PRODUCT MONOGRAPH

PrEDURANT®

rilpivirine tablets
25 mg rilpivirine as rilpivirine hydrochloride

Human Immunodeficiency Virus (HIV) non-nucleoside reverse transcriptase inhibitor

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SUMMARY PRODUCT INFORMATION

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<thead>
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<th>Route of Administration</th>
<th>Pharmaceutical Form/Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>tablet, 25 mg</td>
<td>lactose monohydrate</td>
</tr>
</tbody>
</table>

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

INDICATIONS AND CLINICAL USE

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

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

- In the pooled analysis from the Phase III trials, more EDURANT®-treated subjects with baseline HIV-1 RNA >100,000 copies/mL experienced virologic failure compared to subjects with HIV-1 RNA ≤100,000 copies/mL at baseline (see WARNINGS AND PRECAUTIONS, Resistance/Cross-resistance, MICROBIOLOGY, Resistance, Cross-resistance).
- Regardless of HIV-1 RNA at the start of therapy, more EDURANT®-treated subjects with CD4+ cell count less than 200 cells/mm$^3$ at the start of therapy experienced virologic failure compared to subjects with CD4+ cell count greater than or equal to 200 cells/mm$^3$ (see CLINICAL TRIALS).
- The observed virologic failure rate in EDURANT®-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to the control (efavirenz) (see WARNINGS AND PRECAUTIONS, Resistance/Cross-resistance, MICROBIOLOGY, Resistance, Cross-resistance).
- More subjects treated with EDURANT® developed tenofovir and lamivudine/emtricitabine associated resistance compared to the control (see WARNINGS AND PRECAUTIONS, Resistance/Cross-resistance, MICROBIOLOGY, Resistance, Cross-resistance).
• As with other antiretroviral medicinal products, resistance testing should guide the use of EDURANT® (see MICROBIOLOGY).

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

Pediatrics
(12 to <18 years of age and weighing at least 35 kg):
The safety, efficacy and pharmacokinetics of EDURANT® were evaluated in a single arm, open-label, Phase II trial that enrolled 36 antiretroviral treatment-naïve, HIV-1 infected pediatric subjects 12 to less than 18 years of age and weighing at least 35 kg (DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

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

CONTRAINDICATIONS

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

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

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs Within Class That Are Contraindicated EDURANT®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>carbamazepine, oxcarbazepine, phenobarbital, phenytoin</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>rifapentine, rifampin</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>systemic dexamethasone (more than a single dose)</td>
</tr>
<tr>
<td>Herbal products</td>
<td>St. John’s wort (Hypericum perforatum)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole</td>
</tr>
</tbody>
</table>

WARNINGS AND PRECAUTIONS

General

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood or sexual contact. Appropriate precautions to prevent the transmission of HIV should continue to be employed.
Caution should be exercised when prescribing EDURANT® with drugs that may reduce the exposure of rilpivirine (see CONTRAINDICATIONS and DRUG INTERACTIONS).

**Cardiovascular**

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

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

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

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

**Carcinogenesis and Mutagenesis**

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

**Depressive Disorders**

During the Phase III trials (N=686), the incidence of depressive disorder adverse drug reactions (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) of at least moderate intensity (Grades 2 to 4) was 5%. The incidence of discontinuation due to depressive disorders was 1%. Suicide attempt was reported in 2 subjects while suicide ideation was reported in 4 subjects taking in EDURANT®. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to EDURANT®, and if so, to determine whether the risks of continued therapy outweigh the benefits. The incidence of these events was similar in the control (efavirenz) group.

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

**Endocrine and Metabolism**

**Fat Redistribution**
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushionoid 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.

**Gastrointestinal**

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

**Hepatic**

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

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

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

Autoimmune disorders (such as Graves’ disease, polymyositis and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment. Sometimes there can be an atypical presentation.

**Renal**

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

**Resistance/Cross-resistance**

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

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

In the 36 adolescents 12 to less 18 years of age, treatment-emergent rilpivirine resistance mutations were detected in 5/8 (62.5%) subjects with virologic failure, treatment-emergent NNRTI resistance mutations were detected in 6 (75%) subjects. In 4/5 subjects, treatment-emergent NRTI resistance was also detected. The observed treatment-emergent rilpivirine, NNRTI and NRTI resistance mutations were previously identified in adults (see MICROBIOLOGY, Resistance, Cross-resistance).
In study C213, phenotypic resistance to NRTIs and phenotypic cross-resistance between rilpivirine and other NNRTIs was shown for efavirenz, nevirapine, and etravirine in 4/5 (80%) subjects with rilpivirine associated mutations.

