]	16	1.17 (1.08-1.27)	1.25 (1.16-1.35)	1.18 (1.09-1.28)
Ethinylestradiol/ Norethindrone	0.035 mg q.d./ 1 mg q.d.	25 mg q.d.	15	↔*	↔*	↔*
Famotidine	40 mg single dose taken 12 hours before rilpivirine	150 mg single dose [†]	24	0.99 (0.84-1.16)	0.91 (0.78-1.07)	N.A.
Famotidine	40 mg single dose taken 2 hours before rilpivirine	150 mg single dose [†]	23	0.15 (0.12-0.19)	0.24 (0.20-0.28)	N.A.
Famotidine	40 mg single dose taken 4 hours after rilpivirine	150 mg single dose [†]	24	1.21 (1.06-1.39)	1.13 (1.01-1.27)	N.A.
Ketoconazole	400 mg q.d.	150 mg q.d. [†]	15	1.30 (1.13-1.48)	1.49 (1.31-1.70)	1.76 (1.57-1.97)
Methadone	60-100 mg q.d., individualised dose	25 mg q.d.	12	↔*	↔*	↔*
Omeprazole	20 mg q.d.	150 mg q.d. [†]	16	0.60 (0.48-0.73)	0.60 (0.51-0.71)	0.67 (0.58-0.78)
Rifabutin	300 mg q.d.	150 mg q.d. [†]	16	0.65 (0.58-0.74)	0.54 (0.50-0.58)	0.51 (0.48-0.54)
Rifampin	600 mg q.d.	150 mg q.d. [†]	16	0.31 (0.27-0.36)	0.20 (0.18-0.23)	0.11 (0.10-0.13)
Sildenafil	50 mg single dose	75 mg q.d. [†]	16	0.92 (0.85-0.99)	0.98 (0.92-1.05)	1.04 (0.98-1.09)

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increase; ↓ = decrease; ↔ = no change; q.d. = once daily; b.i.d. = twice daily
* comparison based on historic controls
† This interaction study has been performed with a dose higher than the recommended dose for EDURANT (25 mg once daily) assessing the maximal effect on the co-administered drug.

Table 7: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of EDURANT

Co-administered Drug	Dose/Schedule		N	Mean Ratio of <u>Co-administered Drug</u> Pharmacokinetic Parameters With/Without EDURANT (90% CI); No effect = 1.00		
	Co-administered Drug	Rilpivirine		C _{max}	AUC	C _{min}
Co-Administration With Protease Inhibitors (PIs)						
Darunavir/ ritonavir	800/100 mg q.d.	150 mg q.d. [†]	15	0.90 (0.81-1.00)	0.89 (0.81-0.99)	0.89 (0.68-1.16)
Lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	150 mg q.d. [†]	15	0.96 (0.88-1.05)	0.99 (0.89-1.10)	0.89 (0.73-1.08)
Co-Administration With Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)						
Didanosine	400 mg q.d. delayed release capsules taken 2 hours before rilpivirine	150 mg q.d. [†]	13	0.96 (0.80-1.14)	1.12 (0.99-1.27)	N.A.
Tenofovir disoproxil fumarate	300 mg q.d.	150 mg q.d. [†]	16	1.19 (1.06-1.34)	1.23 (1.16-1.31)	1.24 (1.10-1.38)
Co-Administration With Drugs other than Antiretrovirals						
Acetaminophen	500 mg single dose	150 mg q.d. [†]	16	0.97 (0.86-1.10)	0.92 (0.85-0.99)	N.A.
Atorvastatin	40 mg q.d.	150 mg q.d. [†]	16	1.35 (1.08-1.68)	1.04 (0.97-1.12)	0.85 (0.69-1.03)
2-hydroxy-atorvastatin			16	1.58 (1.33-1.87)	1.39 (1.29-1.50)	1.32 (1.10-1.58)
4-hydroxy-atorvastatin			16	1.28 (1.15-1.43)	1.23 (1.13-1.33)	N.A.
Chlorzoxazone	500 mg single dose	150 mg q.d. [†]	16	0.98 (0.85-1.13)	1.03 (0.95-1.13)	N.A.

