EDURANT® (rilpivirine) tablets

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

EDURANT® (rilpivirine) tablets


5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

5.2 Skin and Hypersensitivity Reactions

5.3 Depressive Disorders

5.4 Hepatotoxicity

5.5 Fat Redistribution

5.6 Immune Reconstitution Syndrome

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience: Adults

6.2 Clinical Trials Experience: Pediatric Patients

6.3 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Treatment-Naïve Adult Subjects

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

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

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Full Prescribing Information: Contents*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

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Not all possible interactions are listed. Refer to the Information Summary 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)

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

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

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*Sections or subsections omitted from the full prescribing information are not listed.
EDURANT® (rilpivirine) tablets

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/mm³ experienced virologic failure compared to EDURANT treated subjects with CD4+ cell count greater than or equal to 200 cells/mm³ [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/ entecitabine 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 weighing at least 35 kg is one 25 mg tablet once daily 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 275 mg of rilpivirine hydrochloride, which is equivalent to 25 mg of rilpivirine.

4 CONTRAINDICATIONS
EDURANT should not be co-administered with the following drugs, as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to EDURANT or to the class of NNRTIs [see 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 (12.3)). EDURANT should be used with caution when co-administered with a drug with a known risk of torsade de points.

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 patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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 1389 patients in the Phase 3 controlled trials TMC278-C220 (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 104.2 and 104.1 weeks, respectively. Most ADRs occurred in the first 48 weeks of treatment. The proportion of subjects who discontinued treatment with

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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 = 1388) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among EDURANT (n = 686) and efavirenz (n = 682) was 3% 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 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 for 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 periodic 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.

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.

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)].

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)]
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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

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)

<table>
<thead>
<tr>
<th>System Organ Class, Preferred Term,</th>
<th>Pooled Data from the Phase 3 TMC278-C209 and TMC278-C215 Trials</th>
<th>N=686</th>
<th>N=682</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive disorders†</td>
<td>5%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>3%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>2%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

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

Metabolism and Nutrition Disorders: decreased appetite

Nervous System Disorders: somnolence

Psychiatric Disorders: sleep disorders, anxiety

Renal and Urinary Disorders: glomerulonephritis membranous, glomerulonephritis mesangiproliferative, 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.
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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 NNRTI regimen.

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

<table>
<thead>
<tr>
<th>Table 3: Lipid Values, Mean Change from Baseline*</th>
<th>Pooled Data from the Week 96 Analysis of the Phase 3 TMC278-C209 and TMC278-C215 Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Baseline</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Total Cholesterol (fasted)</td>
<td>546</td>
</tr>
<tr>
<td>HDL-cholesterol (fasted)</td>
<td>545</td>
</tr>
<tr>
<td>LDL-cholesterol (fasted)</td>
<td>542</td>
</tr>
<tr>
<td>Triglycerides (fasted)</td>
<td>546</td>
</tr>
</tbody>
</table>

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-naive 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.

ADR reports were received 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 (13.4%), depression (13.4%), somnolence (13.3%), nausea (11.6%), dizziness (8.2%), abdominal pain (8.3%), vomiting (5.8%) 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.

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)

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7 DRUG INTERACTIONS
[See Dosage and Administration (2), Contraindications (4) and Clinical Pharmacology (12.3).]
Rilpivirine is primarily metabolized by cytochrome P450 (CYP3A), and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine. Co-administration of EDURANT and drugs that induce CYP3A may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs. Co-administration of EDURANT and drugs that inhibit CYP3A may result in increased plasma concentrations of rilpivirine. Co-administration of EDURANT with drugs that increase gastric pH may result in decreased plasma concentrations of rilpivirine and loss of virologic response and possible resistance to rilpivirine or to the class of NNRTIs.

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

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

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

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentration of Rilpivirine or Concomitant Drug</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>didanosine*†</td>
<td>↔ rilpivirine ↔ didanosine</td>
<td>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).</td>
</tr>
<tr>
<td>NNRTI (delavirdine)</td>
<td>↑ rilpivirine ↔ delavirdine</td>
<td>It is not recommended to co-administer EDURANT with delavirdine and other NNRTIs.</td>
</tr>
<tr>
<td>Other NNRTIs (efavirenz, etravirine, nevirapine)</td>
<td>↓ rilpivirine ↔ other NNRTIs</td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>darunavir/ritonavir*†</td>
<td>↑ rilpivirine ↔ boosted darunavir</td>
<td>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.</td>
</tr>
<tr>
<td>lopinavir/ritonavir*†</td>
<td>↑ rilpivirine ↔ boosted lopinavir</td>
<td>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.</td>
</tr>
<tr>
<td>other boosted PIs (atazanavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir, tipranavir/ritonavir)</td>
<td>↑ rilpivirine ↔ boosted PI</td>
<td>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.</td>
</tr>
</tbody>
</table>
## EDURANT® (rilpivirine) tablets