**Skin and Hypersensitivity Reactions**

Severe skin and hypersensitivity reactions have been reported during the post-marketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. During the Phase III clinical trials, treatment-related rashes with at least Grade 2 severity were reported in 3% of subjects receiving EDURANT®. No grade 4 rash was reported. Overall, most rashes were Grade 1 or 2 and occurred in the first four to six weeks of therapy (see ADVERSE REACTIONS). Discontinue EDURANT® immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, including but not limited to, severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema, angioedema, hepatitis or eosinophilia. Clinical status including laboratory parameters should be monitored and appropriate therapy should be initiated.

**Special Populations**

**Pregnant Women**

No adequate and well-controlled clinical or pharmacokinetic studies of EDURANT® use in pregnant women have been conducted. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function (see Product Monograph Part II: TOXICOLOGY, Reproductive and Developmental Toxicity).

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

**Antiretroviral Pregnancy Registry**

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

**Nursing Women**

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

**Pediatrics (<12 years of age)**

Safety and effectiveness in pediatric patients less than 12 years of age has not been established.
Geriatrics (>65 years of age)
Clinical studies of EDURANT® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from adult subjects < 65 years of age. EDURANT® should be used with caution in this population.

ADVERSE REACTIONS

Adults

Adverse Drug Reaction Overview

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

Clinical Trial Adverse Drug Reactions

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

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

| Table 2: Treatment-Emergent Adverse Drug Reactions* of at Least Moderate Intensity† (Grades 2-4) in ≥1% of Antiretroviral Treatment-Naïve, HIV-1-Infected Adult Subjects Treated with EDURANT® |
|--------------------------------------------------|------------------|------------------|
| System Organ Class, Preferred Term               | Pooled Data from the TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials (Week 96 Analysis) |
|                                                  | EDURANT® + BR N=686 | Efavirenz + BR N=682 |
| Gastrointestinal Disorders                       |                   |                   |
| Abdominal Pain                                   | 14 (2.0%)         | 13 (1.9%)         |
| Nausea‡                                          | 9 (1.3%)          | 19 (2.8%)         |
| Vomiting                                         | 7 (1.0%)          | 14 (2.1%)         |
| Diarrhea                                         | 7 (1.0%)          | 9 (1.3%)          |
| General Disorders and Administration Site Conditions |
| Fatigue                                          | 11 (1.6%)         | 14 (2.1%)         |
### Table 2: Treatment-Emergent Adverse Drug Reactions* of at Least Moderate Intensity† (Grades 2-4) in ≥1% of Antiretroviral Treatment-Naïve, HIV-1-Infected Adult Subjects Treated with EDURANT®

<table>
<thead>
<tr>
<th>System Organ Class, Preferred Term</th>
<th>Pooled Data from the TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials (Week 96 Analysis)</th>
<th>EDURANT® + BR N=686</th>
<th>Efavirenz + BR N=682</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>8 (1.2%)</td>
<td>4 (0.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache‡</td>
<td>24 (3.5%)</td>
<td>26 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness‡#</td>
<td>7 (1.0%)</td>
<td>46 (6.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>28 (4.1%)</td>
<td>22 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>24 (3.5%)</td>
<td>24 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>Abnormal Dreams‡£</td>
<td>11 (1.6%)</td>
<td>27 (4.0%)</td>
<td></td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td>9 (1.3%)</td>
<td>6 (0.9%)</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>16 (2.3%)</td>
<td>65 (9.5%)</td>
<td></td>
</tr>
</tbody>
</table>

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

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### Less Common Clinical Trial Adverse Drug Reactions (<1%)

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

**Gastrointestinal Disorders:** abdominal discomfort

**Hepatobiliary Disorders:** cholecystitis*, cholelithiasis*

**Nervous System Disorders:** somnolence

**Psychiatric Disorders:** anxiety, depressed mood

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

### Abnormal Hematologic and Clinical Chemistry Findings
Selected treatment-emergent clinical laboratory abnormalities (Grade 3 or Grade 4), considered as ADRs, reported in EDURANT®-treated subjects are shown in Table 3.

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

<table>
<thead>
<tr>
<th>Laboratory Parameter Abnormality</th>
<th>DAIDS Toxicity Range</th>
<th>Pooled Data from the TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EDURANT® + BR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=686</td>
</tr>
<tr>
<td>HEMATOLOGY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>&lt; 4.5 mmol/L</td>
<td>0.1%</td>
</tr>
<tr>
<td></td>
<td>&lt; 7.4 g/dl</td>
<td></td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>&lt; 49999/mm³</td>
<td>0.1%</td>
</tr>
<tr>
<td></td>
<td>&lt; 49999 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>Decreased white blood cell count</td>
<td>&lt; 1499/mm³</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.499 giga/L</td>
<td></td>
</tr>
<tr>
<td>BIOCHEMISTRY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>&gt; 1.8 x ULN</td>
<td>0.1%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>&gt; 5.0 x ULN</td>
<td>2.3%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>&gt; 5.0 x ULN</td>
<td>1.6%</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>&gt; 2.5 x ULN</td>
<td>0.7%</td>
</tr>
<tr>
<td>Increased pancreatic amylase</td>
<td>&gt; 2 x ULN</td>
<td>3.8%</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>&gt; 3 x ULN</td>
<td>0.9%</td>
</tr>
<tr>
<td>Increased total cholesterol (fasted)†</td>
<td>&gt; 7.77 mmol/L</td>
<td>0.1%</td>
</tr>
<tr>
<td></td>
<td>&gt; 300 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Increased LDL cholesterol (fasted)†</td>
<td>≥ 4.91 mmol/L</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>≥ 191 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Increased Triglycerides (fasted)†</td>
<td>≥ 8.49 mmol/L</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>≥ 751 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