Ethinylestradiol	0.035 mg q.d.	25 mg q.d.	17	1.17 (1.06-1.30)	1.14 (1.10-1.19)	1.09 (1.03-1.16)
Norethindrone	1 mg q.d.		17	0.94 (0.83-1.06)	0.89 (0.84-0.94)	0.99 (0.90-1.08)
Ketoconazole	400 mg q.d.	150 mg q.d. [†]	14	0.85 (0.80-0.90)	0.76 (0.70-0.82)	0.34 (0.25-0.46)
R(-) methadone	60-100 mg q.d., individualised dose	25 mg q.d.	13	0.86 (0.78-0.95)	0.84 (0.74-0.95)	0.78 (0.67-0.91)
S(+) methadone			13	0.87 (0.78-0.97)	0.84 (0.74-0.96)	0.79 (0.67-0.92)
Omeprazole	20 mg q.d.	150 mg q.d. [†]	15	0.86 (0.68-1.09)	0.86 (0.76-0.97)	N.A.
Rifampin	600 mg q.d.	150 mg q.d. [†]	16	1.02 (0.93-1.12)	0.99 (0.92-1.07)	N.A.
25-desacetyl-rifampin			16	1.00 (0.87-1.15)	0.91 (0.77-1.07)	N.A.
Sildenafil	50 mg single dose	75 mg q.d. [†]	16	0.93 (0.80-1.08)	0.97 (0.87-1.08)	N.A.
N-desmethyl-sildenafil			16	0.90 (0.80-1.02)	0.92 (0.85-0.99)	N.A.

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increase; ↓ = decrease; ↔ = no change; q.d. = once daily ; b.i.d. = twice daily
[†] This interaction study has been performed with a dose higher than the recommended dose for EDURANT (25 mg once daily) assessing the maximal effect on the co-administered drug.

12.4 Microbiology

Mechanism of Action

Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1) and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α , β and γ .

Antiviral Activity in Cell Culture

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC₅₀ value for HIV-1_{IIIB} of 0.73 nM (0.27 ng/mL). Rilpivirine demonstrated limited activity in cell culture against HIV-2 with a median EC₅₀ value of 5220 nM (range 2510 to 10830 nM) (920 to 3970 ng/mL).

Rilpivirine demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC₅₀ values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/ml) and was less active against group O primary isolates with EC₅₀ values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/ml).

The antiviral activity of rilpivirine was not antagonistic when combined with the NNRTIs efavirenz, etravirine or nevirapine; the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir or tipranavir; the fusion inhibitor enfuvirtide; the CCR5 co-receptor antagonist maraviroc, or the integrase strand transfer 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 frequently observed amino acid substitutions that emerged and conferred decreased phenotypic susceptibility to rilpivirine included: L100I, K101E, V106I and A, V108I, E138K and G, Q, R, V179F and I, Y181C and I, V189I, G190E, H221Y, F227C and M230I and L.

In Treatment-Naïve Subjects

In the pooled resistance analysis from the Phase 3 Studies C209 and C215, the emergence of resistance among subjects was greater in the EDURANT arm compared to the efavirenz arm (see Table 8). In the combined studies, 41% (38/92) of the virologic failures in the rilpivirine arms had genotypic and phenotypic resistance to rilpivirine compared to 25% (15/60) of the virologic failures in the efavirenz arms who had genotypic and phenotypic resistance to efavirenz. Moreover, resistance to a background drug (emtricitabine, lamivudine, tenofovir, abacavir or zidovudine) emerged in 48% (44/92) of the virologic failures in the rilpivirine arms compared to 15% (9/60) in the efavirenz arms.

Emerging NNRTI substitutions in the rilpivirine virologic failures included V90I, K101E/P/T, E138K/G, V179I/L, Y181I/C, V189I, H221Y, F227C/L and M230L, which were associated with a rilpivirine phenotypic fold change range of 2.6 - 621. The E138K substitution emerged most frequently on rilpivirine treatment commonly in combination with the M184I substitution. The emtricitabine and lamivudine resistance-associated substitutions M184I or V and the tenofovir resistance-associated substitutions K65R or N emerged more frequently in rilpivirine virologic failures compared to efavirenz virologic failures (see Table 8).

