## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**EDURANT (rilpivirine) tablets for oral use**
**Initial U.S. Approval: 2011**

### ----------INDICATIONS AND USAGE ----------

EDURANT is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated
- in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve patients with HIV-1 RNA less than or equal to 100,000 copies/mL (1).

Limitations of Use:

- More EDURANT treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥ 50 copies/mL) compared to EDURANT treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL. (1, 14)
- 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$^3$. (1, 14)
- The observed virologic failure rate in EDURANT treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz. (1, 12.4)
- More subjects treated with EDURANT developed tenofovir and lamivudine/emtricitabine associated resistance compared to efavirenz. (1, 12.4, 14)

### ----------DOSAGE AND ADMINISTRATION ----------

- 25 mg (one 25 mg tablet) taken once daily with a meal. (2)
- EDURANT is not recommended for patients less than 12 years of age. (8.4)
- With rifabutin co-administration, the EDURANT dose should be increased to 50 mg (two tablets of 25 mg each) taken once daily with a meal. When rifabutin co-administration is stopped, the EDURANT dose should be decreased to 25 mg taken once daily with a meal. (2, 7, 12.3)

### ----------DOSAGE FORMS AND STRENGTHS ----------

25 mg tablets (3)

### ----------CONTRAINDICATIONS ----------

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

### ----------WARNINGS AND PRECAUTIONS ----------

- Caution should be given to prescribing EDURANT with drugs that may reduce the exposure of rilpivirine. (5.1)
- Caution should be given to prescribing EDURANT with drugs with a known risk of Torsade de Pointes. (5.1)
- Skin and Hypersensitivity Reactions: Severe skin and hypersensitivity reactions have been reported during postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. Immediately discontinue treatment if hypersensitivity or rash with systemic symptoms or elevations in hepatic serum biochemistries develop and closely monitor clinical status, including hepatic serum biochemistries. (5.2)
- Depressive Disorders: Severe depressive disorders have been reported. Immediate medical evaluation is recommended for severe depressive disorders. (5.3)
- Hepatotoxicity: Hepatic adverse events have been reported in patients with underlying liver disease, including hepatitis B or C co-infection, or in patients with elevated baseline transaminases. A few cases of hepatotoxicity have occurred in patients with no pre-existing hepatic disease. Monitor liver function tests before and during treatment with EDURANT in patients with underlying hepatic disease, such as hepatitis B or C co-infection, or marked elevations in transaminase. Also consider monitoring liver functions tests in patients without pre-existing hepatic dysfunction or other risk factors. (5.4)
- Patients may develop redistribution/accumulation of body fat (5.5) or immune reconstitution syndrome. (5.6)

### ----------ADVERSE REACTIONS ----------

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

**To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

### ----------DRUG INTERACTIONS ----------

- EDURANT should not be used in combination with NNRTIs. (7)
- Co-administration of EDURANT with drugs that induce or inhibit CYP3A may affect the plasma concentrations of rilpivirine. (7)
- Co-administration of EDURANT with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine. (7)
- Refer to the Full Prescribing Information for other drugs that should not be co-administered with EDURANT and for other drugs that may require a change in dose or regimen. (7)

### ----------USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk.(8.1)
- Nursing Mothers: Mothers should not breastfeed due to the potential for HIV transmission. (8.3)
- Pediatrics: Safety and effectiveness have not been established in patients less than 12 years of age. (8.4)

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

**Revised: 9/2017**

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

EDURANT®, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

Limitations of Use:

- More EDURANT treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥ 50 copies/mL) compared to EDURANT treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL *[see Clinical Studies (14.1)]*.

- Regardless of HIV-1 RNA at the start of therapy, more EDURANT treated subjects with CD4+ cell count less than 200 cells/mm$^3$ experienced virologic failure compared to EDURANT treated subjects with CD4+ cell count greater than or equal to 200 cells/mm$^3$ *[see Clinical Studies (14.1)]*.

- The observed virologic failure rate in EDURANT treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz *[see Microbiology (12.4)]*.

- More subjects treated with EDURANT developed tenofovir and lamivudine/emtricitabine associated resistance compared to efavirenz *[see Microbiology (12.4)]*.

## 2 DOSAGE AND ADMINISTRATION

The recommended dosage of EDURANT in patients 12 years of age and older and weighing at least 35 kg is one 25 mg tablet once daily taken orally with a meal *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*. EDURANT is not recommended for patients less than 12 years of age.

*Rifabutin Co-administration:* 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 (7), Clinical Pharmacology (12.3)]*.

## 3 DOSAGE FORMS AND STRENGTHS

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



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## 4 CONTRAINDICATIONS

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

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Drug Interactions

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

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

### 5.2 Skin and Hypersensitivity Reactions

Severe skin and hypersensitivity reactions have been reported during the postmarketing 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 3 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 (6 and 6.2)]*. 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.



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## 5.3 Depressive Disorders

The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with EDURANT. 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.

During the Phase 3 trials in adults (N = 1368) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among EDURANT (n = 686) or efavirenz (n = 682) was 9% and 8%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both EDURANT and efavirenz. The incidence of discontinuation due to depressive disorders among EDURANT or efavirenz was 1% in each arm. Suicidal ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the EDURANT arm.

During the Phase 2 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.

## 5.4 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 adult 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.

## 5.5 Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.



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## 5.6 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including EDURANT. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, 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.

# 6 ADVERSE REACTIONS

The following adverse drug reactions (ADRs) are discussed in greater detail in other sections of the package insert:

- Skin and Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Depressive Disorders *[see Warnings and Precautions (5.3)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*

## 6.1 Clinical Trials Experience: Adults

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety assessment is based on the Week 96 pooled data from 1368 patients in the Phase 3 controlled trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in antiretroviral treatment-naïve HIV-1 infected adult patients, 686 of whom received EDURANT (25 mg once daily) *[see Clinical Studies (14.1)]*. The median duration of exposure for patients in the EDURANT arm and efavirenz arm was 104.3 and 104.1 weeks, respectively. Most ADRs occurred in the first 48 weeks of treatment. The proportion of subjects who discontinued treatment with EDURANT or efavirenz due to ADR, regardless of severity, was 2% and 4%, respectively. The most common ADRs leading to discontinuation were psychiatric disorders: 10 (1%) subjects in the EDURANT arm and 11 (2%) subjects in the efavirenz arm. Rash led to discontinuation in 1 (0.1%) subject in the EDURANT arm and 10 (1.5%) subjects in the efavirenz arm.