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

Adrenal Function

In the pooled analysis of Phase III trials, at Week 48, the overall mean change from baseline in basal cortisol showed a decrease of 13.1 nmol/L in the EDURANT® group and an increase of 9.0 nmol/L in the efavirenz (control) group. At Week 96, the overall mean change from baseline in basal cortisol showed a decrease of 19.1 nmol/L in the EDURANT® group and a decrease of 0.6 nmol/L in the efavirenz group. At Week 48 and Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the EDURANT® group (+16.5 ± 6.14 nmol/L and +18.4 ± 8.36 nmol/L, respectively) than in the efavirenz group (+58.1 ± 6.66 nmol/L and +54.1 ± 7.24 nmol/L, respectively). Mean values for both basal and ACTH-stimulated cortisol values at Week 48 and Week 96 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency.

Serum Creatinine
In the pooled Phase III trials, an increase in serum creatinine was observed over the 96 weeks of treatment with EDURANT®. Most of this increase occurred within the first four weeks of treatment, with a mean change of 0.1 mg/dL (range: -0.3 mg/dL to 0.6 mg/dL) observed after 96 weeks of treatment. In subjects who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects with normal renal function. These changes are not considered to be clinically relevant and no subject discontinued treatment due to increases in serum creatinine. Serum creatinine increases occurred regardless of the background N(t)RTI regimen.

**Serum Lipids**

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

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

<table>
<thead>
<tr>
<th>Lipid Parameters</th>
<th>EDURANT® + BRb</th>
<th>Efavirenz + BR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=686</td>
<td>N=682</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 96</td>
</tr>
<tr>
<td></td>
<td>Mean (mg/dL)</td>
<td>Mean (mg/dL)</td>
</tr>
<tr>
<td>Total cholesterolf</td>
<td>546 (161)</td>
<td>166 (5)</td>
</tr>
<tr>
<td>HDL-cholesterolf</td>
<td>545 (41)</td>
<td>46 (4)</td>
</tr>
<tr>
<td>LDL-cholesterolf</td>
<td>543 (96)</td>
<td>98 (1)</td>
</tr>
<tr>
<td>Triglyceridesf</td>
<td>546 (122)</td>
<td>116 (-6)</td>
</tr>
</tbody>
</table>

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

**Bone Effects**

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

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

**Patients Co-infected with Hepatitis B and/or Hepatitis C Virus**

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

**Electrocardiogram Findings**

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

**Adverse Drug Reaction from a Clinical Trial in Pediatric Patients (12 to less than 18 Years of Age and weighing at least 32 kg)**

The safety assessment is based on the Week 48 analysis of the single-arm, open-label, Phase II trial, TMC278-C213, in which 36 antiretroviral treatment-naïve HIV-1 infected patients 12 to less than 18 years of age and weighing at least 32 kg received EDURANT® (25 mg once daily) in combination with other antiretroviral agents (see CLINICAL TRIALS). The median duration of exposure was 63.5 weeks. There were no patients who discontinued treatment due to ADRs. No new ADRs were identified compared to those seen in adults.

ADRs were reported in nineteen pediatric subjects (52.8%). Most ADRs were Grade 1 or 2. The most common ADRs (all grades, in at least two subjects) were headache (19.4%), depression (19.4%), somnolence (13.9%), and nausea (11.1%), dizziness (8.3%), abdominal pain (8.3%), vomiting (5.6%) and rash (5.6%). Observed laboratory abnormalities were comparable to those in adults.

**Adrenal Function**

In trial TMC278-C213, at Week 48, the overall mean change from baseline in basal cortisol showed an increase of 1.59 (0.24, 2.93) micrograms/dL.
Six of 30 (20%) subjects with a normal 250 micrograms ACTH stimulation test at baseline developed an abnormal 250 micrograms ACTH stimulation test (peak cortisol level < 18.1 micrograms/dL) during the trial. Three of these subjects had an abnormal 250 micrograms ACTH stimulation test at Week 48. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the abnormal 250 micrograms ACTH stimulation tests is not known.