### 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)] (continued)

<table>
<thead>
<tr>
<th>Concomitant Drug Class: Drug Name</th>
<th>Effect on Concentration of Rilpivirine or Concomitant Drug</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>unboosted PIs (atazanavir, fosamprenavir, indinavir, nelfinavir)</td>
<td>↑ rilpivirine ↔ unboosted PI</td>
<td>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.</td>
</tr>
<tr>
<td>Antacids: antacids (e.g., aluminum or magnesium hydroxide, calcium carbonate)</td>
<td>↔ rilpivirine (antacids taken at least 2 hours before or at least 4 hours after rilpivirine) ↓ rilpivirine (concomitant intake)</td>
<td>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.</td>
</tr>
<tr>
<td>Azole Antifungal Agents: fluconazole (itraconazole ketoconazole voriconazole)</td>
<td>↑ rilpivirine ↓ ketoconazole</td>
<td>Concomitant use of EDURANT with azole antifungals may cause an increase 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.</td>
</tr>
<tr>
<td>H₂-Receptor Antagonists: cimetidine nizatidine ranitidine</td>
<td>↑ rilpivirine (famotidine taken 12 hours before rilpivirine or 4 hours after rilpivirine) ↓ rilpivirine (famotidine taken 2 hours before rilpivirine)</td>
<td>The combination of EDURANT and H₂-receptor antagonists should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). H₂-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EDURANT.</td>
</tr>
<tr>
<td>Macrolide or ketolide antibiotics: clarithromycin erythromycin telithromycin</td>
<td>↑ rilpivirine ↔ clarithromycin erythromycin or telithromycin</td>
<td>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.</td>
</tr>
</tbody>
</table>

### Other Agents

| Antimycobacterials: rifabutin* | ↓ rilpivirine | Concomitant use of EDURANT with rifabutin may cause a decrease in the plasma concentrations of rifabutin (induction of CYP3A enzymes). Throughout co-administration of EDURANT with rifabutin, the rifabutin dose should be increased from 300 mg once daily to 600 mg once daily. When rifabutin co-administration is stopped, the EDURANT dose should be decreased to 25 mg once daily. |

### Narcotic Analgesics:

| methadone* | ↓ S(+) methylmethadone ↑ R(-) methylmethadone | 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)]: acenocinate, atorvastatin, chloroquine, ethinylestradiol, norethindrone, rifampin, sildenafl, simprevir 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.

### 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 for 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.

Safety and effectiveness in pediatric patients less than 12 years of age have not been established.
EDURANT® (rilpivirine) tablets

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 proteins, 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-(2-cyanoethyl)-2,6-dimethylphenyl]amino)-2-pyrimidinyl]amino)benzonitrile monohydrochloride. Its molecular formula is C22H18N6 • HCl and its molecular weight is 402.88. 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 mP.a.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 Cmax approximately 2.6-fold and 6.7-fold, respectively, higher than the mean Cmax observed with the recommended 25 mg once daily dose of EDURANT [see Warnings and Precautions (5.1)].
**EDURANT® (rilpivirine) tablets**

**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-naive 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).

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rilpivirine 25 mg once daily N = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0h&lt;/sub&gt; (mg·h/mL)</td>
<td>2424 ± 1024</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>2269 (417 - 5166)</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (ng/mL)</td>
<td>Mean ± Standard Deviation 85 ± 40</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>79 (7 - 202)</td>
</tr>
</tbody>
</table>

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<sub>0h</sub>, AUC, and C<sub>min</sub> values of rilpivirine are summarized in Table 7 (effect of other drugs on EDURANT). The effect of co-administration of EDURANT on the C<sub>0h</sub>, AUC, and C<sub>min</sub> values of other drugs are summarized in Table 8 (effect of EDURANT on other drugs). [For information regarding clinical recommendations, see Drug Interactions (7)].