***Common Adverse Drug Reactions***



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

**Table 1: Selected Treatment-Emergent Adverse Drug Reactions of at least Moderate Intensity* (Grades 2-4) Occurring in at Least 2% of Antiretroviral Treatment-Naïve HIV-1 Infected Adult Subjects (Week 96 Analysis)**

| System Organ Class, Preferred Term, % | Pooled Data from the Phase 3 TMC278-C209 and TMC278-C215 Trials | |
|---|---|---|
| | EDURANT + BR N=686 | Efavirenz + BR N=682 |
| **Gastrointestinal Disorders** | | |
| Abdominal pain | 2% | 2% |
| Nausea | 1% | 3% |
| Vomiting | 1% | 2% |
| **General Disorders and Administration Site Conditions** | | |
| Fatigue | 2% | 2% |
| **Nervous System Disorders** | | |
| Headache | 3% | 4% |
| Dizziness | 1% | 7% |
| **Psychiatric Disorders** | | |
| Depressive disorders† | 5% | 4% |
| Insomnia | 3% | 4% |
| Abnormal dreams | 2% | 4% |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Rash | 3% | 11% |

N = total number of subjects per treatment group; BR = background regimen

* Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).

† Includes adverse drug reactions reported as depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicide ideation.

No new ADR terms were identified in adult subjects in the Phase 3 TMC278-C209 and TMC278-C215 trials between 48 weeks and 96 weeks nor in the Phase 2b TMC278-C204 trial through 240 weeks. The incidence of adverse events in the Phase 2b TMC278-C204 trial was similar to the Phase 3 trials through 96 weeks.

*Less Common Adverse Drug Reactions*

Treatment-emergent ADRs of at least moderate intensity (≥ Grade 2) occurring in less than 2% 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*: diarrhea, abdominal discomfort

*Hepatobiliary Disorders*: cholecystitis, cholelithiasis



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*Metabolism and Nutrition Disorders*: decreased appetite

*Nervous System Disorders*: somnolence

*Psychiatric Disorders*: sleep disorders, anxiety

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

*Laboratory Abnormalities in Treatment-Naïve Subjects*

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

**Table 2: Selected Treatment-Emergent Changes in Laboratory Parameters (Grades 1 to 4) Observed in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects (Week 96 Analysis)**

| **Laboratory Parameter Abnormality, (%)** | **DAIDS Toxicity Range** | **Pooled Data from the Phase 3 TMC278-C209 and TMC278-C215 Trials** | |
|---|---|---|---|
| | | **EDURANT + BR N=686** | **Efavirenz + BR N=682** |
| ***BIOCHEMISTRY*** | | | |
| Increased Creatinine | | | |
| Grade 1 | ≥ 1.1-≤ 1.3 x ULN | 6% | 1% |
| Grade 2 | > 1.3-≤ 1.8 x ULN | 1% | 1% |
| Grade 3 | > 1.8-≤ 3.4 x ULN | <1% | 0 |
| Grade 4 | > 3.4 x ULN | 0 | <1% |
| Increased AST | | | |
| Grade 1 | ≥ 1.25-≤ 2.5 x ULN | 16% | 19% |
| Grade 2 | > 2.5-≤ 5.0 x ULN | 4% | 7% |
| Grade 3 | > 5.0-≤ 10.0 x ULN | 2% | 2% |
| Grade 4 | > 10.0 x ULN | 1% | 1% |
| Increased ALT | | | |
| Grade 1 | ≥ 1.25-≤ 2.5 x ULN | 18% | 20% |
| Grade 2 | > 2.5-≤ 5.0 x ULN | 5% | 7% |
| Grade 3 | > 5.0-≤ 10.0 x ULN | 1% | 2% |
| Grade 4 | > 10.0 x ULN | 1% | 1% |
| Increased Total Bilirubin | | | |
| Grade 1 | ≥ 1.1-≤ 1.5 x ULN | 5% | <1% |
| Grade 2 | > 1.5-≤ 2.5 x ULN | 3% | 1% |
| Grade 3 | > 2.5-≤ 5.0 x ULN | 1% | <1% |
| Grade 4 | > 5.0 x ULN | 0 | 0 |
| Increased Total Cholesterol (fasted) | | | |
| Grade 1 | 5.18-6.19 mmol/L<br>200-239 mg/dL | 17% | 31% |
| Grade 2 | 6.20-7.77 mmol/L<br>240-300 mg/dL | 7% | 19% |



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| | | | |
|---|---|---|---|
| Grade 3 | > 7.77 mmol/L<br>> 300 mg/dL | <1% | 3% |
| Increased LDL Cholesterol (fasted) | | | |
| Grade 1 | 3.37-4.12 mmol/L<br>130-159 mg/dL | 14% | 26% |
| Grade 2 | 4.13-4.90 mmol/L<br>160-190 mg/dL | 5% | 13% |
| Grade 3 | ≥ 4.91 mmol/L<br>≥ 191 mg/dL | 1% | 5% |
| Increased Triglycerides (fasted) | | | |
| Grade 2 | 5.65-8.48 mmol/L<br>500-750 mg/dL | 2% | 2% |
| Grade 3 | 8.49-13.56 mmol/L<br>751-1,200 mg/dL | 1% | 3% |
| Grade 4 | > 13.56 mmol/L<br>> 1,200 mg/dL | 0 | 1% |

BR = background regimen; ULN = upper limit of normal
N = number of subjects per treatment group
Note: Percentages were calculated versus the number of subjects in ITT.

*Adrenal Function*

In the pooled Phase 3 trials, at Week 96, there was an overall mean change from baseline in basal cortisol of -0.69 (-1.12, 0.27) micrograms/dL in the EDURANT group and of -0.02 (-0.48, 0.44) micrograms/dL in the efavirenz group.

In the EDURANT group, 43/588 (7.3%) of 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 compared to 18/561 (3.2%) in the efavirenz group. Of the subjects who developed an abnormal 250 micrograms ACTH stimulation test during the trial, fourteen subjects in the EDURANT group and nine subjects in the efavirenz group had an abnormal 250 micrograms ACTH stimulation test at Week 96. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the higher abnormal rate of 250 micrograms ACTH stimulation tests in the EDURANT group is not known.