**Post-Market Adverse Drug Reactions**

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

**Renal and Genitourinary Disorders:** nephrotic syndrome

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

**DRUG INTERACTIONS**

**Overview**

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

**Drug-Drug Interactions**

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

<table>
<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>Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin</td>
<td>↓ rilpivirine</td>
<td>EDURANT® is contraindicated with these anticonvulsants as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT® and possible development of resistance to EDURANT® and other NNRTIs.</td>
</tr>
<tr>
<td>Antimycobacterials:</td>
<td>↓ rilpivirine</td>
<td>EDURANT® is contraindicated with rifampin or rifapentine as co-</td>
</tr>
</tbody>
</table>
### Table 5: Drugs that Should Not Be Co-administered with EDURANT®

<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>rifampin*† and rifapentine</td>
<td>⇔ rifampin, ⇔ rifapentine</td>
<td>administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT® and possible development of resistance to EDURANT® and other NNRTIs.</td>
</tr>
<tr>
<td><strong>Glucocorticoids:</strong> dexamethasone (systemic)</td>
<td>↓ rilpivirine, ⇔ dexamethasone</td>
<td>EDURANT® is contraindicated with systemic dexamethasone as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT® and possible development of resistance to EDURANT® and other NNRTIs. Alternatives should be considered, particularly for long-term use.</td>
</tr>
<tr>
<td><strong>Proton Pump Inhibitors:</strong> omeprazole*† and lansoprazole, rabeprazole, pantoprazole, esomeprazole</td>
<td>↓ rilpivirine, ↓ omeprazole</td>
<td>EDURANT® is contraindicated with proton pump inhibitors as co-administration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). This may result in loss of therapeutic effect of EDURANT® and possible development of resistance to EDURANT® and other NNRTIs.</td>
</tr>
<tr>
<td><strong>Herbal Products:</strong> St. John’s wort (Hypericum perforatum)</td>
<td>↓ rilpivirine</td>
<td>EDURANT® is contraindicated with products containing St. John’s wort as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT® and possible development of resistance to EDURANT® and other NNRTIs.</td>
</tr>
</tbody>
</table>

↑ = increase; ↓ = decrease; ⇔ = no change
* The interaction between EDURANT® and the drug was evaluated in a clinical study. All other drug-drug interactions shown are predicted.
† This interaction study has been performed with a dose higher than the recommended dose for EDURANT® assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of EDURANT® 25 mg once daily.

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

### Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (see Tables 7 and 8)

<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 should be administered on an empty stomach and at least 2 hours before or at least four hours after EDURANT® (which should be administered with a meal).</td>
</tr>
</tbody>
</table>
Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (see Tables 7 and 8)

<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>Other NRTIs (abacavir, emtricitabine, lamivudine, stavudine and zidovudine)</td>
<td>↔ rilpivirine ↔ other NRTIs</td>
<td>Based on the different elimination routes for rilpivirine and these other NRTIs, no clinically relevant drug-drug interactions are expected between these drugs and EDURANT®.</td>
</tr>
<tr>
<td>HIV-Antiviral Agents: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI (delavirdine)</td>
<td>↑ rilpivirine ↔ delavirdine</td>
<td>It is not recommended to co-administer EDURANT® with 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). An interaction trial between rilpivirine (150 mg q.d.) and darunavir/ritonavir (800 mg/100 mg q.d.) demonstrated that darunavir/ritonavir increased the mean exposure of rilpivirine by 2.3-fold and from 2.7-fold to 3.8-fold in a subset (31%) of subjects. Caution should be exercised when these drugs are co-administered with EDURANT®.</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). An interaction trial between rilpivirine (150 mg q.d.) and lopinavir/ritonavir (400 mg/100 mg q.d.) demonstrated that lopinavir/ritonavir increased the mean exposure (AUC) of rilpivirine by 1.52-fold. Caution should be exercised when these drugs are co-administered with EDURANT®.</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>
<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>HIV-Antiviral Agents: CCR5 Antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>maraviroc</td>
<td>↔ rilpivirine ↔ maraviroc</td>
<td>No clinically relevant drug-drug interaction is expected when EDURANT® is co-administered with maraviroc.</td>
</tr>
<tr>
<td>HIV-Antiviral Agents: Integrase Strand Transfer Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Drug Class: Drug Name</td>
<td>Effect on Concentration of Rilpivirine or Concomitant Drug</td>
<td>Clinical Comment</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>raltegravir</td>
<td>↔ rilpivirine • ↔ raltegravir</td>
<td>No dose adjustment is required when EDURANT® is co-administered with raltegravir.</td>
</tr>
<tr>
<td><strong>Other Antiviral Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ribavirin</td>
<td>↔ rilpivirine • ↔ ribavirin</td>
<td>No clinically relevant drug-drug interaction is expected when EDURANT® is co-administered with ribavirin.</td>
</tr>
<tr>
<td>Simeprevir*</td>
<td>↔ rilpivirine • ↔ simeprevir</td>
<td>No dose adjustment is required for either drug when EDURANT® is co-administered with simeprevir.</td>
</tr>
<tr>
<td><strong>Other Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacids: antacids (e.g., aluminum or magnesium hydroxide, calcium carbonate)</td>
<td>↔ rilpivirine</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>Antiarrhythmics: digoxin</td>
<td>↔ rilpivirine • ↔ digoxin</td>
<td>No dose adjustment is required when EDURANT® is co-administered with digoxin.</td>
</tr>
<tr>
<td>Antidiabetics: metformin</td>
<td>↔ rilpivirine • ↔ metformin</td>
<td>Co-administration of EDURANT® with metformin produced no changes in plasma concentration of metformin. No dose adjustment is required when EDURANT® is co-administered with metformin.</td>
</tr>
<tr>
<td>Antimycobacterials: rifabutin*†</td>
<td>↓ rilpivirine • ↔ rifabutin</td>
<td>Concomitant use of EDURANT® with rifabutin may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT®. Throughout co-administration of EDURANT® with rifabutin, the EDURANT® dose should be increased from 25 mg once daily to 50 mg once daily. When rifabutin co-administration is stopped, the EDURANT® dose should be decreased to 25 mg once daily.</td>
</tr>
<tr>
<td>Azole Antifungal Agents:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ketoconazole*†</td>
<td>↑ rilpivirine • ↓ ketoconazole</td>
<td>Concomitant use of EDURANT® with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). An interaction trial between rilpivirine (150 mg q.d.) and ketoconazole (400 mg q.d.) demonstrated that ketoconazole increased the mean exposure of rilpivirine by 1.49-fold. The concomitant use of EDURANT® with other azole antifungals is expected to result in increased mean exposure (AUC) of rilpivirine (see QT prolonging drugs). Caution should be exercised when these drugs are co-administered with EDURANT®. Clinical monitoring for breakthrough infections is recommended when azole antifungals are co-administered with EDURANT®.</td>
</tr>
<tr>
<td>ketoconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>itraconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>posaconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>voriconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>atorvastatin*†</td>
<td>↔ rilpivirine • ↔ atorvastatin</td>
<td>No dose adjustment is required when EDURANT® is co-administered with HMG-CoA reductase inhibitors.</td>
</tr>
<tr>
<td>pravastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rosuvastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>simvastatin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (see Tables 7 and 8)

