PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrEDURANT®

rilpivirine as rilpivirine hydrochloride
Tablets, 25 mg Oral
Human Immunodeficiency Virus (HIV) non-nucleoside reverse transcriptase inhibitor

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RECENT MAJOR LABEL CHANGES

INDICATIONS (1),	05/2018
DOSAGE AND ADMINISTRATION, Dosing Considerations (3.1)	05/2018
DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Pregnancy and Postpartum (3.2)	05/2018
WARNINGS AND PRECAUTIONS, General (6)	05/2018
WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, (6)	05/2018
WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women (6.1.1)	05/2018
WARNINGS AND PRECAUTIONS, Immune (6)	02/2019
WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women (6.1.1)	02/2019

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EDURANT® (rilpivirine), 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 and pediatric patients 12 years of age and older (and weighing ≥ 35 kg) with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

1.1 Pediatrics

Pediatrics (12 to <18 years of age and weighing at least 35 kg):
The safety, efficacy and pharmacokinetics of EDURANT® has been established in antiretroviral treatment-naïve, HIV-1 infected pediatric subjects 12 to less than 18 years of age and weighing at least 35 kg (**DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY** and **CLINICAL TRIALS**).

Pediatrics (<12 years of age): EDURANT® is not recommended for patients less than 12 years of age (see **WARNINGS AND PRECAUTIONS**).

1.2 Geriatrics

Geriatrics (> 65 years of age):
Clinical studies of EDURANT® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from adult subjects <65 years of age. EDURANT® should be used with caution in this population (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

2 CONTRAINDICATIONS

EDURANT® (rilpivirine) is contraindicated in patients who are hypersensitive to rilpivirine or to any ingredient in the formulation. For a complete listing of ingredients, see the **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Co-administration of EDURANT® is contraindicated with drugs which induce CYP3A enzymes or increase gastric pH as this may result in significant decreases in the plasma concentrations of rilpivirine, a loss of virologic response and possible resistance to EDURANT® and to the NNRTI class of antiretrovirals. These drugs are listed in Table 1 (see **DRUG INTERACTIONS**).

Table 1: Drugs that Are Contraindicated with EDURANT®

Drug Class	Drugs Within Class That Are Contraindicated EDURANT®
Anticonvulsants	carbamazepine, oxcarbazepine, phenobarbital, phenytoin
Antimycobacterials	rifapentine, rifampin

Glucocorticoids	systemic dexamethasone (more than a single dose)
Herbal products	St. John's wort (*Hypericum perforatum*)
Proton pump inhibitors	esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

Viral load must be determined prior to initiation of therapy. Therapy must not be initiated in patients with a vial load ≥ 100 000 copies/mL.

EDURANT® (rilpivirine) must always be given in combination with other antiretroviral medicinal products.

EDURANT® must always be given with a meal.

3.2 Recommended Dose and Dosage Adjustment

Adults
The recommended dose of EDURANT® is one 25 mg tablet once daily which must be taken with a meal (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

Geriatric Patients
Clinical studies of EDURANT® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from adult subjects < 65 years of age. EDURANT® should be used with caution in this population (see **INDICATIONS**, **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatric Patients
Pediatric (12 to <18 years of age and weighing ≥ 35 kg)
The recommended dose of EDURANT® for pediatric patients 12 years to <18 years of age and weighing at least 35 kg is one 25 mg tablet once daily which must be taken with a meal (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

Pediatric (less than 12 years of age or < 35 kg)
The safety and efficacy of EDURANT® in children less than 12 years of age or weighing < 35 kg has not been established. (see **INDICATIONS**, **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Pregnancy and Postpartum
The recommended dose of EDURANT® in pregnant patients is one 25 mg tablet once daily taken with a meal. Lower exposures of rilpivirine were observed during the 2nd and 3rd trimesters of pregnancy, therefore viral load should be monitored closely (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**, **Pregnancy and Breastfeeding, Pregnancy and Postpartum**).

Hepatic Impairment
EDURANT® has not been studied in patients with severe hepatic impairment (Child-Pugh score C) and the use of EDURANT® is not recommended in this population. No dose adjustment of EDURANT® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. However, given that the metabolism of EDURANT® is cytochrome P450-mediated and that clinical experience in patients with mild or moderate hepatic impairment is limited, caution should be exercised when administering EDURANT® to this population (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**, **Hepatic Impairment** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Renal Impairment
EDURANT® has not been studied in patients with renal impairment. Caution should be exercised when administering EDURANT® to patients with severe renal impairment or end-stage renal disease whose drug absorption, distribution and metabolism may be altered secondary to renal dysfunction. No dose adjustment of EDURANT® is required in patients with mild to moderate renal impairment. As 99.7% of rilpivirine is bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis (see **WARNINGS AND PRECAUTIONS**, **Renal** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions, Renal Insufficiency**).

3.3 Missed Dose

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.

Co-administration with Rifabutin

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 **DRUG INTERACTIONS**).

4 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

There is no specific antidote for overdose with EDURANT® (rilpivirine). 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. Since rilpivirine is highly protein bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet, 25 mg	croscarmellose sodium, hypromellose 2910 6 mPa.s, lactose monohydrate, magnesium stearate, polyethylene glycol 3000, polysorbate 20, povidone K30, silicified microcrystalline cellulose, titanium dioxide and triacetin.

EDURANT® (rilpivirine) tablets are supplied as white to off-white, film-coated, round, biconvex, tablets for oral administration containing rilpivirine hydrochloride 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 high-density polyethylene (HDPE) bottles in the following configuration: 25 mg tablets—bottles of 30.

6 WARNINGS AND PRECAUTIONS

General
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.

In the pooled analysis from the Phase III trials, more EDURANT®-treated subjects with baseline HIV-1 RNA >100,000 copies/mL experienced virologic failure compared to subjects with HIV-1 RNA ≤100,000 copies/mL at baseline (see **WARNINGS AND PRECAUTIONS, Sensitivity/Resistance, Resistance/Cross-resistance,** and **MICROBIOLOGY, Resistance, Cross-resistance**).

Regardless of HIV-1 RNA at the start of therapy, more EDURANT®-treated subjects with CD4+ cell count less than 200 cells/mm^3 at the start of therapy experienced virologic failure compared to subjects with CD4+ cell count greater than or equal to 200 cells/mm^3 (see **CLINICAL TRIALS**).

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 the control (efavirenz) (see **WARNINGS AND PRECAUTIONS, Sensitivity/Resistance, Resistance/Cross-resistance,** and **MICROBIOLOGY, Resistance, Cross-resistance**).

More subjects treated with EDURANT® developed tenofovir and lamivudine/emtricitabine associated resistance compared to the control (see **WARNINGS AND PRECAUTIONS, Sensitivity/Resistance, Resistance/Cross-resistance,** and **MICROBIOLOGY, Resistance, Cross-resistance**).

Caution should be exercised when prescribing EDURANT® (rilpivirine) with drugs that may

reduce the exposure of rilpivirine (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

As with other antiretroviral medicinal products, resistance testing should guide the use of EDURANT® (see **MICROBIOLOGY**).

Carcinogenesis and Mutagenesis
Rilpivirine induced benign and malignant tumors in the liver of mice and rats. These tumors are caused by the enzyme induction that rilpivirine caused in these species which may be rodent-specific. In rats rilpivirine caused benign and malignant tumors of the thyroid follicular cells. These tumors are the result of continuous stimulation of the follicular cells due to the increased clearance of thyroxine caused by rilpivirine in this species. This effect is considered rat-specific.

Cardiovascular
EDURANT® should be administered with caution to patients who are suspected to be at an increased risk of experiencing proarrhythmic conditions such as hypokalemia, clinically significant bradycardia, acute myocardial ischemia, congestive heart failure or congenital prolongation of QTc interval (see **ADVERSE REACTIONS, DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

In healthy subjects, rilpivirine has been associated with prolongation of the QT interval of the electrocardiogram at doses of 75 mg and 300 mg once daily. In antiretroviral naïve, HIV-1 infected patients receiving EDURANT® 25 mg once daily in Phase III clinical trials, which excluded subjects with high risk factors for proarrhythmia, the mean QTc interval increased gradually over 48 weeks and remained stable through Week 96. An increase of >60 ms in QTcF interval resulting in abnormal values of >480 ms was reported in one patient. Prolongation of QT interval may increase the risk of cardiac arrhythmias.

There is limited information available on the potential for a pharmacodynamic interaction between EDURANT® and drugs that prolong the QTc interval of the electrocardiogram.

EDURANT® should be used with caution when co-administered with drugs with a known risk of Torsade de Pointes.

Depressive Disorders
During the Phase III trials (N=686), the incidence of depressive disorder adverse drug reactions (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) of at least moderate intensity (Grades 2 to 4) was 5%. The incidence of discontinuation due to depressive disorders was 1%. Suicide attempt was reported in 2 subjects while suicide ideation was reported in 4 subjects taking in EDURANT®. 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. The incidence of these events was similar in the control (efavirenz) group.