**EDURANT® (rilpivirine) tablets**

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

<table>
<thead>
<tr>
<th>Co-administered Drug</th>
<th>Dose/Schedule</th>
<th>Rilpivirine</th>
<th>Mean Ratio of Rilpivirine Pharmacokinetic Parameters With/Without Co-administered Drug (90% CI); No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir/ritonavir</td>
<td>800/100 mg q.d.</td>
<td>150 mg q.d.</td>
<td>14 1.79 (1.56-2.06)</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>400/100 mg b.i.d.</td>
<td>150 mg q.d.</td>
<td>15 1.29 (1.18-1.40)</td>
</tr>
</tbody>
</table>

**Co-Administration With HIV Protease Inhibitors (PIs)**

<table>
<thead>
<tr>
<th>Co-Administration With HIV Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[Nt]RTIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Co-Administration With Drugs other than Antiretrovirals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Atorvastatin</td>
</tr>
<tr>
<td>Chloroxazone</td>
</tr>
<tr>
<td>Ethinylestradiol/ Norethindrone</td>
</tr>
<tr>
<td>Famotidine</td>
</tr>
<tr>
<td>Famotidine</td>
</tr>
<tr>
<td>Famotidine</td>
</tr>
<tr>
<td>Ketocazole</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td>Omeprazole</td>
</tr>
<tr>
<td>Rifabutin</td>
</tr>
<tr>
<td>Rifabutin</td>
</tr>
<tr>
<td>(reference arm for comparison was 25 mg q.d. rilpivirine administered alone)</td>
</tr>
<tr>
<td>Rifampin</td>
</tr>
<tr>
<td>Sildenafil</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Co-administered Drug</th>
<th>Dose/Schedule</th>
<th>Mean Ratio of Co-administered Drug Pharmacokinetic Parameters With/Without EDURANT (90% CI)</th>
<th>No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Co-administered Drug</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cmax</td>
</tr>
<tr>
<td>Co-Administration With HIV Protease Inhibitors (PIs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>800/100 mg q.d.</td>
<td>150 mg q.d.</td>
<td>15</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (soft gel capsule)</td>
<td>400/100 mg b.i.d.</td>
<td>150 mg q.d.</td>
<td>16</td>
</tr>
<tr>
<td>Co-Administration With HIV Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[rt]RTIs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>400 mg q.d. delayed release capsules taken 2 hours before rilpivirine</td>
<td>150 mg q.d.</td>
<td>16</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>300 mg q.d.</td>
<td>150 mg q.d.</td>
<td>16</td>
</tr>
<tr>
<td>Co-Administration With HIV Integrase Strand Transfer Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>400 mg b.i.d.</td>
<td>25 mg q.d.</td>
<td>23</td>
</tr>
<tr>
<td>Co-Administration With Other Antivirals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simprevir</td>
<td>150 mg q.d.</td>
<td>25 mg q.d.</td>
<td>21</td>
</tr>
<tr>
<td>Co-Administration With Drugs other than Antiretrovirals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azetidinephen</td>
<td>500 mg single dose</td>
<td>150 mg q.d.</td>
<td>16</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40 mg q.d.</td>
<td>150 mg q.d.</td>
<td>16</td>
</tr>
<tr>
<td>2-hydroxy-atorvastatin</td>
<td>150 mg q.d.</td>
<td>16</td>
<td>1.58 (1.33-1.87)</td>
</tr>
<tr>
<td>4-hydroxy-atorvastatin</td>
<td>150 mg q.d.</td>
<td>16</td>
<td>1.28 (1.15-1.43)</td>
</tr>
<tr>
<td>Chlorzoxzone</td>
<td>500 mg single dose taken 2 hours after rilpivirine</td>
<td>150 mg q.d.</td>
<td>16</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.5 mg single dose</td>
<td>25 mg q.d.</td>
<td>22</td>
</tr>
<tr>
<td>Ethinylestradiol</td>
<td>0.055 mg q.d.</td>
<td>25 mg q.d.</td>
<td>17</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>1 mg q.d.</td>
<td>25 mg q.d.</td>
<td>17</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>400 mg q.d.</td>
<td>150 mg q.d.</td>
<td>14</td>
</tr>
<tr>
<td>Rif(+) methadone</td>
<td>60-100 mg q.d., individualised dose</td>
<td>25 mg q.d.</td>
<td>13</td>
</tr>
<tr>
<td>S(+) methadone</td>
<td>100 mg q.d.</td>
<td>25 mg q.d.</td>
<td>13</td>
</tr>
<tr>
<td>Metformin</td>
<td>850 mg single dose</td>
<td>25 mg q.d.</td>
<td>20</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg q.d.</td>
<td>150 mg q.d.</td>
<td>15</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg q.d.</td>
<td>150 mg q.d.</td>
<td>16</td>
</tr>
<tr>
<td>25-desacyclframpipin</td>
<td>600 mg q.d.</td>
<td>150 mg q.d.</td>
<td>16</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>50 mg single dose</td>
<td>75 mg q.d.</td>
<td>16</td>
</tr>
<tr>
<td>N-desmethyl-sildenafil</td>
<td>50 mg single dose</td>
<td>150 mg q.d.</td>
<td>16</td>
</tr>
</tbody>
</table>