<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><strong>H₂-Receptor Antagonists:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>famotidine*†</td>
<td>↔ rilpivirine (famotidine taken 12 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>cimetidine</td>
<td>↓ rilpivirine (famotidine taken 2 hours before rilpivirine)</td>
<td></td>
</tr>
<tr>
<td>nizatidine</td>
<td>↔ rilpivirine (famotidine taken 4 hours after rilpivirine)</td>
<td></td>
</tr>
<tr>
<td>ranitidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolide Antibiotics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clarithromycin</td>
<td>↑ rilpivirine</td>
<td>Concomitant use of EDURANT® with clarithromycin or erythromycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.</td>
</tr>
<tr>
<td>erythromycin</td>
<td>↔ clarithromycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↔ erythromycin</td>
<td></td>
</tr>
<tr>
<td>Narcotic Analgesics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>methadone*</td>
<td>↓ R(-) methadone</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>↓ S(+) methadone</td>
<td></td>
</tr>
<tr>
<td>PDE-5 Inhibitors:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sildenafil*†</td>
<td>↔ sildenafil</td>
<td>No dose adjustment is required when EDURANT® is co-administered with PDE-5 inhibitors used in dosage regimens for the treatment of erectile dysfunction or pulmonary arterial hypertension.</td>
</tr>
<tr>
<td>tadalafil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vardenafil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

↑ = increase; ↓ = decrease; ↔ = no change
* The interaction between EDURANT® and the drug was evaluated in a clinical study. All other drug-drug interactions shown are predicted.
† This interaction study has been performed with a dose higher than the recommended dose for EDURANT® assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of EDURANT® 25 mg once daily.

Drug interaction studies were performed with EDURANT® and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. The effects of co-administration of other drugs on the C_{max}, AUC, and C_{min} values of rilpivirine are summarized in Table 7 (effect of other drugs on EDURANT®). The effect of co-administration of EDURANT® on the C_{max}, AUC, and C_{min} values of other drugs are summarized in Table 8 (effect of EDURANT® on other drugs).
Table 7: Drug Interactions: Pharmacokinetic Parameters for Rilpivirine in the Presence of Co-administered Drugs