During the Phase II trial in pediatric subjects 12 to less than 18 years of age (N = 36) receiving EDURANT® through 48 weeks, the incidence of depressive disorders (regardless of causality, severity) was 19.4% (7/36). Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 5.6% (2/36). None of the subjects discontinued due to depressive disorders. Suicidal ideation and suicide attempt were reported in 1 subject.

Endocrine and Metabolism

Serum Lipids and Blood Glucose
Serum lipids and blood glucose may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Gastrointestinal
EDURANT® contains lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance (severe lactase deficiency or glucose-galactose malabsorption).

Hepatic/Biliary/Pancreatic

Hepatotoxicity
Hepatic adverse events have been reported in patients receiving a rilpivirine containing regimen. Patients with underlying hepatitis B or C, or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations with use of EDURANT®. A few cases of hepatic toxicity have been reported in patients receiving a rilpivirine-containing regimen who had no pre-existing hepatic disease or other identifiable risk factors. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with EDURANT® is recommended in patients with underlying hepatic disease such as hepatitis B or C, or in patients with marked elevations in transaminases prior to treatment initiation. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors.

Hepatic Impairment
EDURANT® has not been studied in patients with severe hepatic impairment (Child-Pugh score C) and the use of EDURANT® is not recommended in this population. No dose adjustment of EDURANT® is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. However, given that the metabolism of EDURANT® is cytochrome P450-mediated and that clinical experience in patients with mild or moderate hepatic impairment is limited, caution should be exercised when administering EDURANT® to this population (see **DOSAGE AND ADMINISTRATION, Recommended Dosage and Dosage Adjustment, Hepatic Impairment** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Immune

Immune Reconstitution Inflammatory Syndrome
Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including EDURANT®. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, polymyositis and Guillain-Barré syndrome) have also been reported to occur in the setting of immune

reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment. Sometimes there can be an atypical presentation.

Renal

Renal Impairment
EDURANT® has not been studied in patients with renal impairment. Caution should be exercised when administering EDURANT® to patients with severe renal impairment or end-stage renal disease whose drug absorption, distribution and metabolism may be altered secondary to renal dysfunction. No dose adjustments are required in patients with mild to moderate renal impairment. As 99.7% of rilpivirine is bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Insufficiency**).

Sensitivity/Resistance

Resistance/Cross-resistance
In the pooled analysis from two Phase III trials in adults, the emergence of resistance among subjects was greater in the EDURANT® arm as compared to the control (efavirenz) arm at Week 48 (10.6%, 5.3%, respectively) and at Week 96 (14%, 7.6%, respectively). More EDURANT®-treated subjects with baseline HIV-1 RNA > 100,000 copies/mL experienced virologic failure compared to subjects with HIV-1 RNA ≤ 100,000 copies/mL at baseline.

The observed virologic failures in EDURANT®-treated subjects conferred a higher cross-resistance to the NNRTI class as compared to those in control-treated subjects. More subjects treated with EDURANT® developed lamivudine/emtricitabine associated resistance as compared to those treated with the control (see **MICROBIOLOGY, Resistance, Cross-resistance**).

In the 36 adolescents 12 to less 18 years of age, treatment-emergent rilpivirine resistance mutations were detected in 5/8 (62.5%) subjects with virologic failure, treatment-emergent NNRTI resistance mutations were detected in 6 (75%) subjects. In 4/5 subjects, treatment-emergent NRTI resistance was also detected. The observed treatment-emergent rilpivirine, NNRTI and NRTI resistance mutations were previously identified in adults (see **MICROBIOLOGY, Resistance, Cross-resistance**).

In study C213, phenotypic resistance to NRTIs and phenotypic cross-resistance between rilpivirine and other NNRTIs was shown for efavirenz, nevirapine, and etravirine in 4/5 (80%) subjects with rilpivirine associated mutations.

Skin
Severe skin and hypersensitivity reactions have been reported during the post-marketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. During the Phase III clinical trials, treatment-related rashes with at least Grade 2 severity were reported in 3% of subjects receiving EDURANT®. No grade 4 rash was reported. Overall, most rashes were Grade 1 or 2

and occurred in the first four to six weeks of therapy (see **ADVERSE REACTIONS**). Discontinue EDURANT® immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, including but not limited to, severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema, angioedema, hepatitis or eosinophilia. Clinical status including laboratory parameters should be monitored and appropriate therapy should be initiated.

6.1 Special Populations

6.1.1 Pregnant Women

No well-controlled clinical 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 (see **NON-CLINICAL TOXICOLOGY**, **Reproductive and Developmental Toxicity**).

There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily (see **NON-CLINICAL TOXICOLOGY**; **Reproductive and Developmental Toxicity**). EDURANT® should not be used during pregnancy unless the potential benefits outweigh the potential risks.

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.

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

6.1.2 Breast-feeding

It is not known whether rilpivirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving EDURANT®** (see **NON-CLINICAL TOXICOLOGY**, **Reproductive and Developmental Toxicity**).

6.1.3 Pediatrics

Pediatrics (<12 years of age): Safety and effectiveness in pediatric patients less than 12 years

of age has not been established.

6.1.4 Geriatrics

Geriatrics (>65 years of age)
Clinical studies of EDURANT® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from adult subjects < 65 years of age. EDURANT® should be used with caution in this population.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The safety assessment of EDURANT® (rilpivirine) at Week 48 and Week 96 is based on pooled data from 686 patients in the Phase III controlled trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in antiretroviral treatment-naïve HIV-1 infected adult patients who received EDURANT® (25 mg once daily) (see **CLINICAL TRIALS**). In the Week 96 analysis, the median duration of exposure was 104.3 weeks. The proportion of subjects who discontinued treatment with EDURANT® due to adverse drug reactions (ADRs) was 1.7%. The most frequently reported ADRs (≥2%) that were at least Grade 2 in severity were depression (4.1%), insomnia (3.5%), headache (3.5%), rash (2.3%), and abdominal pain (2.0%) (see Table 2). Most ADRs occurred during the first 48 weeks of treatment and no new ADR terms were identified between 48 weeks and 96 weeks (Phase III trials TMC278-C209 and TMC278-C215) and in the Phase IIb trial (TMC278-C204) through 240 weeks.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical ADRs of at least moderate intensity or greater (≥Grade 2) reported in adult subjects treated with EDURANT® are presented in Table 2.

Table 2: Treatment-Emergent Adverse Drug Reactions* of at Least Moderate Intensity† (Grades 2-4) in ≥1% of Antiretroviral Treatment-Naïve, HIV-1-Infected Adult Subjects Treated with EDURANT®

System Organ Class, Preferred Term	Pooled Data from the TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials (Week 96 Analysis)	
	EDURANT® + BR N=686	Efavirenz + BR N=682
Gastrointestinal Disorders		
Abdominal Pain	14 (2.0%)	13 (1.9%)
Nausea‡	9 (1.3%)	19 (2.8%)
Vomiting	7 (1.0%)	14 (2.1%)
Diarrhea	7 (1.0%)	9 (1.3%)

Table 2: Treatment-Emergent Adverse Drug Reactions* of at Least Moderate Intensity† (Grades 2-4) in ≥1% of Antiretroviral Treatment-Naïve, HIV-1-Infected Adult Subjects Treated with EDURANT®		
System Organ Class, Preferred Term	**Pooled Data from the TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials (Week 96 Analysis)**	
	EDURANT® + BR N=686	**Efavirenz + BR N=682**
General Disorders and Administration Site Conditions		
Fatigue	11 (1.6%)	14 (2.1)
Metabolism and Nutrition Disorders		
Decreased Appetite	8 (1.2%)	4 (0.6%)
Nervous System Disorders		
Headache‡	24 (3.5%)	26 (3.8%)
Dizziness‡#	7 (1.0%)	46 (6.7%)
Psychiatric Disorders		
Depression	28 (4.1%)	22 (3.2)
Insomnia	24 (3.5%)	24 (3.5%)
Abnormal Dreams‡£	11 (1.6%)	27 (4.0%)
Sleep Disorders	9 (1.3%)	6 (0.9%)
Skin and Subcutaneous Tissue Disorders		
Rash‡#	16 (2.3%)	65 (9.5%)

N = total number of subjects per treatment group; BR = background regimen
* Includes adverse reactions at least possibly, probably, or very likely related to the drug.
† Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
‡ Treatment comparison was pre-specified for these ADRs (Fisher's Exact Test)
£ p-value <0.01
p-value <0.0001

7.3 Less Common Clinical Trial Adverse Reactions

Treatment-emergent ADRs of at least moderate intensity (≥Grade 2) occurring in less than 1% of antiretroviral treatment-naïve subjects receiving EDURANT® are listed below by System Organ Class. Some adverse 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: abdominal discomfort

Hepatobiliary Disorders: cholecystitis*, cholelithiasis*

Nervous System Disorders: somnolence

Psychiatric Disorders: anxiety, depressed mood

Renal and Urinary Disorders: glomerulonephritis membranous*, glomerulonephritis mesangioproliferative*, nephrolithiasis*

7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Selected treatment-emergent clinical laboratory abnormalities (Grade 3 or Grade 4), considered as ADRs, reported in EDURANT®-treated subjects are shown in Table 3.