*Serum Creatinine*

In the pooled Phase 3 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.



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*Serum Lipids*

Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are presented in Table 3. The clinical benefit of these findings has not been demonstrated.

**Table 3: Lipid Values, Mean Change from Baseline***

| | **Pooled Data from the Week 96 Analysis of the Phase 3 TMC278-C209 and TMC278-C215 Trials** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **EDURANT + BR** | | | | **Efavirenz + BR** | | | |
| | **N** | **Baseline** | **Week 96** | | **N** | **Baseline** | **Week 96** | |
| Mean (95% CI) | | **Mean (mg/dL)** | **Mean (mg/dL)** | **Mean Change† (mg/dL)** | | **Mean (mg/dL)** | **Mean (mg/dL)** | **Mean Change† (mg/dL)** |
| Total Cholesterol (fasted) | 546 | 161 | 166 | 5 | 507 | 160 | 187 | 28 |
| HDL-cholesterol (fasted) | 545 | 41 | 46 | 4 | 505 | 40 | 51 | 11 |
| LDL-cholesterol (fasted) | 543 | 96 | 98 | 1 | 503 | 95 | 109 | 14 |
| Triglycerides (fasted) | 546 | 122 | 116 | -6 | 507 | 130 | 141 | 11 |

N = number of subjects per treatment group; BR = background regimen

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

† The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 96 values

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

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

## 6.2 Clinical Trials Experience: Pediatric Patients

The safety assessment is based on the Week 48 analysis of the single-arm, open-label, Phase 2 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 32 kg received EDURANT (25 mg once daily) in combination with other antiretroviral agents *[see Clinical Studies (14.2)]*. 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 reported in at least 2 subjects (regardless of severity) include headache (19.4%), depression (19.4%), somnolence (13.9%), nausea (11.1%), dizziness (8.3%), abdominal pain (8.3), vomiting (5.6%) and rash (5.6%).



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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.

### 6.3 Postmarketing Experience

Adverse reactions have been identified during postmarketing experience 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)

## 7 DRUG INTERACTIONS

*[See Dosage and Administration (2), Contraindications (4)* and *Clinical Pharmacology (12.3).]*

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

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

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



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**Table 4: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction** ***[see Clinical Pharmacology (12.3)]***

| **Concomitant Drug Class: Drug Name** | **Effect on Concentration of Rilpivirine or Concomitant Drug** | **Clinical Comment** |
|---|---|---|
| **HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)** | | |
| didanosine*† | ↔ rilpivirine<br>↔ didanosine | No dose adjustment is required when EDURANT is co-administered with didanosine. Didanosine is to be administered on an empty stomach and at least two hours before or at least four hours after EDURANT (which should be administered with a meal). |
| **HIV-Antiviral Agents: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** | | |
| NNRTI<br>(delavirdine)<br><br>Other NNRTIs<br>(efavirenz, etravirine, nevirapine) | ↑ rilpivirine<br>↔ delavirdine<br><br>↓ rilpivirine<br>↔ other NNRTIs | It is not recommended to co-administer EDURANT with delavirdine and other NNRTIs. |
| **HIV-Antiviral Agents: Protease Inhibitors (PIs)-Boosted (i.e., with co-administration of low-dose ritonavir) or Unboosted (i.e., without co-administration of low-dose ritonavir)** | | |
| darunavir/ritonavir*† | ↑ rilpivirine<br>↔ boosted darunavir | Concomitant use of EDURANT with darunavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EDURANT is co-administered with darunavir/ritonavir. |
| lopinavir/ritonavir*† | ↑ rilpivirine<br>↔ boosted lopinavir | Concomitant use of EDURANT with lopinavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EDURANT is co-administered with lopinavir/ritonavir. |
| other boosted PIs (atazanavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir, tipranavir/ritonavir) | ↑ rilpivirine<br>↔ 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<br>↔ unboosted PI | Concomitant use of EDURANT with unboosted PIs may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). EDURANT is not expected to affect the plasma concentrations of co-administered PIs. |
| **Other Agents** | | |
| **Antacids:**<br>antacids (e.g., aluminum or magnesium hydroxide, calcium carbonate) | ↔ rilpivirine (antacids taken at least 2 hours before or at least 4 hours after rilpivirine)<br><br>↓ rilpivirine (concomitant intake) | 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. |



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| | | |
|---|---|---|
| **Antimycobacterials:**<br>rifabutin* | ↓ rilpivirine | Concomitant use of EDURANT with rifabutin may cause a decrease in the plasma concentrations of rilpivirine (induction of CYP3A enzymes). Throughout co-administration of EDURANT with rifabutin, the EDURANT dose should be increased from 25 mg once daily to 50 mg once daily. When rifabutin co-administration is stopped, the EDURANT dose should be decreased to 25 mg once daily. |
| **Azole Antifungal Agents**:<br>fluconazole<br>itraconazole<br>ketoconazole*†<br>posaconazole<br>voriconazole | ↑ rilpivirine<br>↓ ketoconazole | Concomitant use of EDURANT with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No rilpivirine dose adjustment is required when EDURANT is co-administered with azole antifungal agents. Clinically monitor for breakthrough fungal infections when azole antifungals are co-administered with EDURANT. |
| **$H_2$-Receptor Antagonists**:<br>cimetidine<br>famotidine*†<br>nizatidine<br>ranitidine | ↔ rilpivirine (famotidine taken 12 hours before rilpivirine or 4 hours after rilpivirine)<br><br>↓ rilpivirine (famotidine taken 2 hours before rilpivirine) | The combination of EDURANT and $H_2$-receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). $H_2$-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EDURANT. |
| **Macrolide or ketolide antibiotics**:<br>clarithromycin erythromycin<br>telithromycin | ↑ rilpivirine<br>↔ clarithromycin<br>↔ erythromycin<br>↔ telithromycin | Concomitant use of EDURANT with clarithromycin, erythromycin or telithromycin 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**:<br>methadone* | ↓ R(-) methadone<br>↓ S(+) methadone | No dose adjustments are required when initiating co-administration of methadone with EDURANT. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients. |

↑ = 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.