<table>
<thead>
<tr>
<th>Co-administered Drug</th>
<th>Dose/Schedule</th>
<th>Co-administered Drug</th>
<th>Rilpivirine</th>
<th>N</th>
<th>Exposure</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;, AUC, C&lt;sub&gt;min&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>Co-administration With HIV Protease Inhibitors (PIs)</td>
<td></td>
<td></td>
<td></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>14 ↑</td>
<td></td>
<td>↑</td>
<td>1.79 (1.56-2.06), 2.30 (1.98-2.67), 2.78 (2.39-3.24)</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>400/100 mg b.i.d. (soft gel capsule)</td>
<td>150 mg q.d.†</td>
<td>15 ↑</td>
<td></td>
<td>↑</td>
<td>1.29 (1.18-1.40), 1.52 (1.36-1.70), 1.74 (1.46-2.08)</td>
</tr>
<tr>
<td>Co-administration with HIV Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>400 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>21 ↔</td>
<td></td>
<td>↔</td>
<td>1.00 (0.90-1.10), 1.00 (0.95-1.06), 1.00 (0.92-1.09)</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>300 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>16 ↔</td>
<td></td>
<td>↔</td>
<td>0.96 (0.81-1.13), 1.01 (0.87-1.18), 0.99 (0.83-1.16)</td>
</tr>
<tr>
<td>Co-administration with HIV Integrase Strand Inhibitors</td>
<td></td>
<td></td>
<td></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>
<td></td>
<td>↔</td>
<td>1.12 (1.04-1.20), 1.12 (1.05-1.19), 1.03 (0.96-1.12)</td>
</tr>
<tr>
<td>Co-administration with other Antivirals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>150 mg q.d.</td>
<td>25 mg q.d.</td>
<td>23 ↔</td>
<td></td>
<td>↔</td>
<td>1.04 (0.95-1.13), 1.12 (1.05-1.19), 1.25 (1.16-1.35)</td>
</tr>
<tr>
<td>Co-administration with Drugs other than Antiretrovirals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>500 mg single dose</td>
<td>150 mg q.d.†</td>
<td>16 ↔</td>
<td></td>
<td>↔</td>
<td>1.09 (1.01-1.18), 1.16 (1.10-1.22), 1.26 (1.16-1.38)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>16 ↔</td>
<td></td>
<td>↔</td>
<td>0.91 (0.79-1.06), 0.90 (0.81-0.99), 0.90 (0.84-0.96)</td>
</tr>
<tr>
<td>Ethinylestradiol/ Norethindrone</td>
<td>0.035 mg q.d./ 1 mg q.d.</td>
<td>25 mg q.d.</td>
<td>15 ↔</td>
<td></td>
<td>↔</td>
<td>↔* ↔* ↔* (as compared to 25 mg q.d. rilpivirine alone)</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg single dose taken 12 hours before rilpivirine</td>
<td>150 mg single dose†</td>
<td>24 ↔</td>
<td></td>
<td>↔</td>
<td>0.99 (0.84-1.16), 0.91 (0.78-1.07), N.A.</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg single dose taken 2 hours before rilpivirine</td>
<td>150 mg single dose†</td>
<td>23 ↓</td>
<td></td>
<td>↓</td>
<td>0.15 (0.12-0.19), 0.24 (0.20-0.28), N.A.</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg single dose taken 4 hours after rilpivirine</td>
<td>150 mg single dose†</td>
<td>24 ↔</td>
<td></td>
<td>↔</td>
<td>1.21 (1.06-1.39), 1.13 (1.01-1.27), N.A.</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>400 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>15 ↑</td>
<td></td>
<td>↑</td>
<td>1.30 (1.13-1.48), 1.49 (1.31-1.70), 1.76 (1.57-1.97)</td>
</tr>
<tr>
<td>Methadone</td>
<td>60-100 mg q.d., individualized dose</td>
<td>25 mg q.d.</td>
<td>12 ↔</td>
<td></td>
<td>↔</td>
<td>↔* ↔* ↔*</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>16 ↓</td>
<td></td>
<td>↓</td>
<td>0.60 (0.48-0.73), 0.60 (0.51-0.71), 0.67 (0.58-0.78)</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>300 mg q.d.</td>
<td>25 mg q.d.</td>
<td>18 ↓</td>
<td></td>
<td>↓</td>
<td>0.69 (0.62-0.76), 0.58 (0.52-0.65), 0.52 (0.46-0.59)</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>300 mg q.d.</td>
<td>50 mg q.d.†</td>
<td>18 ↔</td>
<td></td>
<td>↔</td>
<td>1.43 (1.30-1.56), 1.16 (1.06-1.26), 0.93 (0.85-1.01)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>16 ↓</td>
<td></td>
<td>↓</td>
<td>0.31 (0.27-0.36), 0.20 (0.18-0.23), 0.11 (0.10-0.13)</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>50 mg single dose</td>
<td>75 mg q.d.†</td>
<td>16 ↔</td>
<td></td>
<td>↔</td>
<td>0.92 (0.85-0.99), 0.98 (0.92-1.05), 1.04 (0.98-1.09)</td>
</tr>
</tbody>
</table>
## 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>Mean Ratio of Rilpivirine Pharmacokinetic Parameters With/Without Co-administered Drug (90% CI); No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Co-administered Drug</td>
<td>Rilpivirine</td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* comparison based on historic controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>† 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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 8: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of EDURANT®