Table 3: Selected Treatment Emergent Laboratory Abnormalities (Grade 3 or Grade 4) Observed in Antiretroviral Treatment-Naïve, HIV-1 Infected Adult Patients (Week 96 Analysis)

Laboratory Parameter Abnormality	DAIDS Toxicity Range	Pooled Data from the TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials	
		EDURANT® + BR N=686	Efavirenz + BR N=682
HEMATOLOGY			
Decreased hemoglobin	< 4.5 mmol/L < 7.4 g/dl	0.1%	0.6%
Decreased platelet count	< 49999/mm^3 < 49999 x 10^9/L	0.1%	0.3%
Decreased white blood cell count	< 1499/mm^3 < 1.499 giga/L	1.2%	1.0%
BIOCHEMISTRY			
Increased creatinine	> 1.8 x ULN	0.1%	0.1%
Increased AST	> 5.0 x ULN	2.3%	3.3%
Increased ALT	> 5.0 x ULN	1.6%	3.7%
Increased bilirubin	> 2.5 x ULN	0.7%	0.3%
Increased pancreatic amylase	> 2 x ULN	3.8%	4.8%
Increased lipase	> 3 x ULN	0.9%	1.6%
Increased total cholesterol (fasted) †	> 7.77 mmol/L > 300 mg/dL	0.1%	3.3%
Increased LDL cholesterol (fasted) †	≥ 4.91 mmol/L ≥ 191 mg/dL	1.5%	5.3%
Increased Triglycerides (fasted) †	≥ 8.49 mmol/L ≥ 751 mg/dL	0.6%	3.3%

BR = background regimen; ULN=upper limit of normal
N = number of subjects per treatment group
† p ≤0.001 according to Fisher's Exact test (difference in grade 3 plus 4 abnormalities between the two treatment groups).
Note: Percentages were calculated for the number of subjects with results for the analyte.

Adrenal Function

In the pooled analysis of Phase III 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 (control) group. At Week 96, the overall mean change from baseline in basal cortisol showed a decrease of 19.1 nmol/L in the EDURANT® group and a decrease of 0.6 nmol/L in the efavirenz group. At Week 48 and Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the EDURANT® group (+16.5 ± 6.14 nmol/L and

+18.4 ± 8.36 nmol/L, respectively) than in the efavirenz group (+58.1 ± 6.66 nmol/L and +54.1 ± 7.24 nmol/L, respectively). Mean values for both basal and ACTH-stimulated cortisol values at Week 48 and Week 96 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
In the pooled Phase III trials, an increase in serum creatinine was observed over the 96 weeks of treatment with EDURANT®. Most of this increase occurred within the first four weeks of treatment, with a mean change of 0.1 mg/dL (range: -0.3 mg/dL to 0.6 mg/dL) observed after 96 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. Serum creatinine increases occurred regardless of the background N(t)RTI regimen.

Serum Lipids
Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are presented in Table 4. The mean changes from baseline were smaller in the EDURANT® arm versus the comparator (efavirenz) arm. The impact of such findings has not been demonstrated.

Table 4: Treatment-Emergent Changes in Serum Lipids from Baseline to Week 96 in Treatment-Naïve HIV-1 Infected Adult Patients[a] (Fasting); Data Pooled from the Phase III Trials, TMC278-C209 (ECHO) and TMC278-C215 (THRIVE)

Lipid Parameters	EDURANT® + BR[b] N[c]=686				Efavirenz + BR N[c]=682			
		Baseline	Week 96			Baseline	Week 96	
	n[d]	Mean (mg/dL)	Mean (mg/dL)	Mean change[e] (mg/dL)	n[d]	Mean (mg/dL)	Mean (mg/dL)	Mean change[e] (mg/dL)
Total cholesterol[f]	546	161	166	5	507	160	187	28
HDL-cholesterol[f]	545	41	46	4	505	40	51	11
LDL-cholesterol[f]	543	96	98	1	503	95	109	14
Triglycerides[f]	546	122	116	-6	507	130	141	11

a: Excludes subjects who recieved lipid lowering agents during the treatment period.
b: BR, Background regimen.
c: N, Number of patients in the treatment groups.
d: n, Number of patients with both baseline and Week 96 values.
e: The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 96 values.
f: p-value <0.001, Wilcoxon rank-sum test for treatment comparison (EDURANT® + BR versus Efavirenz + BR) of change from baseline.
HDL, High Density Lipoprotein. HDL-Cholesterol, cholesterol associated with the High Density Lipoprotein.
LDL, Low Density Lipoprotein. LDL-Cholesterol, cholesterol associated with the Low Density Lipoprotein.

Bone Effects
Dual Energy X-ray Absorptiometry (DEXA) scans were performed in substudies of the Phase III clinical trials, primarily to evaluate changes in body fat distribution; changes in bone mineral density and content were also evaluated. Both treatment groups showed a small but statistically significant median decrease from baseline in bone mineral density (1.4% and 1.5% in the EDURANT® group and 1.4% and 1.5% in the efavirenz (control) group at Week 48 and Week 96, respectively), and bone mineral content (1.8% and 2.1% in the EDURANT® group and 2.0% and 2.5% in the efavirenz group at Week 48 and Week 96, respectively). These changes were not considered to be clinically relevant. No statistically significant differences were observed between treatment groups.

Fat Redistribution
As evaluated in the DEXA substudy, both treatment groups showed a small but statistically significant median increase from baseline in limb fat (11.6% and 10.9% in the EDURANT® and the control (efavirenz) group, respectively), trunk fat (15.5% and 13.9%, respectively), and total body fat (13.5% and 11.4%, respectively) at Week 96. No statistically significant differences were observed between treatment groups.

Patients Co-infected with Hepatitis B and/or Hepatitis C Virus
In HIV patients co-infected with hepatitis B and/or C virus receiving EDURANT®, the incidence of hepatic enzyme elevation was higher than in patients who were not co-infected. The pharmacokinetic exposure of rilpivirine in co-infected patients was comparable to that in patients without co-infection.

Electrocardiogram Findings
A pooled analysis of data from two Phase III clinical trials of antiretroviral-naïve HIV-1 infected patients who received either EDURANT® 25 mg once daily or control (efavirenz), showed statistically significant mean increase from baseline in the QTc interval at Weeks 48 and 96. During treatment with EDURANT®, the mean change from baseline in QTc increased through Week 48 without reaching plateau and remained stable between Week 48 and Week 96 (11.4 ms [95% CI 10.1, 12.8] and 12.4 ms [95% CI 11.0, 13.7], respectively). These trials excluded patients with high risk factors for proarrhythmia. The clinical relevance of these findings is unknown (see **WARNINGS AND PRECAUTIONS, Cardiovascular; DRUG INTERACTIONS, QT Prolonging Drugs; ACTION AND CLINICAL PHARMACOLOGY, Effect on Electrocardiogram**).

7.5 Clinical Trial Adverse Reactions (Pediatrics)

Adverse Drug Reactions from a Clinical Trial in Pediatric Patients (12 to less than 18 Years of Age and weighing at least 35 kg)

The safety assessment is based on the Week 48 analysis of the single-arm, open-label, Phase II trial, TMC278-C213, in which 36 antiretroviral treatment-naïve HIV-1 infected patients 12 to less than 18 years of age and weighing at least 35 kg received EDURANT® (25 mg once daily) in combination with other antiretroviral agents (see **CLINICAL TRIALS**). The median duration of exposure was 63.5 weeks. There were no patients who discontinued treatment due to ADRs. No new ADRs were identified compared to those seen in adults.

ADRs were reported in nineteen pediatric subjects (52.8%). Most ADRs were Grade 1 or 2. The

most common ADRs (all grades, in at least two subjects) were headache (19.4%), depression (19.4%), somnolence (13.9%), and nausea (11.1%), dizziness (8.3%), abdominal pain (8.3%), vomiting (5.6%) and rash (5.6%). Observed laboratory abnormalities were comparable to those in adults.

Adrenal Function
In trial TMC278-C213, at Week 48, the overall mean change from baseline in basal cortisol showed an increase of 1.59 (0.24, 2.93) micrograms/dL.

Six of 30 (20%) subjects with a normal 250 micrograms ACTH stimulation test at baseline developed an abnormal 250 micrograms ACTH stimulation test (peak cortisol level < 18.1 micrograms/dL) during the trial. Three of these subjects had an abnormal 250 micrograms ACTH stimulation test at Week 48. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the abnormal 250 micrograms ACTH stimulation tests is not known.