In addition to the drugs included in Table 4, the interaction between EDURANT and the following drugs was evaluated in clinical studies and no dose adjustment is needed for either drug *[see Clinical Pharmacology (12.3)]*: acetaminophen, atorvastatin, chlorzoxazone, ethinylestradiol, norethindrone, raltegravir, sildenafil, simeprevir and tenofovir disoproxil fumarate. Rilpivirine did not have a clinically significant effect on the pharmacokinetics of digoxin or metformin. No clinically relevant drug-drug interaction is expected when EDURANT is co-administered with maraviroc, ribavirin or the NRTIs abacavir, emtricitabine, lamivudine, stavudine and zidovudine.



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QT Prolonging Drugs

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

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

*Pregnancy Category B*

No adequate and well-controlled or pharmacokinetic studies of EDURANT use in pregnant women have been conducted. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with rilpivirine during pregnancy and lactation, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily. EDURANT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Antiretroviral Pregnancy Registry*

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

## 8.3 Nursing Mothers

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

## 8.4 Pediatric Use

The safety, efficacy and pharmacokinetics of EDURANT were evaluated in a single arm, open-label, Phase 2 trial that enrolled 36 antiretroviral treatment-naïve, HIV-1 infected pediatric subjects 12 to less than 18 years of age and weighing at least 32 kg *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*. Please see *Dosage and Administration (2)* for dosing recommendations for pediatric patients 12 years of age and older.



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Safety and effectiveness in pediatric patients less than 12 years of age have not been established.

### 8.5 Geriatric Use

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

### 8.6 Hepatic Impairment

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

### 8.7 Renal Impairment

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

## 10 OVERDOSAGE

There is no specific antidote for overdose with EDURANT. Human experience of overdose with EDURANT is limited. Treatment of overdose with EDURANT consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. Administration of activated charcoal may be used to aid in removal of unabsorbed active substance. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

## 11 DESCRIPTION

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

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



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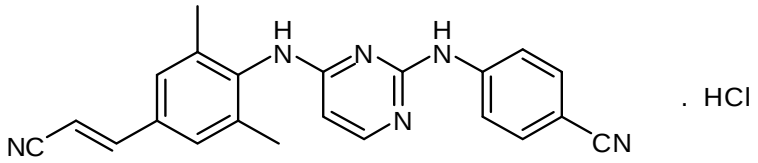


Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

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

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

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

## 12.2 Pharmacodynamics

*Effects on Electrocardiogram*

The effect of EDURANT at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady state. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction was 2.0 (5.0) milliseconds (i.e., below the threshold of clinical concern).

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of EDURANT were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction were 10.7 (15.3) and 23.3 (28.4) milliseconds, respectively. Steady-state administration of EDURANT 75 mg once daily and 300 mg once daily resulted in a mean steady-state $C_{max}$ approximately 2.6-fold and 6.7-fold, respectively, higher than the mean $C_{max}$ observed with the recommended 25 mg once daily dose of EDURANT *[see Warnings and Precautions (5.1)]*.

## 12.3 Pharmacokinetics

*Pharmacokinetics in Adults*

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



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**Table 5: Population Pharmacokinetic Estimates of Rilpivirine 25 mg once daily in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects (Pooled Data from Phase 3 Trials through Week 96)**

| **Parameter** | **Rilpivirine 25 mg once daily N = 679** |
|---|---|
| $AUC_{24h}$ (ng•h/mL) | |
| Mean ± Standard Deviation | 2235 ± 851 |
| Median (Range) | 2096 (198 - 7307) |
| $C_{0h}$ (ng/mL) | |
| Mean ± Standard Deviation | 79 ± 35 |
| Median (Range) | 73 (2 - 288) |

*Absorption and Bioavailability*

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

*Effects of Food on Oral Absorption*

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

*Distribution*

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

*Metabolism*

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

*Elimination*

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

*Hepatic Impairment*



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

*Hepatitis B and/or Hepatitis C Virus Co-infection*

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

*Renal Impairment*

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

*Gender*

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

*Race*

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

*Pediatric Patients*

The pharmacokinetics 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-naïve HIV-1 infected adults receiving EDURANT 25 mg once daily. There



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was no clinically significant impact of body weight on rilpivirine pharmacokinetics in pediatric subjects in trial C213 (33 to 93 kg).

**Table 6: Population Pharmacokinetic Estimates of Rilpivirine 25 mg once daily in Antiretroviral Treatment-Naïve HIV-1-Infected Pediatric Subjects aged 12 to less than 18 years (Data from Phase 2 Trial through Week 48)**

| **Parameter** | **Rilpivirine 25 mg once daily N = 34** |
|---|---|
| $AUC_{24h}$ (ng•h/mL) | |
| Mean ± Standard Deviation | 2424 ± 1024 |
| Median (Range) | 2269 (417 - 5166) |
| $C_{0h}$ (ng/mL) | |
| Mean ± Standard Deviation | 85 ± 40 |
| Median (Range) | 79 (7 - 202) |

The pharmacokinetics and dosing recommendations of rilpivirine in pediatric patients less than 12 years of age have not been established *[see Use in Specific Populations (8.4)]*.

*Drug Interactions*

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

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

EDURANT at a dose of 25 mg q.d. is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes.