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
# AUCD80/400
^
N (maximum number of subjects with data) for AUCD80/400 = 15
Table 9: Proportion of Resistance Analysis Subjects* with FrequentlyEmerging Reverse Transcriptase Substitutions from the Pooled Phase 3 TMC278-C209 and TMC278-C215 Trials in the Week 96 Analysis

<table>
<thead>
<tr>
<th>C209 and C215</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1388</td>
</tr>
<tr>
<td>EDURANT + BR</td>
</tr>
<tr>
<td>N = 686</td>
</tr>
<tr>
<td>Efavirenz + BR</td>
</tr>
<tr>
<td>N = 682</td>
</tr>
</tbody>
</table>

**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/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% (12/43)
- M184V
  - 54% (47/87) 26% (11/43)
- K219E/R
  - 9% (8/87) 5% (2/43)
- A62V, D67N/G, K70E, Y115F, T215S/T or K219E/R
  - 21% (18/87) 2% (1/43)

BR = background regimen

* Subjects who qualified for resistance analysis.
† This combination of NNRTI and NRTI substitutions is a subset of those with the E138K.

No human data on the effect of rilpivirine on fertility are available. In a study conducted in rats, there were no drug-related effects in male and female rats. The observed hepatocellular findings in rats may be rodent-specific. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (male) and 3-fold (female), relative to those observed in humans at the recommended dose (25 mg q.d.).

Impairment of Fertility

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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, 96% (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.
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)

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>EDURANT + BR N=686</th>
<th>Efavirenz + BR N=682</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years (range)</td>
<td>36 (18-78)</td>
<td>36 (19-69)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76%</td>
<td>76%</td>
</tr>
<tr>
<td>Female</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>61%</td>
<td>60%</td>
</tr>
<tr>
<td>Black/African American</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>Asian</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Not allowed to ask per local regulations</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Disease Characteristics</th>
<th>EDURANT + BR N=686</th>
<th>Efavirenz + BR N=682</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Baseline Plasma HIV-1 RNA (log10 copies/mL)</td>
<td>5.0 (2-7)</td>
<td>5.0 (3-7)</td>
</tr>
<tr>
<td>Percentage of Patients with Baseline Plasma Viral Load:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 100,000</td>
<td>54%</td>
<td>48%</td>
</tr>
<tr>
<td>&gt; 100,000 to ≤ 500,000</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>&gt; 500,000</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Median Baseline CD4+ Cell Count, cells/mm³</td>
<td>249 (1-888)</td>
<td>260 (1-1137)</td>
</tr>
<tr>
<td>Percentage of Subjects with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B/C Virus Co-infection</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Percentage of Patients with the following background regimens:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tenofovir disoproxil fumarate plus emtricitabine</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>zidovudine plus lamivudine</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>abacavir plus lamivudine</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

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.
EDURANT® (rilpivirine) tablets

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/mm² in subjects receiving EDURANT 25 mg and 160 cells/mm² 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.

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/mm² (range: 123 to 983 cells/mm²).

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/mm².

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. EDURANT tablets must be kept at temperature controlled room temperature (see USP controlled room temperature).

17 PATIENT COUNSELING INFORMATION

Advising 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.

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.

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 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 for 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, rifabutin; 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: fever, blisters, mucosal involvement, eye inflammation (conjunctivitis), severe allergic reaction (anaphylaxis), severe skin rash, or medical attention. Inform the patient that he or she should not take more or less than the prescribed dose of EDURANT at any one time.

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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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®, Equetrol®, Tegretol®, Tegretol-XR®, Teril®)
    - oxcarbazepine (Oxcarbazepine (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)
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.
### The most common side effects of EDURANT include:

- depression
- headache
- trouble sleeping (insomnia)
- 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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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised 9/2017

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