7.6 Post-Market Adverse Reactions

Adverse reactions have been identified during post-marketing in patients receiving a rilpivirine-containing regimen. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Renal and Genitourinary Disorders: nephrotic syndrome

Skin and Subcutaneous Tissue Disorders: severe skin and hypersensitivity reactions including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

8 DRUG INTERACTIONS

8.1 Overview

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® (rilpivirine) and drugs that induce CYP3A or increase gastric pH may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the NNRTI class of antiretrovirals. Co-administration of EDURANT® and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

8.2 Drug-Drug Interactions

Drugs that are contraindicated for co-administration with EDURANT® are included in Table 5. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and the potential for loss of therapeutic effect.

Table 5: Drugs that Should Not Be Co-administered with EDURANT®		
Concomitant Drug Class: Drug Name	**Effect on Concentration of Rilpivirine or Concomitant Drug**	**Clinical Comment**
Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin	↓ rilpivirine	EDURANT® is contraindicated 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® and possible development of resistance to EDURANT® and other NNRTIs.
Antimycobacterials: rifampin*† rifapentine	↓ rilpivirine ↔ rifampin ↔ rifapentine	EDURANT® is contraindicated with rifampin 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® and possible development of resistance to EDURANT® and other NNRTIs.
Glucocorticoids: dexamethasone (systemic)	↓ rilpivirine ↔ dexamethasone	EDURANT® is contraindicated 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® and possible development of resistance to EDURANT® and other NNRTIs. Alternatives should be considered, particularly for long-term use.
Proton Pump Inhibitors: omeprazole*† lansoprazole, rabeprazole, pantoprazole, esomeprazole	↓ rilpivirine ↓ omeprazole	EDURANT® is contraindicated with proton pump inhibitors as co-administration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). This may result in loss of therapeutic effect of EDURANT® and possible development of resistance to EDURANT® and other NNRTIs.
Herbal Products: St. John's wort (*Hypericum perforatum*)	↓ rilpivirine	EDURANT® is contraindicated 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® and possible development of resistance to EDURANT® and other NNRTIs.

↑ = 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.

Established and other potentially significant drug interactions with EDURANT® are included in Table 6. These recommendations are based on either drug interaction studies or predicted interactions.

Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (see Table 7 and Table 8)		
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 should be administered on an empty stomach and at least 2 hours before or at least four hours after EDURANT® (which should be administered with a meal).
Other NRTIs (abacavir, emtricitabine, lamivudine, stavudine and zidovudine)	↔ rilpivirine ↔ other NRTIs	Based on the different elimination routes for rilpivirine and these other NRTIs, no clinically relevant drug-drug interactions are expected between these drugs and EDURANT®.
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 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). An interaction trial between rilpivirine (150 mg q.d.) and darunavir/ritonavir (800 mg/100 mg q.d.) demonstrated that darunavir/ritonavir increased the mean exposure of rilpivirine by 2.3-fold and from 2.7-fold to 3.8-fold in a subset (31%) of subjects. Caution should be exercised when these drugs are co-administered with EDURANT®.
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). An interaction trial between rilpivirine (150 mg q.d.) and lopinavir/ritonavir (400 mg/100 mg q.d.) demonstrated that lopinavir/ritonavir increased the mean exposure (AUC) of rilpivirine by 1.52-fold. Caution should be exercised when these drugs are co-administered with EDURANT®.

Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (see Table 7 and Table 8)		
Concomitant Drug Class: Drug Name	**Effect on Concentration of Rilpivirine or Concomitant Drug**	**Clinical Comment**
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.
HIV-Antiviral Agents: CCR5 Antagonists		
maraviroc	↔ rilpivirine ↔ maraviroc	No clinically relevant drug-drug interaction is expected when EDURANT® is co-administered with maraviroc.
HIV-Antiviral Agents: Integrase Strand Transfer Inhibitors		
raltegravir	↔ rilpivirine ↔ raltegravir	No dose adjustment is required when EDURANT® is co-administered with raltegravir.
Other Antiviral Agents		
ribavirin	↔ rilpivirine ↔ ribavirin	No clinically relevant drug-drug interaction is expected when EDURANT® is co-administered with ribavirin.
Simeprevir*	↔rilpivirine ↔ simeprevir	No dose adjustment is required for either drug when EDURANT® is co-administered with simeprevir.
Other Agents		
Antacids: antacids (e.g., aluminum or magnesium hydroxide, calcium carbonate)	↔ 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®.
Antiarrhythmics: digoxin	↔ rilpivirine ↔ digoxin	No dose adjustment is required when EDURANT® is co-administered with digoxin.
Antidiabetics: metformin	↔ rilpivirine ↔ metformin	Co-administration of EDURANT® with metformin produced no changes in plasma concentration of metformin. No dose adjustment is required when EDURANT® is co-administered with metformin.
Antimycobacterials: rifabutin*†	↓ rilpivirine ↔ rifabutin	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

Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (see Table 7 and Table 8)		
Concomitant Drug Class: **Drug Name**	**Effect on Concentration of Rilpivirine or Concomitant Drug**	**Clinical Comment**
		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.
Azole Antifungal Agents: ketoconazole*† fluconazole itraconazole 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). An interaction trial between rilpivirine (150 mg q.d.) and ketoconazole (400 mg q.d.) demonstrated that ketoconazole increased the mean exposure of rilpivirine by 1.49-fold. The concomitant use of EDURANT® with other azole antifungals is expected to result in increased mean exposure (AUC) of rilpivirine (see **QT prolonging drugs**). Caution should be exercised when these drugs are co-administered with EDURANT®. Clinical monitoring for breakthrough infections is recommended when azole antifungals are co-administered with EDURANT®.
HMG-CoA Reductase Inhibitors atorvastatin*† pravastatin rosuvastatin simvastatin	↔ rilpivirine ↔ atorvastatin	No dose adjustment is required when EDURANT® is co-administered with HMG-CoA reductase inhibitors.
H_2-Receptor Antagonists: famotidine*† cimetidine nizatidine ranitidine	↔ rilpivirine (famotidine taken 12 hours before rilpivirine) ↓ rilpivirine (famotidine taken 2 hours before rilpivirine) ↔ rilpivirine (famotidine taken 4 hours after 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	↑ rilpivirine ↔ clarithromycin ↔ erythromycin	Concomitant use of EDURANT® with clarithromycin or erythromycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.
Narcotic Analgesics: methadone*	↓ R(-) methadone ↓ S(+) methadone	No dose adjustments are required when initiating co-administration of methadone with EDURANT®. However,

Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (see Table 7 and Table 8)		
Concomitant Drug Class: Drug Name	**Effect on Concentration of Rilpivirine or Concomitant Drug**	**Clinical Comment**
		clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
PDE-5 Inhibitors: sildenafil*† tadalafil vardenafil	↔ sildenafil	No dose adjustment is required when EDURANT® is co-administered with PDE-5 inhibitors used in dosage regimens for the treatment of erectile dysfunction or pulmonary arterial hypertension.

↑ = 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.

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 7 (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 8 (effect of EDURANT® on other drugs).

Table 7: Drug Interactions: Pharmacokinetic Parameters for Rilpivirine in the Presence of Co-administered Drugs							
	Dose/Schedule				**Mean Ratio of Rilpivirine Pharmacokinetic Parameters With/Without Co-administered Drug (90% CI); No Effect = 1.00**		
Co-administered Drug	**Co-administered Drug**	**Rilpivirine**	**N**	**Exposure**	**C_{max}**	**AUC**	**C_{min}**
Co-administration With HIV 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 HIV Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)							
Didanosine	400 mg q.d.	150 mg q.d.†	21	↔	1.00 (0.90-1.10)	1.00 (0.95-1.06)	1.00 (0.92-1.09)
Tenofovir	300 mg q.d.	150 mg q.d.†	16	↔	0.96	1.01	0.99

Table 7: Drug Interactions: Pharmacokinetic Parameters for Rilpivirine in the Presence of Co-administered Drugs							
	Dose/Schedule				Mean Ratio of Rilpivirine Pharmacokinetic Parameters With/Without Co-administered Drug (90% CI); No Effect = 1.00		
Co-administered Drug	Co-administered Drug	Rilpivirine	N	Exposure	C_{max}	AUC	C_{min}
disoproxil fumarate					(0.81-1.13)	(0.87-1.18)	(0.83-1.16)
Co-administration with HIV Integrase Strand Inhibitors							
Raltegravir	400 mg b.i.d.	25 mg q.d.	23	↔	1.12 (1.04-1.20)	1.12 (1.05-1.19)	1.03 (0.96-1.12)
Co-administration with other Antivirals							
Simeprevir	150 mg q.d	25 mg q.d.	23	↔	1.04 (0.95-1.13)	1.12 (1.05-1.19)	1.25 (1.16-1.35)
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)
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., individualized 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.	25 mg q.d.	18	↓	0.69 (0.62-0.76)	0.58 (0.52-0.65)	0.52 (0.46-0.59)
Rifabutin	300 mg q.d.	50 mg q.d.†	18	↔	1.43 (1.30-1.56)	1.16 (1.06-1.26)	0.93 (0.85-1.01)
					(as compared to 25 mg q.d. rilpivirine alone)		
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	75 mg q.d.†	16	↔	0.92	0.98	1.04