<table>
<thead>
<tr>
<th>Co-administered Drug</th>
<th>Co-administered Drug</th>
<th>Dose/Schedule</th>
<th>Rilpivirine</th>
<th>N Exposure</th>
<th>Mean Ratio of Co-administered Drug Pharmacokinetic Parameters With/Without EDURANT® (90% CI); No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Co-Administration with HIV Protease Inhibitors (PIs)</strong></td>
<td></td>
<td></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>
<td>↔</td>
<td>0.90 (0.81-1.00)</td>
</tr>
<tr>
<td></td>
<td>(soft gel capsule)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Co-Administration with HIV Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>400 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>13</td>
<td>↔</td>
<td>0.96 (0.80-1.14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.19 (1.06-1.34)</td>
</tr>
<tr>
<td><strong>Co-administration with HIV Integrase Strand Inhibitors</strong></td>
<td></td>
<td></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>
<td>↑</td>
<td>1.10 (0.77-1.58)</td>
</tr>
<tr>
<td><strong>Co-administration with other Antivirals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simeprevir</td>
<td>150 mg q.d.</td>
<td>25 mg q.d.</td>
<td>21</td>
<td>↔</td>
<td>1.10 (0.97-1.26)</td>
</tr>
<tr>
<td><strong>Co-Administration with Drugs other than Antiretrovirals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>500 mg single dose</td>
<td>150 mg q.d.†</td>
<td>16</td>
<td>↔</td>
<td>0.97 (0.86-1.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.17 (1.06-1.30)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>16</td>
<td>↔</td>
<td>1.35 (1.08-1.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.94 (0.83-1.06)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.5 mg single dose</td>
<td>25 mg q.d.</td>
<td>22</td>
<td>↔</td>
<td>0.96 (0.97-1.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.17 (1.06-1.30)</td>
</tr>
<tr>
<td>Ethinylestradiol</td>
<td>0.035 mg q.d.</td>
<td>25 mg q.d.</td>
<td>17</td>
<td>↔</td>
<td>0.86 (0.78-0.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.94 (0.83-1.06)</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>1 mg q.d.</td>
<td></td>
<td>17</td>
<td>↔</td>
<td>0.85 (0.80-0.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.85 (0.80-0.90)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>400 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>14</td>
<td>↓</td>
<td>0.86 (0.80-0.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.85 (0.80-0.90)</td>
</tr>
<tr>
<td>R(-) methadone</td>
<td>60-100 mg q.d., individualised dose</td>
<td>25 mg q.d.</td>
<td>13</td>
<td>↓</td>
<td>0.84 (0.74-0.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86 (0.78-0.95)</td>
</tr>
<tr>
<td>S(+) methadone</td>
<td></td>
<td></td>
<td>13</td>
<td>↓</td>
<td>0.87 (0.78-0.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.87 (0.78-0.97)</td>
</tr>
<tr>
<td>Metformin</td>
<td>850 mg single dose</td>
<td>25 mg q.d.</td>
<td>20</td>
<td>↔</td>
<td>1.02 (0.95-1.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.02 (0.95-1.10)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>15</td>
<td>↓</td>
<td>0.86 (0.68-1.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86 (0.68-1.09)</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>300 mg q.d.</td>
<td>150 mg q.d.†</td>
<td>17</td>
<td>↔</td>
<td>1.07 (0.98-1.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.07 (0.98-1.17)</td>
</tr>
<tr>
<td>25-O-desacetyl-rifabutin</td>
<td></td>
<td></td>
<td>17</td>
<td>↔</td>
<td>1.07 (0.98-1.17)</td>
</tr>
</tbody>
</table>
Drug-Food Interactions

The exposure to rilpivirine was approximately 40% lower when EDURANT® was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or a high-fat high-caloric meal (928 kcal). When EDURANT® was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal. These decreases in plasma concentrations of rilpivirine may result in a loss of virologic response and possible resistance to EDURANT® and the NNRTI class of antiretrovirals.

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

Drug-Herb Interactions

EDURANT® should not be used in combination with products containing St. John’s wort as co-administration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EDURANT® (see Drug-Drug Interactions, Table 5).

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

QT Prolonging Drugs

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

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

Caution should be observed when using EDURANT® with drugs that can disrupt electrolyte levels, including, but not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.
EDURANT® should be used with caution when co-administered with a drug with a known risk of Torsade de Pointes (see WARNINGS AND PRECAUTIONS, Cardiovascular).

**DOSAGE AND ADMINISTRATION**

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

**Recommended Dosage and Dosage Adjustment**

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

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

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

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

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

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

**Missed Dose**

If the patient misses a dose of EDURANT® within 12 hours of the time it is usually taken, the patient should take EDURANT® with a meal as soon as possible, and then take the next dose of EDURANT® at the regularly scheduled time.