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



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

| Co-administered Drug | Dose/Schedule: Co-administered Drug | Dose/Schedule: Rilpivirine | N | Mean Ratio of Rilpivirine Pharmacokinetic Parameters With/Without Co-administered Drug (90% CI); No Effect = 1.00: $C_{max}$ | 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. delayed release capsules taken 2 hours before rilpivirine | 150 mg q.d.† | 21 | 1.00 (0.90-1.10) | 1.00 (0.95-1.06) | 1.00 (0.92-1.09) |
| Tenofovir disoproxil fumarate | 300 mg q.d. | 150 mg q.d.† | 16 | 0.96 (0.81-1.13) | 1.01 (0.87-1.18) | 0.99 (0.83-1.16) |
| **Co-Administration With HIV Integrase Strand Transfer 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) |
| Chlorzoxazone | 500 mg single dose taken 2 hours after rilpivirine | 150 mg q.d.† | 16 | 1.17 (1.08-1.27) | 1.25 (1.16-1.35) | 1.18 (1.09-1.28) |
| Ethinylestradiol/ Norethindrone | 0.035 mg q.d./ 1 mg q.d. | 25 mg q.d. | 15 | ↔* | ↔* | ↔* |
| Famotidine | 40 mg single dose taken 12 hours before rilpivirine | 150 mg single dose† | 24 | 0.99 (0.84-1.16) | 0.91 (0.78-1.07) | N.A. |
| Famotidine | 40 mg single dose taken 2 hours before rilpivirine | 150 mg single dose† | 23 | 0.15 (0.12-0.19) | 0.24 (0.20-0.28) | N.A. |
| Famotidine | 40 mg single dose taken 4 hours after rilpivirine | 150 mg single dose† | 24 | 1.21 (1.06-1.39) | 1.13 (1.01-1.27) | N.A. |
| Ketoconazole | 400 mg q.d. | 150 mg q.d.† | 15 | 1.30 (1.13-1.48) | 1.49 (1.31-1.70) | 1.76 (1.57-1.97) |
| Methadone | 60-100 mg q.d., individualised dose | 25 mg q.d. | 12 | ↔* | ↔* | ↔* |
| Omeprazole | 20 mg q.d. | 150 mg q.d.† | 16 | 0.60 (0.48-0.73) | 0.60 (0.51-0.71) | 0.67 (0.58-0.78) |



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| | | | | | | |
|---|---|---|---|---|---|---|
| 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) |
| | | | | (reference arm for comparison was 25 mg q.d. rilpivirine administered 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 dose | 75 mg q.d.† | 16 | 0.92 (0.85-0.99) | 0.98 (0.92-1.05) | 1.04 (0.98-1.09) |

CI = Confidence Interval; N = 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**

| Co-administered Drug | Dose/Schedule: Co-administered Drug | Dose/Schedule: Rilpivirine | N | Mean Ratio of Co-administered Drug Pharmacokinetic Parameters With/Without EDURANT (90% CI); No Effect = 1.00: $C_{max}$ | 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. delayed release capsules taken 2 hours before rilpivirine | 150 mg q.d.† | 13 | 0.96 (0.80-1.14) | 1.12 (0.99-1.27) | N.A. |
| Tenofovir disoproxil fumarate | 300 mg q.d. | 150 mg q.d.† | 16 | 1.19 (1.06-1.34) | 1.23 (1.16-1.31) | 1.24 (1.10-1.38) |
| **Co-Administration With HIV Integrase Strand Transfer 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. |



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| | | | | | | |
|---|---|---|---|---|---|---|
| Atorvastatin | 40 mg q.d. | 150 mg q.d.† | 16 | 1.35 (1.08-1.68) | 1.04 (0.97-1.12) | 0.85 (0.69-1.03) |
| 2-hydroxy-atorvastatin | | | 16 | 1.58 (1.33-1.87) | 1.39 (1.29-1.50) | 1.32 (1.10-1.58) |
| 4-hydroxy-atorvastatin | | | 16 | 1.28 (1.15-1.43) | 1.23 (1.13-1.33) | N.A. |
| Chlorzoxazone | 500 mg single dose taken 2 hours after rilpivirine | 150 mg q.d.† | 16 | 0.98 (0.85-1.13) | 1.03 (0.95-1.13) | N.A. |
| 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. |
| 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. |
| *N*-desmethyl-sildenafil | | | 16 | 0.90 (0.80-1.02) | 0.92 (0.85-0.99)# | 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.

# $AUC_{(0\text{-last})}$

^ N (maximum number of subjects with data) for $AUC_{(0\text{-}\infty)}$ = 15

## 12.4 Microbiology

*Mechanism of Action*

Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1) and inhibits HIV-1 replication by



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non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α, β and γ.

*Antiviral Activity in Cell Culture*

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median $EC_{50}$ value for HIV-$1_{IIIB}$ of 0.73 nM (0.27 ng/mL). Rilpivirine demonstrated limited activity in cell culture against HIV-2 with a median $EC_{50}$ value of 5220 nM (range 2510 to 10830 nM) (920 to 3970 ng/mL).

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

The antiviral activity of rilpivirine was not antagonistic when combined with the NNRTIs efavirenz, etravirine or nevirapine; the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir or tipranavir; the fusion inhibitor enfuvirtide; the CCR5 co-receptor antagonist maraviroc, or the integrase strand transfer inhibitor raltegravir.

Resistance

*In Cell Culture*

Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1. The frequently observed amino acid substitutions that emerged and conferred decreased phenotypic susceptibility to rilpivirine included: L100I, K101E, V106I and A, V108I, E138K and G, Q, R, V179F and I, Y181C and I, V189I, G190E, H221Y, F227C and M230I and L.

*In Treatment-Naïve Adult Subjects*

In the Week 96 pooled resistance analysis of the Phase 3 trials C209 and C215, the emergence of resistance was greater among subjects' viruses in the EDURANT arm compared to the efavirenz arm, and was dependent on baseline viral load. In the pooled resistance analysis, 58% (57/98) of the subjects who qualified for resistance analysis (resistance analysis subjects) in the EDURANT arm had virus with genotypic and/or phenotypic resistance to rilpivirine compared to 45% (25/56) of the resistance analysis subjects in the efavirenz arm who had genotypic and/or phenotypic resistance to efavirenz. Moreover, genotypic and/or phenotypic resistance to a background drug (emtricitabine, lamivudine, tenofovir, abacavir or zidovudine) emerged in viruses from 52% (51/98) of the resistance analysis subjects in the rilpivirine arm compared to 23% (13/56) in the efavirenz arm.



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Emerging NNRTI substitutions in the rilpivirine resistance analysis of subjects' viruses included V90I, K101E/P/T, E138K/A/Q/G, V179I/L, Y181C/I, V189I, H221Y, F227C/L and M230L, which were associated with a rilpivirine phenotypic fold change range of 2.6 - 621. The E138K substitution emerged most frequently during rilpivirine treatment commonly in combination with the M184I substitution. The emtricitabine and lamivudine resistance-associated substitutions M184I or V and NRTI resistance-associated substitutions (K65R/N, A62V, D67N/G, K70E, Y115F, T215S/T, or K219E/R) emerged more frequently in rilpivirine resistance analysis subjects compared to efavirenz resistance analysis subjects (see Table 9).