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

Co-administered Drug	Dose/Schedule		N	Exposure	Mean Ratio of Rilpivirine Pharmacokinetic Parameters With/Without Co-administered Drug (90% CI); No Effect = 1.00		
	Co-administered Drug	Rilpivirine			C_{max}	AUC	C_{min}
	dose				(0.85-0.99)	(0.92-1.05)	(0.98-1.09)

CI = confidence interval; N = maximum 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 8: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of EDURANT®							
	Dose/Schedule				Mean Ratio of Co-administered Drug Pharmacokinetic Parameters With/Without EDURANT® (90% CI); No Effect = 1.00		
Co-administered Drug	Co-administered Drug	Rilpivirine	N	Exposure	C_{max}	AUC	C_{min}
Co-Administration with HIV 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 HIV Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)							
Didanosine	400 mg q.d.	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 HIV Integrase Strand Inhibitors							
Raltegravir	400 mg b.i.d.	25 mg q.d.	23	↑	1.10 (0.77-1.58)	1.09 (0.81-1.47)	1.27 (1.01-1.60)
Co-administration with other Antivirals							
Simeprevir	150 mg q.d.	25 mg q.d.	21	↔	1.10 (0.97-1.26)	1.06 (0.94-1.19)	0.96 (0.83-1.11)
Co-Administration with Drugs other than Antiretrovirals							
Acetaminophen	500 mg single dose	150 mg q.d.†	16	↔	0.97 (0.86-1.10)	0.91 (0.86-0.97)	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)
Digoxin	0.5 mg single dose	25 mg q.d.	22	↔	1.06 (0.97-1.17)	0.98 (0.93-1.04)#	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)
Metformin	850 mg single dose	25 mg q.d.	20	↔	1.02 (0.95-1.10)	0.97 (0.90-1.06)	N.A.
Omeprazole	20 mg q.d.	150 mg q.d.†	15	↓	0.86 (0.68-1.09)	0.86 (0.76-0.97)	N.A.
Rifabutin	300 mg q.d.	150 mg q.d.†	17	↔	1.03 (0.93-1.14)	1.03 (0.97-1.09)	1.01 (0.94-1.09)

Table 8: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of EDURANT®

Co-administered Drug	Dose/Schedule		N	Exposure	Mean Ratio of Co-administered Drug Pharmacokinetic Parameters With/Without EDURANT® (90% CI); No Effect = 1.00		
	Co-administered Drug	Rilpivirine			C_{max}	AUC	C_{min}
25-*O*-desacetyl-rifabutin			17	↔	1.07 (0.98-1.17)	1.07 (1.02-1.11)	1.12 (1.03-1.22)
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-desacetylrifampin			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.

CI = confidence interval; N = maximum 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.

AUC_{last}

8.3 Drug-Food Interactions

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 a 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. **These decreases in plasma concentrations of rilpivirine may result in a loss of virologic response and possible resistance to EDURANT® and the NNRTI class of antiretrovirals.**

Grapefruit or grapefruit juice can inhibit CYP3A enzyme activity and should be avoided with EDURANT®.

8.4 Drug-Herb Interactions

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® (see **Drug-Drug Interactions**, Table 5).

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

8.6 QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and drugs that prolong the QTc interval. In a Phase I study of healthy subjects, rilpivirine at doses of 75 mg and 300 mg once daily was shown to prolong the QTc interval of the electrocardiogram.

EDURANT® is a substrate for CYP3A4. Plasma levels of rilpivirine can be increased by inhibitors of CYP3A4. Drugs that inhibit CYP3A4 include, but are not limited to, indinavir, ritonavir, nelfinavir, saquinavir, azole antifungal agents (e.g., ketoconazole, fluconazole, voriconazole), clarithromycin, erythromycin, and telithromycin. Caution should be observed if these drugs are to be used concomitantly with EDURANT®.

Caution should be observed when using EDURANT® with drugs that can disrupt electrolyte levels, including, but not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.

EDURANT® should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes (**see WARNINGS AND PRECAUTIONS, Cardiovascular**).

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Rilpivirine is a diarylpyrimidine NNRTI of human immunodeficiency virus type 1 (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 α, β and γ.

9.2 Pharmacodynamics

Effect on Electrocardiogram: The effect of EDURANT® on the QTc interval of the ECG was evaluated in two Phase I studies in healthy adult volunteers. EDURANT® at the recommended therapeutic dose of 25 mg q.d. was examined in a double-blind, double-dummy, randomized, placebo- and active-controlled, three-way crossover study in healthy adult volunteers (N=60, 35M/25F), with 13 ECG recordings over 24 hours on day 11 of treatment (steady-state). EDURANT® at the dose of 25 mg q.d. was not associated with a statistically significant or clinically relevant effect on the QTc interval. EDURANT® at doses of 75 mg q.d., and 300 mg q.d. was studied in a double-blind, double-dummy, randomized, placebo and active controlled, three-way crossover study in healthy adult volunteers (N=41, 22F/19M), with 13 ECG recordings over 24 hours on day 1 and day 11 of treatment. On day 11 of treatment (steady-state), the maximum mean QTc interval prolongation (baseline- and placebo-adjusted) was 10.7 (90% CI 6.1, 15.3) ms in the 75 mg q.d. treatment arm and 23.3 (90% CI 18.0, 28.7) ms at 4.5 h post-dosing in the 300 mg q.d. arm.

For QTc interval effects with long-term treatment in the target patient population see **ADVERSE REACTIONS**, **Electrocardiogram Findings**. See also **WARNINGS AND PRECAUTIONS**, **Cardiovascular** and **DRUG INTERACTIONS**, **QT Prolonging Drugs**.

Safety Pharmacology
Concentration-dependent inhibition of potassium-currents involved in the repolarisation of the cardiac action potential and prolongation of QT interval from baseline in arterially perfused rabbit left ventricular wedge preparations were observed in the *in vitro* safety pharmacology studies.

In an antibody-based chemoluminescent assay, rilpivirine was found to decrease the surface expression of hERG potassium channels by 29% and 36% at nominal concentrations of 3.7 and 11.0 µg/mL.

9.3 Pharmacokinetics

The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in antiretroviral treatment-naïve HIV-1-infected subjects 12 years of age and older. Exposure to rilpivirine was generally lower in HIV-1 infected subjects than in healthy subjects.

Table 9: Population Pharmacokinetic Estimates of Rilpivirine 25 mg Once Daily in Antiretroviral Treatment-Naïve HIV-1-Infected Subjects (Pooled Data from Phase III Trials at 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: After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours. Steady-state plasma concentrations are reached in approximately 11 days. In a number of healthy subjects, multiple absorption peaks and/or an increase in absorption between 12 hours and 24 hours post-dose is observed. The underlying mechanism(s) for these observations is unknown. The absolute bioavailability of EDURANT® is unknown.

Effect of food on 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. Therefore, to achieve optimal exposure, EDURANT® should be 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.

Elimination: The terminal elimination half-life of rilpivirine is approximately 45 hours. After single-dose oral administration of ^{14}C-rilpivirine, on average 85% and 6.1% of the radioactivity

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

Special Populations and Conditions

Pediatrics: The pharmacokinetics of rilpivirine in antiretroviral treatment naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age receiving EDURANT® 25 mg once daily were comparable to those in treatment-naive HIV-1 infected adults receiving EDURANT® 25 mg once daily. There was no clinically significant impact of body weight on rilpivirine pharmacokinetics in pediatric subjects in trial C213 (33 to 93 kg).

The safety and efficacy of EDURANT® in pediatric patients less than 12 years of age has not been established.

Geriatrics: Clinical studies of EDURANT® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from adult subjects < 65 years of age. EDURANT® should be used with caution in this population (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**).

Sex: Population pharmacokinetic analysis of rilpivirine in HIV-infected patients indicated no clinically relevant differences in the pharmacokinetics of rilpivirine between men and women.

Age: Population pharmacokinetic analysis of rilpivirine in HIV-infected patients indicated no clinically relevant differences in the pharmacokinetics of rilpivirine across the age range of 18–78 years (the analysis included only two subjects above 65 years).

Pregnancy and Breast-feeding:

Pregnancy and Postpartum

The exposure to total rilpivirine after intake of rilpivirine 25 mg once daily as part of an antiretroviral regimen was lower during pregnancy (similar for the 2nd and 3rd trimester) compared with postpartum (see Table 10). The decrease in unbound (i.e., active) rilpivirine pharmacokinetic parameters during pregnancy compared to postpartum was less pronounced than for total rilpivirine.