Table 8. Proportion of Frequently Emergent Reverse Transcriptase Substitutions in Virologic Failures from the Combined Phase 3 Studies		
	C209 and C215 N = 1368	
	Rilpivirine N = 686	EFV Control N = 682
Virologic Failures (As-Treated)	92/652 (14%)	60/604 (10%)
Evaluable Post-Baseline Resistance Data	75	37
Emergent NNRTI Substitutions in Virologic Failures with Post-Baseline Data		
V90I	12% (9/75)	0
K101E/P/T	19% (14/75)	3% (1/37)
K103N	0	32% (12/37)
E138K/G	36% (27/75)	0
E138K+ M184I*	27% (20/75)	0
V179I/D/L	5% (4/75)	3% (1/37)
Y181C/I	9% (7/75)	0
V189I	8% (6/75)	3% (1/37)
H221Y	8% (6/75)	0
Emergent NRTI Substitutions in Virologic Failures with Post-Baseline Data		
M184I or V	53% (40/75)	22% (8/37)
K65R/N	9% (7/75)	5% (2/37)
* This combination of NRTI and NNRTI substitutions is a subset of those with the E138K		

Cross-Resistance

Site-Directed NNRTI Mutant Virus

Cross-resistance has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I and Y181V conferred 52-fold, 15-fold and 12-fold decreased susceptibility to rilpivirine, respectively. The combination of E138K and M184I showed 6.7-fold reduced susceptibility to rilpivirine compared to 2.8-fold for E138K alone. The K103N substitution did not show reduced susceptibility to rilpivirine. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave decreased susceptibility to rilpivirine (fold change range of 3.7 - 554) in 38% and 66% of mutants, respectively.

Treatment-naïve HIV-1-infected subjects

Considering all of the available cell culture and clinical data, any of the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, H221Y, F227C, M230I or M230L.

Cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure and development of rilpivirine resistance. In the pooled analyses of the Phase 3 clinical trials, 38 rilpivirine virologic failure subjects had evidence of rilpivirine resistance. Of these subjects, 89% (n = 34) were resistant to etravirine and efavirenz, and 63% (n = 24) were resistant to nevirapine. In the efavirenz arm, none of the 15 efavirenz-resistant virologic failures were resistant to etravirine at failure. Subjects experiencing virologic failure on EDURANT developed more NNRTI resistance-associated substitutions conferring more cross-resistance to the NNRTI class and had a higher likelihood of cross-resistance to all NNRTIs in the class than subjects who failed on efavirenz.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

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. In rats, there were no drug related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. 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 absence and presence of a metabolic activation system in the *in vitro* Ames reverse mutation assay and the *in vitro* clastogenicity mouse lymphoma assay. Rilpivirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Impairment of 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 once daily.

14 CLINICAL STUDIES

14.1 Treatment-Naïve Subjects

The evidence of efficacy of EDURANT is based on the analyses of 48-week data from 2 randomized, double-blinded, active controlled, Phase 3 trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) and from a 96-week (with extension to 192 weeks) randomized, active-controlled, dose-comparison Phase 2b trial in antiretroviral treatment-naïve adults. Antiretroviral treatment-naïve HIV-1 infected subjects enrolled in the Phase 3 trials had a plasma HIV-1 RNA \geq 5000 copies/mL and were screened for susceptibility to N(t)RTI and for absence of specific NNRTI RAMs. The Phase 3 trials were identical in design, with the exception of the background regimen (BR). In TMC278-C209, the BR was fixed to the N(t)RTIs, tenofovir disoproxil fumarate plus emtricitabine. In TMC278-C215, the BR consisted of 2 investigator-selected N(t)RTIs: tenofovir disoproxil fumarate plus emtricitabine or zidovudine plus lamivudine or abacavir plus lamivudine. In both trials, randomization was stratified by screening viral load. In TMC278-C215, randomization was also stratified by N(t)RTI BR.

In the pooled analysis for TMC278-C209 and TMC278-C215, demographics and baseline characteristics were balanced between the EDURANT arm and the efavirenz arm. Table 9 displays selected demographic and baseline disease characteristics of the subjects in the EDURANT and efavirenz arms.