NNRTI- and NRTI-resistance substitutions emerged less frequently in resistance analysis of viruses from subjects with baseline viral load of ≤ 100,000 copies/mL compared to viruses from subjects with baseline viral load of > 100,000 copies/mL: 26% (14/54) compared to 74% (40/54) of NNRTI-resistance substitutions and 22% (11/50) compared to 78% (39/50) of NRTI-resistance substitutions. This difference was also observed for the individual emtricitabine/lamivudine and tenofovir resistance substitutions: 23% (11/47) compared to 77% (36/47) for M184I/V and 0% (0/8) compared to 100% (8/8) for K65R/N. Additionally, NNRTI- and NRTI-resistance substitutions emerged less frequently in the resistance analysis of viruses from subjects with baseline CD4+ cell counts ≥ 200 cells/mm$^3$ compared to viruses from subjects with baseline CD4+ cell counts < 200 cells/mm$^3$: 37% (20/54) compared to 63% (34/54) of NNRTI-resistance substitutions and 28% (14/50) compared to 72% (36/50) of NRTI-resistance substitutions.

**Table 9: Proportion of Resistance Analysis Subjects* with Frequently Emerging Reverse Transcriptase Substitutions from the Pooled Phase 3 TMC278-C209 and TMC278-C215 Trials in the Week 96 Analysis**

| | **C209 and C215 N = 1368** | |
|---|---|---|
| | **EDURANT + BR N = 686** | **Efavirenz + BR N = 682** |
| **Subjects who Qualified for Resistance Analysis** | 15% (98/652) | 9% (56/604) |
| **Subjects with Evaluable Post-Baseline Resistance Data** | 87 | 43 |
| **Emerging NNRTI Substitutions**[†] | | |
| Any | 62% (54/87) | 53% (23/43) |
| V90I | 13% (11/87) | 2% (1/43) |
| K101E/P/T/Q | 20% (17/87) | 9% (4/43) |
| K103N | 1% (1/87) | 40% (17/43) |
| E138K/A/Q/G | 40% (35/87) | 2% (1/43) |
| E138K+ M184I[‡] | 25% (22/87) | 0 |
| V179I/L/D | 6% (5/87) | 7% (3/43) |
| Y181C/I/S | 10% (9/87) | 2% (1/43) |
| V189I | 8% (7/87) | 2% (1/43) |
| H221Y | 9% (8/87) | 0 |
| **Emerging NRTI Substitutions**[§] | | |
| Any | 57% (50/87) | 30% (13/43) |
| M184I/V | 54% (47/87) | 26% (11/43) |
| K65R/N | 9% (8/87) | 5% (2/43) |
| A62V, D67N/G, K70E, Y115F, T215S/T or K219E/R[¶] | 21% (18/87) | 2% (1/43) |



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BR = background regimen
* Subjects who qualified for resistance analysis.
† V90, L100, K101, K103, V106, V108, E138, V179, Y181, Y188, V189, G190, H221, P225, F227 or M230
‡ This combination of NNRTI and NRTI substitutions is a subset of those with the E138K.
§ A62V, K65R/N, D67N/G, K70E, L74I, V75I, Y115F, M184I/V, L210F, T215S/T, K219E/R
¶ These substitutions emerged in addition to the primary substitutions M184V/I or K65R/N; A62V (n=3), D67N/G (n=3), K70E (n=4), Y115F (n=2), T215S/T (n=1), K219E/R (n=8) in rilpivirine resistance analysis subjects.

Cross-Resistance

*Site-Directed NNRTI Mutant Virus*

Cross-resistance has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I and Y181V conferred 52-fold, 15-fold and 12-fold decreased susceptibility to rilpivirine, respectively. The combination of E138K and M184I showed 6.7-fold reduced susceptibility to rilpivirine compared to 2.8-fold for E138K alone. The K103N substitution did not result in reduced susceptibility to rilpivirine by itself. However, the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine. Combinations of 2 or 3 NNRTI resistance-associated substitutions had decreased susceptibility to rilpivirine (fold change range of 3.7 - 554) in 38% and 66% of mutants analyzed, respectively.

*Treatment-naïve HIV-1-infected adult subjects*

Considering all of the available cell culture and clinical data, any of the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I or M230L.

Cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure and development of rilpivirine resistance. In the Week 96 pooled analyses of the Phase 3 TMC278-C209 and TMC278-C215 clinical trials, 50 of the 87 (57%) rilpivirine resistance analysis subjects with post-baseline resistance data had virus with decreased susceptibility to rilpivirine (≥ 2.5 fold change). Of these, 86% (n= 43/50) were resistant to efavirenz (≥ 3.3 fold change), 90% (n= 45/50) were resistant to etravirine (≥ 3.2 fold change) and 62% (n= 31/50) were resistant to nevirapine (≥ 6 fold change). In the efavirenz arm, 3 of the 21 (14%) efavirenz resistance analysis subjects' viruses were resistant to etravirine and rilpivirine, and 95% (n= 20/21) were resistant to nevirapine. Virus from subjects experiencing virologic failure on EDURANT developed more NNRTI resistance-associated substitutions conferring more cross-resistance to the NNRTI class and had a higher likelihood of cross-resistance to all NNRTIs in the class compared to virus from subjects who failed on efavirenz.



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# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*Carcinogenesis and Mutagenesis*

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1500 mg/kg/day were administered to rats. In rats, there were no drug related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg q.d.).

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

*Impairment of Fertility*

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

# 14 CLINICAL STUDIES

## 14.1 Treatment-Naïve Adult Subjects

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

In the pooled analysis for TMC278-C209 and TMC278-C215, demographics and baseline characteristics were balanced between the EDURANT arm and the efavirenz arm. Table 10 displays selected demographic and baseline disease characteristics of the subjects in the EDURANT and efavirenz arms.