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

Table 10: Pharmacokinetic Results of Total Rilpivirine After Administration of Rilpivirine 25 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total rilpivirine (mean ±SD, t_{max}: median [range])	**Postpartum (6-12 Weeks) (n=11)**	**2nd Trimester of pregnancy (n=15)**	**3rd Trimester of pregnancy (n=13)**
C_{min}, ng/mL	84.0 ± 58.8	54.3 ± 25.8	52.9 ± 24.4

C_{max}, ng/mL	167 ± 101	121 ±45.9	123 ± 47.5
t_{max}, h	4.00 (2.03-25.08)	4.00 (1.00-9.00)	4.00 (2.00-24.93)
AUC_{24h}, ng.h/mL	2714 ± 1535	1792 ± 711	1762 ± 662

Ethnic origin: Population pharmacokinetic analysis of rilpivirine in HIV-infected patients indicated that race had no clinically relevant effect on the pharmacokinetics of rilpivirine.

Hepatic Insufficiency: 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. EDURANT® has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) (see **WARNINGS AND PRECAUTIONS**, **Hepatic Impairment** and **DOSAGE AND ADMINISTRATION**).

Hepatitis B 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 Insufficiency: The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. Therefore, the impact of renal impairment on rilpivirine elimination is expected to be minimal. As 99.7% of rilpivirine is bound to plasma, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis (see **WARNINGS AND PRECAUTIONS**, **Renal** and **DOSAGE AND ADMINISTRATION**, **Renal Impairment**).

10 STORAGE, STABILITY AND DISPOSAL

Store EDURANT® (rilpivirine) tablets between 15–30°C. Store in the original bottle and protect from light.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

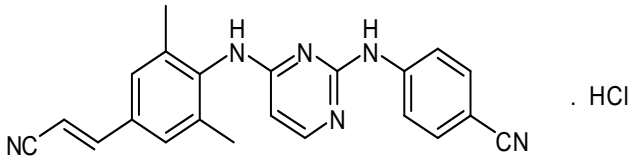
Drug Substance

Proper name: rilpivirine hydrochloride

Chemical name: 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride

Molecular formula and molecular mass: $C_{22}H_{18}N_6 . HCl$
402.88 – rilpivirine hydrochloride
366.42 – rilpivirine

Structural formula:



Physicochemical properties:

Description:	Rilpivirine hydrochloride is a white to almost white powder.
Solubility:	Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.
pKa:	The pKa is 5.6 (pyrimidine moiety)

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

Treatment-Naïve Adult Patients

Trial TMC278-C209 (ECHO) and TMC278-C215 (THRIVE)

The evidence of efficacy of EDURANT® (rilpivirine) is based on the analyses of 48 and 96-week data from two Phase III trials in antiretroviral treatment-naïve HIV-1 infected adult subjects (Table 11). Similar efficacy for EDURANT® was seen in each trial demonstrating non-inferiority to efavirenz.

Subjects with plasma HIV-1 RNA ≥5000 copies/mL, who were screened for susceptibility to N(t)RTIs and for absence of specific NNRTI RAMs, were included in the trials. The treatments are summarized in Table 11:

Table 11: Study Design, Dosage and Administration in the Treatment and Active Control Arms, and Type of Background Regimens used in Antiretroviral Treatment-Naïve HIV-1 Infected Adult Patients in Studies TMC278-C209 (ECHO) and TMC278-C215 (THRIVE)

Study	EDURANT® + BR	Efavirenz + BR (Control)
TMC278-C209 (ECHO) *Phase III, randomized, double-blind, active control, multicentre.*	**EDURANT®[a] 25 mg** (Oral) once daily **BR[c]**, Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC)	**Efavirenz[b] 600 mg** (Oral) once daily **BR[c]**, Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC)
TMC278-C215 (THRIVE) *Phase III, randomized, double-blind, active control, multicentre.*	**EDURANT®[a] 25 mg** (Oral) once daily **BR[d]**, Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC), or ● Zidovudine (ZDV) plus Lamivudine (3TC), or ● Abacavir (ABV) plus Lamivudine (3TC).	**Efavirenz[b] 600 mg** (Oral) once daily **BR[d]**, Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) or ● Zidovudine (ZDV) plus Lamivudine (3TC) or ● Abacavir (ABV) plus Lamivudine (3TC).

a: See EDURANT®'s DOSAGE AND ADMINISTRATION section for complete guidance on clinical usage.
b: See efavirenz (SUSTIVA) Product Monograph for additional information.
c: BR = Background regimen. See TRUVADA Product Monograph or the individual Product Monographs of EMTRIVA or VIREAD for complete guidance on the dosage and administration of background regimens.
d: BR = Background regimen. The choice of background regimen was at the discretion of the investigator. See Product Monographs of the individual drugs for complete guidance on dosage and administration.

In the pooled analyses of TMC278-C209 and TMC278-C215 the demographic and baseline disease characteristics were balanced between the EDURANT® arm and efavirenz (control) arms (Table 12).

Table 12: Demographic and Baseline Disease Characteristics of Antiretroviral Treatment-Naïve HIV-1 Infected Adult Patients in Studies TMC278-C209 (ECHO) and TMC278-C215 (THRIVE), Pooled Analysis

	Pooled Data from Trials TMC278-C209 and TMC278-C215	
	EDURANT® + BR N=686	**Efavirenz + BR N=682**
Demographic Characteristics		
Medium 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)
Percent of Patients with Baseline Plasma Viral Load; ≤ 100,000 > 100,000 to ≤ 500,000 > 500,000	 54% 36% 10%	 48% 40% 12%
Median Baseline CD4+ Cell Count (range), cells/mm^3	249 (1-888)	260 (1-1137)
Percent of Patients with Hepatitis B/C Virus Co-infection	7%	10%
Percent of Patients with the following background regimens: ●Tenofovir disoproxil fumarate plus emtricitabine ● zidovudine plus lamivudine ● abacavir plus lamivudine	 80% 15% 5%	 80% 15% 5%
BR = Background regimen		

12.2 Study Results

Efficacy at Week 48 and Week 96 for subjects in the EDURANT® and efavirenz arms for the pooled data from the TMC278-C209 and TMC278-C215 study populations are shown in Table 13. The response rate (confirmed undetectable viral load < 50 HIV-1 RNA copies/mL) at Week 96 was comparable between the EDURANT® arm and the efavirenz arm. The incidence of virologic failure was higher in the EDURANT® arm than the efavirenz arm at Week 96; however, most of the virologic failures occurred within the first 48 weeks of treatment. Discontinuations due to adverse events were higher in the efavirenz arm than the EDURANT® arm.

Table 13: Virologic Outcome of Randomized Treatment in the TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials in Adults (Pooled Analysis at Week 48 and Week 96; ITT-TLOVR[a])

Outcomes	Outcome at Week 48		Outcome at Week 96	
	EDURANT® + BR N=686	**Efavirenz + BR N=682**	**EDURANT® + BR N=686**	**Efavirenz + BR N=682**
Confirmed Undetectable Viral Load (< 50 HIV-1 RNA copies/mL) [bc]				
Overall	84.3%	82.3%	77.6%	77.6%
≤ 100,000	90.2%	83.6%	84.0%	79.9%
> 100,000	77.4%	81.0%	70.1%	75.4%

Virologic Failure[e]				
Overall	9.0%	4.8%	11.5%	5.9%
≤ 100,000	3.8%	3.3%	5.7%	3.6%
> 100,000	15.1%	6.3%	18.2%	7.9%
Death	0.1%	0.4%	0.1%	0.9%
Discontinued due to adverse event (AE)	2.0%	6.7%	3.8%	7.6%
Discontinued for non-AE reason[d]	4.5%	5.7%	7.0%	8.1%

N = number of subjects per treatment group
BR = Background regimen
a: ITT, Intent-to-treat time to loss of virologic response
b: Subjects achieved virologic response (two consecutive viral loads < 50 copies/mL) and maintained it through Week 48/96.
c: Predicted difference of response rates (95% CI) at Week 48: 1.6% (-2.2%; 5.3%) and at week 96: -0.4%(-4.6%:3.8%); both p-values < 0.0001 (non-inferiority at 12% margin) from logistic regression model, including stratification factors and study.
d: e.g., lost to follow-up, non-compliance, withdrew consent
e: Virologic failure in pooled efficacy analysis: includes subjects who were rebounder (confirmed viral load ≥ 50 copies/mL after being responder) or who were never suppressed (no confirmed viral load < 50 copies/mL, either ongoing or discontinued due to lack or loss of efficacy).

At week 48, the mean change from baseline in CD4+ cell count was 192 cells/mm^3 in the EDURANT®-treated subjects and 176 cells/mm^3 in the efavirenz-treated subjects in the pooled analysis of the ECHO and THRIVE trials [estimated treatment difference (95% CI): 18.0 (2.2; 33.7)].