Table 9: Demographic and Baseline Disease Characteristics of Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects in the TMC278-C209 and TMC278-C215 Trials (Pooled Analysis)		
	Pooled Data from the TMC278-C209 and TMC278-C215 Trials	
	EDURANT + BR N=686	Efavirenz + BR N=682
Demographic Characteristics		
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%
Baseline Disease Characteristics		
Median Baseline Plasma HIV-1 RNA (range), log ₁₀ copies/mL	5.0 (2-7)	5.0 (3-7)
Percentage of Patients with Baseline Plasma Viral Load:		
≤ 100,000	54%	48%
> 100,000 to ≤ 500,000	36%	40%
> 500,000	10%	12%
Median Baseline CD4+ Cell Count (range), cells/mm ³	249 (1-888)	260 (1-1137)
Percentage of Subjects with: Hepatitis B/C Virus Co-infection	7%	10%
Percentage of Patients with the following background regimens:		
tenofovir disoproxil fumarate plus emtricitabine	80%	80%
zidovudine plus lamivudine	15%	15%
abacavir plus lamivudine	5%	5%
BR=background regimen		

Week 48 efficacy outcome for subjects treated with EDURANT 25 mg once daily from the pooled analysis are shown in Table 10.

Table 10: Virologic Outcome of Randomized Treatment of Studies TMC278-C209 and TMC278-C215 (Pooled Data) at Week 48		
	EDURANT + BR N=686	Efavirenz + BR N=682
HIV-1 RNA < 50 copies/mL*	83%	80%
Virologic failure[†]	13%	9%
No virologic data at Week 48 window		
Reasons		
Discontinued study due to adverse event or death [‡]	2%	7%
Discontinued study for other reasons and last available HIV-1 RNA < 50 copies/mL (or missing) [§]	2%	3%
Missing data during window but on study	1%	< 1%
HIV-1 RNA < 50 copies/mL by Baseline Plasma Viral Load (copies/mL)		
≤ 100,000	89%	83%
> 100,000 to ≤ 500,000	78%	78%
> 500,000	65%	73%
Virologic failure[†] by Baseline Plasma Viral Load (copies/mL)		
≤ 100,000	5%	5%
> 100,000 to ≤ 500,000	20%	11%
> 500,000	29%	17%
N = total number of subjects per treatment group * CI = Predicted difference (95% CI) of response rates is 2.0 (-2.1; 6.1) † Includes subjects who had ≥ 50 copies/mL in the Week 48 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL, and subjects who had a switch in background regimen that was not permitted by the protocol. ‡ Includes subjects who discontinued due to an adverse event or death if this resulted in no on-treatment virologic data in the Week 48 window. § Includes subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc. Note: Analysis was based on the last observed viral load data within the Week 48 window (Week 44-54).		

Based on the pooled data from the TMC278-C209 and TMC278-C215 trials at 48 weeks of treatment, the mean CD4+ cell count increase from baseline was 192 cells/mm³ for EDURANT-treated subjects and 176 cells/mm³ for efavirenz-treated subjects.

Study TMC278-C204 is a randomized, active-controlled, Phase 2b trial in antiretroviral treatment-naïve HIV-1-infected adult subjects consisting of 2 parts: an initial 96 weeks, partially-blinded dose-finding part [EDURANT doses blinded] followed by a long-term, open-label part. After Week 96, subjects randomized to one of the 3 doses of EDURANT were switched to EDURANT 25 mg once daily. Subjects 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 subjects who had a plasma HIV-1 RNA ≥ 5000 copies/ml, previously received ≤ 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 subjects with <50 HIV-1 RNA copies/ml receiving EDURANT 25 mg (N = 93) compared to subjects receiving efavirenz (N = 89) was 76% and 71%, respectively. The mean increase from baseline in CD4+ counts was 146×10^6 cells/mm³ in subjects receiving EDURANT 25 mg and 160×10^6 cells/mm³ in subjects receiving efavirenz.

At 192 weeks, 63% (59/93) of subjects who originally received 25 mg once daily achieved HIV RNA < 50 copies/mL compared to 61% (54/89) of subjects in the control group.

16 HOW SUPPLIED/STORAGE AND HANDLING

EDURANT (rilpivirine) tablets are supplied as white to off-white, film-coated, round, biconvex, 6.4 mm tablets. Each tablet contains 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of rilpivirine. Each tablet is debossed with “TMC” on one side and “25” on the other side.

EDURANT tablets are packaged in bottles in the following configuration: 25 mg tablets-bottles of 30 (NDC 59676-278-01).

Store EDURANT tablets in the original bottle in order to protect from light. Store EDURANT tablets at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Patient Information*).

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with EDURANT from your healthcare provider.** A Patient Package Insert for EDURANT is available for patient information.