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**Table 10: Demographic and Baseline Disease Characteristics of Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects in the TMC278-C209 and TMC278-C215 Trials (Pooled Analysis)**

| | Pooled Data from the Phase 3 TMC278-C209 and TMC278-C215 Trials | |
|---|---|---|
| | **EDURANT + BR N=686** | **Efavirenz + BR N=682** |
| **Demographic Characteristics** | | |
| Median Age, years (range) | 36 (18-78) | 36 (19-69) |
| Sex | | |
| Male | 76% | 76% |
| Female | 24% | 24% |
| Race | | |
| White | 61% | 60% |
| Black/African American | 24% | 23% |
| Asian | 11% | 14% |
| Other | 2% | 2% |
| Not allowed to ask per local regulations | 1% | 1% |
| **Baseline Disease Characteristics** | | |
| Median Baseline Plasma HIV-1 RNA (range), $\log_{10}$ copies/mL | 5.0 (2-7) | 5.0 (3-7) |
| Percentage of Patients with Baseline Plasma Viral Load: | | |
| ≤ 100,000 | 54% | 48% |
| > 100,000 to ≤ 500,000 | 36% | 40% |
| > 500,000 | 10% | 12% |
| Median Baseline CD4+ Cell Count (range), cells/$mm^3$ | 249 (1-888) | 260 (1-1137) |
| Percentage of Subjects with: | | |
| Hepatitis B/C Virus Co-infection | 7% | 10% |
| Percentage of Patients with the following background regimens: | | |
| tenofovir disoproxil fumarate plus emtricitabine | 80% | 80% |
| zidovudine plus lamivudine | 15% | 15% |
| abacavir plus lamivudine | 5% | 5% |

BR=background regimen

Week 96 efficacy outcomes for subjects treated with EDURANT 25 mg once daily from the pooled analysis are shown in Table 11. The incidence of virologic failure was higher in the EDURANT arm than the efavirenz arm at Week 96. Virologic failures and discontinuations due to adverse events mostly occurred in the first 48 weeks of treatment.

**Table 11: Virologic Outcome of Randomized Treatment of Studies TMC278-C209 and TMC278-C215 (Pooled Data) at Week 96**

| | **EDURANT + BR N=686** | **Efavirenz + BR N=682** |
|---|---|---|
| **HIV-1 RNA < 50 copies/mL*** | 76% | 77% |
| **HIV-1 RNA ≥ 50 copies/mL**[†] | 16% | 10% |
| **No virologic data at Week 96 window** | | |
| Reasons | | |
| Discontinued study due to adverse event or death[‡] | 4% | 8% |
| Discontinued study for other reasons and last available HIV-1 RNA < 50 copies/mL (or missing)[§] | 4% | 5% |
| Missing data during window but on study | < 1% | < 1% |
| **HIV-1 RNA < 50 copies/mL by Baseline HIV-1 RNA (copies/mL)** | | |



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| | | |
|---|---|---|
| ≤ 100,000 | 82% | 78% |
| > 100,000 | 70% | 75% |
| **HIV-1 RNA ≥ 50 copies/mL† by Baseline HIV-1 RNA (copies/mL)** | | |
| ≤ 100,000 | 9% | 8% |
| > 100,000 | 24% | 11% |
| **HIV-1 RNA < 50 copies/mL by CD4+ cell count (cells/mm$^3$)** | | |
| < 200 | 68% | 74% |
| ≥ 200 | 81% | 77% |
| **HIV-1 RNA ≥ 50 copies/mL† by CD4+ cell count (cells/mm$^3$)** | | |
| < 200 | 27% | 10% |
| ≥ 200 | 10% | 9% |

N = total number of subjects per treatment group; BR = background regimen.

* CI = Predicted difference (95% CI) of response rate is -0.2 (-4.7; 4.3) at Week 96.

† Includes subjects who had ≥ 50 copies/mL in the Week 96 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL, and subjects who had a switch in background regimen that was not permitted by the protocol.

‡ Includes subjects who discontinued due to an adverse event or death if this resulted in no on-treatment virologic data in the Week 96 window.

§ Includes subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Note: Analysis was based on the last observed viral load data within the Week 96 window (Week 90-103), respectively.

At Week 96, the mean CD4+ cell count increase from baseline was 228 cells/mm$^3$ for EDURANT-treated subjects and 219 cells/mm$^3$ for efavirenz-treated subjects in the pooled analysis of the TMC278-C209 and TMC278-C215 trials.

Study TMC278-C204 was a randomized, active-controlled, Phase 2b trial in antiretroviral treatment-naïve HIV-1-infected adult subjects consisting of 2 parts: an initial 96 weeks, partially-blinded dose-finding part [EDURANT doses blinded] followed by a long-term, open-label part. After Week 96, subjects randomized to one of the 3 doses of EDURANT were switched to EDURANT 25 mg once daily. Subjects in the control arm received efavirenz 600 mg once daily in addition to a BR in both parts of the study. The BR consisted of 2 investigator-selected N(t)RTIs: zidovudine plus lamivudine <u>or</u> 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.



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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.

### 14.2 Treatment-Naïve Pediatric Subjects (12 to less than 18 years of age)

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 2 trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age and weighing at least 32 kg. Thirty six (36) subjects were enrolled in the trial to complete at least 48 weeks of treatment. 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 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 21.4% (6/28), versus 37.5% (3/8) in those with >100,000 copies/mL. At Week 48, the mean increase in CD4+ cell count from baseline was 201.2 cells/mm$^3$.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

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



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

Female patients should be advised not to breastfeed because it is unknown if EDURANT can be passed to the baby in the breast milk and whether it could harm the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Patients should be advised to take EDURANT with a meal once a day as prescribed. A protein drink alone does not replace a meal. EDURANT must always be used in combination with other antiretroviral drugs. Patients should not alter the dose of EDURANT or discontinue therapy with EDURANT without consulting their physician. If the patient misses a dose of EDURANT within 12 hours of the time it is usually taken, the patient should take EDURANT with a meal as soon as possible and then take the next dose of EDURANT at the regularly scheduled time. If a patient misses a dose of EDURANT by more than 12 hours, the patient should not take the missed dose, but resume the usual dosing schedule. Inform the patient that he or she should not take more or less than the prescribed dose of EDURANT at any one time.

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

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

For patients concomitantly receiving rifabutin, the EDURANT dose should be increased to 50 mg 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.

Patients should be informed that skin reactions ranging from mild to severe, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported with rilpivirine-containing regimens. Instruct patients to immediately stop taking EDURANT tablets and seek medical attention if they develop a rash associated with any of the following symptoms:



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fever, blisters, mucosal involvement, eye inflammation (conjunctivitis), severe allergic reaction causing a swelling of the face, eyes, lips, mouth, tongue or throat, which may lead to difficulty swallowing or breathing, and any signs and symptoms of liver problems as it may be a sign of a more serious reaction. Patients should understand that if severe rash occurs, they will be closely monitored, laboratory tests will be performed and appropriate therapy will be initiated.