At week 96, the mean change from baseline in CD4+ cell count was 228 cells/mm^3 in the EDURANT®-treated subjects and 219 cells/mm^3 in the efavirenz-treated subjects [estimated treatment difference (95% CI): 11.3 (-6.8; 29.4)].

A subgroup analysis of the virological response (<50 HIV-1 RNA copies/mL, TLOVR) at 48 and 96 weeks by background NRTIs, and by CD4+ cell count, and virological failure by CD4+ cell count (pooled data from the TMC278-C209 and TMC278-C215 trials) is presented in Table 14.

Table 14: Subgroup Outcomes (ITT-TLOVR) at Week 48 (primary) and Week 96 in the Pooled TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials in Adults, by Background NRTI, and Baseline CD4+ Cell Count

	Week-48 Outcomes HIV-RNA (<50 copies/mL)		***Week-96 Outcomes HIV-RNA (<50 copies/mL)***	
Variable	**EDURANT® + BR N=686 n/N (%)**	**Efavirenz + BR N=682 n/N (%)**	**EDURANT® + BR N=686 n/N (%)**	**Efavirenz + BR N=682 n/N (%)**
Virological Response by Background NRTI				
tenofovir disoproxil fumarate plus emtricitabine	459/550 (83.5)	450/546 (82.4)	423/550 (76.9)	422/546 (77.3)

zidovudine plus lamivudine	88/101 (87.1)	83/103 (80.6)	82/101 (81.2)	79/103 (76.7)
abacavir plus lamivudine	31/35 (88.6)	28/33 (84.8)	27/35 (77.1)	28/33 (84.8)
Virological Response by Baseline CD4+ Cell Count (cells/mm^3)				
<50	20/34 (58.8)	29/36 (80.6)	19/34 (55.9)	25/36 (69.4)
≥50 - <200	156/194 (80.4)	143/175 (81.7)	138/194 (71.1)	131/175 (74.9)
≥200 - <350	272/313 (86.9)	253/307 (82.4)	252/313 (80.5)	244/307 (79.5)
≥350	130/144 (90.3)	136/164 (82.9)	123/144 (85.4)	129/164 (78.7)
Virological Failure[a] by Baseline CD4+ Cell Count (cells/mm^3)				
<50	6/34 (17.6)	1/36 (2.8)	6/34 (17.6)	4/36 (11.1)
≥50 - <200	27/194 (13.9)	14/175 (8.0)	37/194 (19.1)	14/175 (8.0)
≥200 - <350	21/313 (6.7)	14/307 (4.6)	26/313 (8.3)	15/307 (4.9)
≥350	8/144 (5.6)	4/164 (2.4)	10/144 (6.9)	7/164 (4.3)

N = number of subjects per treatment group
n = number of observations
* Imputations according to the TLOVR algorithm.
a: Includes subjects who were rebounder (confirmed viral load ≥50 copies/mL after being responder) or who were never suppressed (no confirmed viral load <50 copies/mL, either ongoing or discontinued due to lack or loss of efficacy).

Trial TMC278-C204

Study TMC278-C204 was a randomized, active-controlled, Phase IIb 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 cells/mm^3 in subjects receiving EDURANT® 25 mg and 160 cells/mm^3 in subjects receiving efavirenz.

At 240 weeks, 60% (56/93) of subjects who originally received 25 mg once daily achieved HIV RNA <50 copies/mL compared to 57% (51/89) of subjects in the control group.

Treatment-Naïve Pediatric Patients (12 years to less than 18 years of age)

Trial TMC278-C213

The pharmacokinetics, safety, tolerability and efficacy of EDURANT® 25 mg once daily, in combination with an investigator-selected background regimen (BR) containing two NRTIs, was evaluated in trial TMC278-C213, a single-arm, open-label Phase II trial in antiretroviral treatment-naive HIV-1 infected pediatric subjects 12 to less than 18 years of age and weighing at least 32 kg. This analysis included 36 patients who had completed at least 48 weeks of treatment or discontinued earlier. The 36 subjects had a median age of 14.5 years (range: 12 to 17 years), and were 55.6% female, 88.9% Black and 11.1% Asian.

In the efficacy analysis, most subjects (75%; 28/36) had baseline HIV RNA <100,000 copies/mL. For these 28 subjects, the median baseline plasma HIV-1 RNA was 44,250 (range: 2,060-92,600 copies/mL) and the median baseline CD4+ cell count was 445.5 cells/mm^3 (range: 123 to 983 cells/mm^3).

Among the subjects who had baseline HIV RNA ≤ 100,000, the proportion with HIV-1 RNA <50 copies/mL at Week 48 (TLOVR) was 79% (22/28), versus 50.0% (4/8) in those with >100,000 copies/mL. The proportion of virologic failures among subjects with a baseline viral load ≤100,000 copies/mL was 17.9% (5/28), versus 37.5% (3/8) in those with >100,000 copies/mL. One subject discontinued due to an adverse event and one subject discontinued due to reasons other than an adverse event or virological failure. At Week 48, the mean increase in CD4+ cell count from baseline was 201.2 cells/mm^3.

13 MICROBIOLOGY

Antiviral Activity In Vitro

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM (0.27 ng/mL).

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_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/mL) and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL).

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

Resistance

Resistance *in Vitro*

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_{50} value (FC) above the biological cut-off (BCO) of the assay.

Resistance in Treatment-Naïve Adult Subjects

Considering all of the available *in vitro* and *in vivo* data, 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, Y188L, H221Y, F227C, M230I, and M230L.

In the pooled analysis from two Phase III trials, the emergence of resistance among subjects was greater in the EDURANT® (rilpivirine) arm as compared to the control (efavirenz) arm at Week 48 (10.6%, 5.3%, respectively) and at Week 96 (14%, 7.6% respectively). Fewer virologic failures due to resistance occurred between Week 48 and Week 96 in each of the treatment arms (3.2% and 2.3% in the rilpivirine and control arms, respectively).

Most common emergent NNRTI substitutions in rilpivirine virologic failures at Week 96 included V90I, K101E/P, E138K/G/Q, V179I/L, Y181I/C, V189I, H221Y, F227C/L and M230L. The E138K substitution emerged most frequently during rilpivirine treatment at Week 48 and Week 96, commonly in combination with the M184I mutation. The most common mutations were the same in the Week 48 and Week 96 analyses.

In the Week 96 pooled analysis of the two Phase III trials, of the 35 subjects with virologic failure on EDURANT® and with phenotypic resistance to rilpivirine, 35 (100%) lost susceptibility to lamivudine/emtricitabine. Of the 17 subjects with virologic failure on efavirenz (control) and with phenotypic resistance to efavirenz, 6 (35%) lost susceptibility to lamivudine/emtricitabine. These data were similar to those obtained in the Week 48 pooled analyses.

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 show 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. Clinical isolates resistant to rilpivirine (FC>BCO) were usually also resistant to etravirine.

Cross-Resistance in Treatment-Naïve Adult Subjects
In the Week 48 pooled analysis of the two Phase III trials, of the 62 subjects with virologic failure on EDURANT® for whom phenotypic resistance data was available, 31 (50%) lost susceptibility to rilpivirine and within that subset 28 (90%) were resistant to etravirine, 27 (87%) to efavirenz, and 14 (45%) to nevirapine. Of the 28 subjects with virologic failure on efavirenz (control) for whom phenotypic resistance data was available, 12 (43%) lost susceptibility to efavirenz and within that subset none were resistant to etravirine or to rilpivirine, and 12 (100%) to nevirapine.

In the Week 96 pooled analysis of the two Phase III trials, of the 81 subjects with virologic failure on EDURANT® for whom phenotypic resistance data was available, 35 (43%) lost susceptibility to rilpivirine and within that subset 32 (91%) were resistant to etravirine, 30 (86%) to efavirenz, and 16 (45%) to nevirapine. Of the 41 subjects with virologic failure on efavirenz (control) for whom phenotypic resistance data was available, 17 (41%) lost susceptibility to efavirenz and within that subset 1 (6%) were resistant to etravirine, none to rilpivirine, and 15 (88%) to nevirapine.

In the week 96 pooled analyses, among virologic failures in the EDURANT® arm with baseline viral load ≤ 100,000 copies/mL and with resistance to rilpivirine, there were fewer patients with phenotypic cross-resistance than among those in the EDURANT® arm with baseline viral load > 100,000 copies/mL. 3, 4 and 1 rilpivirine virologic failures with baseline viral load ≤ 100,000 copies/mL and with resistance to rilpivirine (N = 5) had cross-resistance to efavirenz, etravirine and nevirapine, respectively, compared to 27, 28, and 15 rilpivirine virologic failures with baseline viral load > 100,000 copies/mL (N = 30), respectively.

14 NON-CLINICAL TOXICOLOGY

General Toxicology

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

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. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in both 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 may be rodent-specific, associated with liver enzyme induction. The follicular cell findings may be rat-specific, associated with increased clearance of thyroxine. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg q.d.).