Patients should be informed that EDURANT is not a cure for HIV infection. Patients must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should also be advised to never re-use or share needles. Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using EDURANT.

Patients should be advised to take EDURANT with a meal once a day as prescribed. EDURANT must always be used in combination with other antiretroviral drugs. Patients should not alter the dose of EDURANT or discontinue therapy with EDURANT without consulting their physician. 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. Inform the patient that he or she should not take more or less than the prescribed dose of EDURANT at any one time.

EDURANT may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort.

EDURANT should not be co-administered with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to EDURANT or to the class of NNRTIs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin; the antimycobacterials rifabutin, rifampin, rifapentine; proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole; the glucocorticoid systemic dexamethasone (more than a single dose); or St. John's wort (*Hypericum perforatum*).

Patients should be informed that depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported with EDURANT. If they experience depressive symptoms, they should seek immediate medical evaluation.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including EDURANT, and that the cause and long-term health effects of these conditions are not known at this time.



Product of Ireland
Finished Product Manufactured by:
Janssen-Cilag S.p.A., Latina, Italy
Manufactured for:
Tibotec Therapeutics, Division of Centocor Ortho Biotech Products, L.P., Raritan NJ 08869

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Patient Information
EDURANT (ee' dur ant)
(rilpivirine)
Tablets

Important: Ask your doctor or pharmacist about medicines that should not be taken with EDURANT. For more information, see the section “What should I tell my doctor before taking EDURANT?”

Read this Patient Information before you start taking EDURANT and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You and your doctor should discuss your treatment with EDURANT when you start taking it and at regular checkups. You should not change or stop treatment without first talking with your doctor.

What is EDURANT?

- **EDURANT is a prescription HIV medicine that:**
 - helps to treat HIV (Human Immunodeficiency Virus) infection in adults. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). EDURANT is a type of HIV medicine called a non-nucleoside reverse transcriptase inhibitor (NNRTI).
 - is used in adults who have **never** taken HIV medicines before.
 - EDURANT **must** be taken with other HIV medicines.
- It is not known if EDURANT is safe and effective in children.

When used with other HIV medicines, EDURANT may help:

1. Reduce the amount of HIV in your blood. This is called your “viral load”.
2. Increase the number of white blood cells called CD4+ (T) cells that help fight off other infections.

Reducing the amount of HIV and increasing the CD4+ (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

EDURANT does not cure HIV infection or AIDS.

Patients must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

- Always practice safer sex.
- Use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- Never re-use or share needles.

Ask your doctor if you have any questions about how to prevent passing HIV to other people.

Who should not take EDURANT?

- Do not take EDURANT if your HIV infection has been previously treated with HIV medicines.
- **Do not take EDURANT if you are taking certain medicines.** For more information about medicines that **must not** be taken with EDURANT, see “**What should I tell my doctor before taking EDURANT?**”

What should I tell my doctor before taking EDURANT?

Before taking EDURANT, tell your doctor if you:

- have had or currently have liver problems, including hepatitis B or C.
- have ever had a mental health problem.
- are pregnant or planning to become pregnant.
- It is not known if EDURANT will harm your unborn baby.
Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. The Centers for Disease Control and Prevention recommends that mothers with HIV not breastfeed because they can pass the HIV through their milk to the baby. It is not known if EDURANT passes through your breast milk and can harm your baby. Talk to your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

EDURANT may affect the way other medicines work, and other medicines may affect how EDURANT works, and may cause serious side effects. If you take certain medicines with EDURANT, the amount of EDURANT in your body may be too low and it may not work to help control your HIV infection. The HIV virus in your body may become resistant to EDURANT or other HIV medicines that are like it.

Do not take EDURANT if you also take these medicines:

- the anti-seizure medicines carbamazepine (Carbatrol[®], Equetro[®], Tegretol[®], Tegretol- XR[®], Teril[®], Epitol[®]), oxcarbazepine (Trileptal[®]), phenobarbital (Luminal[®]), phenytoin (Dilantin[®], Dilantin-125[®], Phenytek[®])
- the anti-TB medicines rifabutin (Mycobutin), rifampin (Rifater[®], Rifamate[®], Rimactane[®], Rifadin[®]) and rifapentine (Priftin[®])
- a proton pump inhibitor medicine for certain stomach or intestinal problems, including esomeprazole (Nexium[®], Vimovo[®]), lansoprazole (Prevacid[®]), omeprazole (Prilosec[®]), pantoprazole sodium (Protonix[®]), rabeprazole (Aciphex[®])
- more than 1 dose of the steroid medicine dexamethasone or dexamethasone sodium phosphate
- St. John’s wort (*Hypericum perforatum*)