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

Patients should be informed that hepatotoxicity has been reported with EDURANT.

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

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**PATIENT INFORMATION**
**EDURANT® (ee' dur ant)**
**(rilpivirine)**
**Tablets**

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

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

**What is EDURANT?**

EDURANT is a prescription HIV-1 (Human Immunodeficiency Virus) medicine that is used with other antiretroviral medicines to treat HIV-1 in people who:

- have **never** taken HIV medicines before, **and**
- have an amount of HIV-1 in their blood (this is called 'viral load') that is no more than 100,000 copies/mL. Your doctor will measure your viral load.

HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

It is not known if EDURANT is safe and effective in children less than 12 years of age.

When used with other antiretroviral medicines to treat HIV-1 infection, EDURANT may help:

- Reduce the amount of HIV-1 in your blood.
- Increase the number of CD4+ (T) cells in your blood that help fight off other infections.

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

**EDURANT does not cure HIV infection or AIDS.** You must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

**Avoid doing things that can spread HIV-1 infection to others**:

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Ask your doctor if you have any questions about how to prevent passing HIV-1 to other people.

**Who should not take EDURANT?**

**Do not take EDURANT if:**

- your HIV-1 infection has been previously treated with HIV-1 medicines
- you are taking any of the following medicines:
  - anti-seizure medicines:
    - carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®, Tegretol- XR®, Teril®)
    - oxcarbazepine (Oxtellar XR®, Trileptal®)
    - phenobarbital (Luminal®)
    - phenytoin (Dilantin®, Dilantin-125®, Phenytek®)
  - anti-tuberculosis (anti-TB) medicines:
    - rifampin (Rifater®, Rifamate®, Rimactane®, Rifadin®)
    - rifapentine (Priftin®)
  - proton pump inhibitor (PPI) medicine for certain stomach or intestinal problems:
    - esomeprazole (Nexium®, Vimovo®)
    - lansoprazole (Prevacid®)
    - omeprazole (Prilosec®, Zegerid®)
    - pantoprazole sodium (Protonix®)
    - rabeprazole (Aciphex®, Aciphex Sprinkle®)
  - more than 1 dose of the steroid medicine dexamethasone or dexamethasone sodium phosphate
  - St. John's wort (*Hypericum perforatum*)



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**What should I tell my doctor before taking EDURANT?**

**Before taking EDURANT, tell your doctor if you:**

- have or had liver problems, including hepatitis B or C virus infection.
- have ever had a mental health problem.
- are pregnant or planning to become pregnant. It is not known if EDURANT will harm your unborn baby.
  **Pregnancy Registry:** There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. You should not breastfeed if you have HIV because of the risk of passing HIV to your baby. **Do not breastfeed if you take EDURANT.** We do not know if EDURANT can be passed to your baby in your breast milk and whether it could harm your baby. Talk with your doctor about the best way to feed your baby.

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

Some medicines interact with EDURANT. Keep a list of your medicines to show your doctor and pharmacist.

- You can ask your doctor or pharmacist for a list of medicines that interact with EDURANT.
- Do not start taking a new medicine without telling your doctor. Your doctor can tell you if it is safe to take EDURANT with other medicines.

**How should I take EDURANT?**

- Take EDURANT every day exactly as prescribed by your doctor.
- **Always take EDURANT with a meal.** Taking EDURANT with a meal is important to help get the right amount of medicine in your body. A protein drink alone does not replace a meal.
- Do not change your dose or stop taking EDURANT without first talking with your doctor. Stay under the care of your doctor while taking EDURANT.
- If you miss a dose of EDURANT within 12 hours of the time you usually take it, take your dose of EDURANT with a meal as soon as possible. Then, take your next dose of EDURANT at the regularly scheduled time. If you miss a dose of EDURANT by more than 12 hours of the time you usually take it, wait and then take the next dose of EDURANT at the regularly scheduled time.
- Do not take more than your prescribed dose to make up for a missed dose.
- If you take too much EDURANT, call your doctor or go to the nearest hospital emergency room right away.

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.

**What are the possible side effects of EDURANT?**

**EDURANT can cause serious side effects including:**

- **Severe skin rash and allergic reactions.** Skin rash is a common side effect of EDURANT. Skin rash can be serious and may need to be treated in a hospital. Call your doctor right away if you get a rash.
  If you get a rash with any of the following symptoms, **stop taking EDURANT and get medical help right away**:
  - fever
  - skin blisters
  - mouth sores
  - redness or swelling of the eyes (conjunctivitis)
  - swelling of the face, lips, mouth, tongue, or throat
  - trouble breathing or swallowing
  - pain on the right side of the stomach (abdominal) area
  - dark colored urine “tea colored”
- **Depression or mood changes. Tell your doctor right away if you have any of the following symptoms:**
  - feeling sad or hopeless
  - feeling anxious or restless
  - have thoughts of hurting yourself (suicide) or have tried to hurt yourself
- **Liver problems** can happen in people who take EDURANT. People with a history of hepatitis B or C virus infection or who have certain liver function test changes may have an increased risk of developing new or worsening liver problems during treatment with EDURANT. Liver problems have also been reported during treatment with EDURANT in people without history of liver disease. Your doctor may need to do tests to check liver function before and during treatment with EDURANT.
- **Changes in body fat** can happen in people who take HIV medicine. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long- term health effects of these problems are not known.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor right away if you start having any new symptoms after starting your HIV medicine.



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**The most common side effects of EDURANT include:**

- depression
- trouble sleeping (insomnia)
- headache
- rash

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

These are not all of the possible side effects with EDURANT. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store EDURANT?**

- Store EDURANT at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep EDURANT in the original bottle to protect from light.

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

**General information about EDURANT**

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

This leaflet summarizes the most important information about EDURANT. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about EDURANT that is written for health professionals. For more information, call 1-800-526-7736 or go to www.EDURANT.com.

**What are the ingredients in EDURANT?**

**Active ingredient:** rilpivirine.

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

Product of Ireland
Manufactured by: Janssen-Cilag SpA, Latina, Italy
Manufactured for: Janssen Therapeutics, Division of Janssen Products, LP, Titusville NJ 08560
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