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

Reproductive and Developmental Toxicity

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. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function at exposures relevant for human administration.

There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily. In a pre- and postnatal development assessment in rats, rilpivirine had no effect on development of offspring during lactation or post weaning when the mothers were dosed up to 400 mg/kg/day.

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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrEDURANT®
rilpivirine tablets
25 mg rilpivirine as rilpivirine hydrochloride

Read this carefully before you start taking **EDURANT®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EDURANT®**.

What is EDURANT® used for?
- EDURANT® is an anti-HIV (Human Immunodeficiency Virus) medicine that helps to control HIV infection in adults and children (12 years to less than 18 years of age and weighing at least 35 kg). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

How does EDURANT® work?
- EDURANT® blocks an enzyme which the virus (HIV) needs in order to make more virus. The enzyme that EDURANT® blocks is called HIV reverse transcriptase.
- When used with other anti-HIV medicines, EDURANT® may help:
  - reduce the amount of HIV in your blood. This is called "viral load."
  - 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 and, as a result, reduce the risk of death or infections that can happen when your immune system is weak (opportunistic infections).

What are the ingredients in EDURANT®
Medicinal ingredients: rilpivirine in the form of rilpivirine hydrochloride

Non-medicinal ingredients: croscarmellose sodium, hypromellose 2910 6 mPa.s, lactose monohydrate, magnesium stearate, polyethylene glycol 3000, polysorbate 20, povidone K30, silicified microcrystalline cellulose, titanium dioxide and triacetin.

EDURANT® comes in the following dosage forms:
Tablets: 25 mg

Do not use EDURANT® if:
- you are allergic to rilpivirine or any of the other ingredients in EDURANT®
- you take the following drugs:

Type of Drug	Examples of Generic Names
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine, oxcarbazepine, phenytoin, phenobarbital

Type of Drug	Examples of Generic Names
Antimycobacterials	rifapentine, rifampin
Glucocorticoids	Systemic dexamethasone (more than a single dose)
Herbal products	St. John's wort (*Hypericum perforatum*)
Proton Pump Inhibitors (to prevent or treat stomach ulcers, heartburn or acid reflux disease)	omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EDURANT®. Talk about any health conditions or problems you may have, including if you:

- have an eating disorder or are following a strict diet.
- have any drug allergies.
- have heart disease or a heart condition, including a heart rhythm disorder (QT prolongation) or family history of heart rhythm disorders (QT prolongation) or sudden (heart) death under 50 years of age.
- have electrolyte disturbances (e.g., low blood magnesium or potassium levels) or other conditions that could lead to electrolyte disturbances such as dehydration, diarrhea, vomiting.
- have depression or develop depression while taking EDURANT®.
- have had or currently have liver problems, including hepatitis B or C.
- have severe kidney disease.
- are pregnant or planning to become pregnant.
    - It is not known if EDURANT® can harm your unborn baby. You and your doctor will need to decide if taking EDURANT® is right for you.
    - If you take EDURANT® while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- are breast-feeding or plan to breast-feed.
    - Do not breast-feed if you are taking EDURANT®.
    - It is recommended that HIV-infected women not breast-feed their infants because their babies could become infected with HIV through their breast milk. Talk with your doctor about the best way to feed your baby.
- are 65 years of age or older. If you belong to this age group, please discuss the use of EDURANT® with your doctor
- you have a rare hereditary problem of galactose intolerance (severe lactase deficiency or glucose/galactose malabsorption) as this product contains lactose.

Other warnings that you should know about:

Blood Tests:

Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

HIV / AIDS:

EDURANT ® does not cure HIV infection or AIDS. Right now, there is no cure for HIV infection. People taking EDURANT® may still develop opportunistic infections or other conditions that happen with HIV infection.

Opportunistic infections are infections that develop because the immune system is weak. Some of the other conditions that can happen with HIV are: pneumonia, herpes virus infection, and *Mycobacterium avium* complex (MAC) infections.

EDURANT® does **not** reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood.

- 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 on how to prevent passing HIV to other people.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

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®.

EDURANT® can be combined with most HIV medicines while some are not recommended. Your doctor will advise on which HIV medicines can be combined with EDURANT®. Follow your doctor's instruction carefully.

Avoid grapefruit juice as this may increase the blood levels of EDURANT®.

The following may interact with EDURANT®
Tell your doctor if you are taking any of the following medicines. Some of these medicines may be obtained without a prescription and some of these may be available under other names. It is important that you carefully read the package leaflets that are provided with these medicines.

Type of Drug	Examples of Generic Names (Brand Names)	Type of Drug	Examples of Generic Names (Brand Names)
Antacids (to treat heartburn from acid reflux)	Aluminum, magnesium hydroxide, calcium carbonate	**H_2-Receptor Antagonists** (to treat stomach ulcers or used to relieve heartburn from acid reflux)	cimetidine (TAGAMET), famotidine (PEPCID), nizatidine (AXID AR), ranitidine (ZANTAC)

Type of Drug	Examples of Generic Names (Brand Names)	Type of Drug	Examples of Generic Names (Brand Names)
Antimycobacterials: (to treat some bacterial infections)	rifabutin	**Macrolide Antibiotics** (to treat bacterial infections)	clarithromycin (BIAXIN), erythromycin (BENZAMYCIN, AK MYCIN, EES-200/400, EES-600, ERYC, ERYTHRO-S, ERYTHRO-ES, ERYBID, PCE)
Azole Antifungal Agents	ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole	**Narcotic Analgesic**	methadone (METHADOL, METADOL-D, COPHYLAC DROPS)
Corticosteroids (to treat inflammation or asthma)	dexamethasone (DECADRON)		

This is **not** a complete list of medicines that you should tell your doctor about.

How to take EDURANT®:

- **Take EDURANT® tablets every day exactly as prescribed by your doctor.**
- **Always take EDURANT® with a meal.** A meal is important to get the right drug levels in your body. A protein drink alone does not replace a meal.
- Swallow EDURANT® tablets whole with water.
- 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 take:**
    - **rifabutin** (a medicine to treat some bacterial infections), take two tablets of EDURANT® once a day. When you stop taking rifabutin, take one tablet of EDURANT® once a day. Talk to your doctor or pharmacist if you are not sure.
    - **antacids** (a medicine to treat heartburn from acid reflux such as aluminum/magnesium hydroxide, calcium carbonate), take the antacid either at least 2 hours before or at least 4 hours after EDURANT®.
    - **H_2-receptor antagonist** (medicines used to treat stomach ulcers, heartburn or acid reflux disease such as cimetidine, famotidine, nizatidine or ranitidine), take the H_2-receptor antagonist at least 12 hours before or at least 4 hours after EDURANT®.

Usual dose:
The recommended dose is one tablet of EDURANT® one time each day.

Overdose:

If you think you have taken too much EDURANT®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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 double the next dose to make up for a missed dose. Do not take more or less than your prescribed dose of EDURANT® at any one time. Always take EDURANT® with a meal.

What are possible side effects from using EDURANT®?

These are not all the possible side effects you may feel when taking **EDURANT®**. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects (affects less than 1 in 10 people)
- decreased appetite
- depression
- difficulty falling asleep (insomnia), abnormal dreams, sleep disorders
- headache, dizziness
- stomach pain, nausea, vomiting, diarrhea
- rash
- tiredness
- changes in your routine liver tests

Uncommon side effects (affects less than 1 in 100 people)
- depressed mood
- drowsiness
- stomach discomfort

Other side effects include:
- Possible heart rhythm disturbance, such as dizziness, palpitations (feeling rapid heartbeat) fainting or seizures. If you experience any of these symptoms, seek medical help immediately.

Call your doctor right away if you notice any signs or symptoms of an infection after starting EDURANT® with other HIV medicines.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Effect: Depression or mood changes** **Symptoms**: feelings of deep sadness, thoughts of self-harm or suicide.		x	
RARE **Effect: Liver problems** **Symptoms:** abdominal pain, vomiting, nausea, yellowing of the eyes or skin, dark urine or fatigue.		x	
VERY RARE **Effect**: **Severe and potentially life-threatening rash** **Symptoms:** fever, blisters, blisters of the mouth and throat, swollen face or limbs, red spots on the skin, abdominal pain, nausea, vomiting, dark urine, or yellowing of the skin and eyes.		x	
VERY RARE **Effect: Changes to your immune system** **Symptoms:** fever, joint or muscle pain, redness, rash, swelling, abdominal pain, yellowing of the skin and eyes, or fatigue.		x	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store EDURANT® tablets at room temperature between 15–30°C.
- Keep EDURANT® in the bottle given to you by your pharmacist and protect the bottle from light**.**

Keep out of reach and sight of children.

If you want more information about EDURANT®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html) .
- For questions, concerns and the full product monograph go to http://www.janssen.com/canada or contact the manufacturer, Janssen Inc. by calling 1-800-567-3331 or 1-800-387-8781.

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