Also tell your doctor if you take:

- an antacid medicine that contains aluminum, magnesium hydroxide, or calcium carbonate. Take antacids **at least 2 hours before or at least 4 hours after** you take EDURANT.
- a histamine-2 blocker medicine, including famotidine (Pepcid[®]), cimetidine (Tagamet[®]), nizatidine (Axid[®]), or ranitidine hydrochloride (Zantac[®]). Take these medicines **at least 12 hours before or at least 4 hours after** you take EDURANT.
- the antibiotic medicines clarithromycin (Biaxin[®]), erythromycin (E-Mycin[®], Eryc[®], Ery-Tab[®], PCE[®], Pediazole[®], Iloson[®]), and troleandomycin (TAO[®])
- an antifungal medicine by mouth, including fluconazole (Diflucan[®]), itraconazole (Sporanox[®]), ketoconazole (Nizoral[®]), posaconazole (Noxafil[®]), voriconazole (Vfend[®])
- methadone (Dolophine[®])

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

Your doctor and your pharmacist can tell you if you can take these medicines with EDURANT. Do not start any new medicines while you are taking EDURANT without first talking with your doctor or pharmacist. You can ask your doctor or pharmacist for a list of medicines that can interact with EDURANT.

How should I take EDURANT?

- **Stay under the care of your doctor during treatment with EDURANT.**
- **Take EDURANT every day exactly as prescribed by your doctor.**
- **Always take EDURANT with a meal.** Taking EDURANT with a meal is important to help get the right amount of medicine in your body. A protein drink alone does not replace a meal.
- Do not change your dose or stop taking EDURANT without first talking with your doctor. See your doctor regularly while taking EDURANT.
- When your supply of EDURANT starts to run low, get more from your doctor or pharmacy. It is important not to run out of EDURANT. The amount of HIV in your blood may increase if the medicine is stopped even for a short time.
- If you miss a dose of EDURANT within 12 hours of the time you usually take it, take your dose of EDURANT **with a meal** as soon as possible. Then, take your next dose of EDURANT at the regularly scheduled time. If you miss a dose of EDURANT by more than 12 hours of the time you usually take it, wait and then take the next dose of EDURANT at the regularly scheduled time.
- Do not take more than your prescribed dose to make up for a missed dose.
- If you take too much EDURANT, go to your local emergency room right away.

What are the possible side effects of EDURANT?

EDURANT can cause serious side effects including:

- **Depression or mood changes. Tell your doctor right away if you have any of the following symptoms:**
 - feeling sad or hopeless
 - feeling anxious or restless
 - have thoughts of hurting yourself (suicide) or have tried to hurt yourself
- **Changes in body fat** can happen in people taking HIV medicines. These changes may include an increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long- term health effects of these problems are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Call your doctor right away if you start having new symptoms after starting your HIV medicine.

Common side effects of EDURANT include:

- trouble sleeping (insomnia)
- headache
- rash

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects with EDURANT. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EDURANT?

- Store EDURANT at 59°F to 86°F (15°C to 30°C).
- Keep EDURANT in the original bottle to protect from light.

Keep EDURANT and all medicines out of the reach of children.

General information about EDURANT

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EDURANT for a condition for which it was not prescribed. Do not give EDURANT to other people even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about EDURANT. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information

about EDURANT that is written for health professionals. For more information, call 1-877-732-2488 or go to www.EDURANT-info.com.

What are the ingredients in EDURANT?

Active ingredient: rilpivirine.

Inactive ingredients: croscarmellose sodium, magnesium stearate, lactose monohydrate, povidone K30, polysorbate 20 and silicified microcrystalline cellulose. The tablet coating contains hypromellose 2910 6 mPa.s, lactose monohydrate, PEG 3000, titanium dioxide, and triacetin.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Product of Ireland

Finished Product Manufactured by:

Janssen-Cilag S.p.A., Latina, Italy

Manufactured for:

Tibotec Therapeutics, Division of Centocor Ortho Biotech Products, L.P., Raritan NJ 08869



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