If a patient misses a dose of EDURANT® by more than 12 hours, the patient should not take the missed dose, but resume the usual dosing schedule.

**Co-administration with Rifabutin**

For patients concomitantly receiving rifabutin, the EDURANT® dose should be increased to 50 mg (two tablets of 25 mg each) once daily, taken with a meal. When rifabutin co-administration is stopped, the EDURANT® dose should be decreased to 25 mg once daily, taken with a meal (see DRUG INTERACTIONS).

**OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 protein bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

**ACTION AND CLINICAL PHARMACOLOGY**

**Mechanism of Action**

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

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

Table 9: Population Pharmacokinetic Estimates of Rilpivirine 25 mg Once Daily in Antiretroviral Treatment-Naïve HIV-1-Infected Subjects (Pooled Data from Phase III Trials at Week 48)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rilpivirine 25 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=679</td>
</tr>
<tr>
<td>AUC_{24h} (ng•h/mL)</td>
<td>2397 ± 1032</td>
</tr>
<tr>
<td>Mean ± Standard Deviation</td>
<td>2397 ± 1032</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>2204 (482-8601)</td>
</tr>
<tr>
<td>C_{0h} (ng/mL)</td>
<td>80 ± 37</td>
</tr>
<tr>
<td>Mean ± Standard Deviation</td>
<td>80 ± 37</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>74 (1-300)</td>
</tr>
</tbody>
</table>

Absorption

After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours. In a number of healthy subjects, multiple absorption peaks and/or an increase in absorption between 12 hours and 24 hours post-dose is observed. The underlying mechanism(s) for these observations is unknown. The absolute bioavailability of EDURANT® is unknown.

Effect of food on absorption

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

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.

Excretion

The terminal elimination half-life of rilpivirine is approximately 45 hours. After single-dose oral administration of ^14C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in feces and urine, respectively. In feces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.
Special Populations and Conditions

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

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

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

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

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

Hepatic Impairment
Rilpivirine is primarily metabolized and eliminated by the liver. In a study comparing 8 subjects with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment. EDURANT® has not been studied in subjects with severe hepatic impairment (Child-Pugh score C) (see WARNINGS AND PRECAUTIONS, Hepatic Impairment and DOSAGE AND ADMINISTRATION).

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

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

The effect of EDURANT® on the QTc interval of the ECG was evaluated in two Phase I studies in healthy adult volunteers. EDURANT® at the recommended therapeutic dose of 25 mg q.d. was examined in a double-blind, double-dummy, randomized, placebo- and active-controlled, three-way crossover study in healthy adult volunteers (N=60, 35M/25F), with 13 ECG recordings over 24 hours on day 11 of treatment (steady-state). EDURANT® at the dose of 25 mg q.d. was not associated with a statistically significant or clinically relevant effect on the QTc interval. EDURANT® at doses of 75 mg q.d., and 300 mg q.d. was studied in a double-blind, double-dummy, randomized, placebo and active controlled, three-way crossover study in healthy adult volunteers (N=40, 22F/19M), with 13 ECG recordings over 24 hours on day 1 and day 11 of treatment. On day 11 of treatment (steady-state), the maximum mean QTc interval prolongation (baseline- and placebo-adjusted) was 10.7 (90% CI 6.1, 15.3) ms in the 75 mg q.d. treatment arm and 23.3 (90% CI 18.0, 28.7) ms at 4.5 h post-dosing in the 300 mg q.d. arm.

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

STORAGE AND STABILITY
Store EDURANT® tablets between 15–30°C. Store in the original bottle and protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING
EDURANT® tablets are supplied as white to off-white, film-coated, round, biconvex, tablets for oral administration containing rilpivirine hydrochloride equivalent to 25 mg of rilpivirine.

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

Each tablet is debossed with “TMC” on one side and “25” on the other side. EDURANT® tablets are packaged in high-density polyethylene (HDPE) bottles in the following configuration: 25 mg tablets—bottles of 30.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: rilpivirine hydrochloride


Molecular formula: C_{22}H_{18}N_{6}.HCl

Molecular mass: 402.88 – rilpivirine hydrochloride
366.42 – rilpivirine

Structural formula:

Physicochemical properties

Description: Rilpivirine hydrochloride is a white to almost white powder.

Solubility: Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

pKa: The pKa is 5.6 (pyrimidine moiety)
CLINICAL TRIALS

Study Demographics and Trial Design

Treatment-Naïve Adult Patients

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

The evidence of efficacy of EDURANT® is based on the analyses of 48 and 96-week data from two Phase III trials in antiretroviral treatment-naïve HIV-1 infected adult subjects (Table 10). Similar efficacy for EDURANT® was seen in each trial demonstrating non-inferiority to efavirenz.

Subjects with plasma HIV-1 RNA $\geq 5000$ copies/mL, who were screened for susceptibility to N(t)RTIs and for absence of specific NNRTI RAMs, were included in the trials. The treatments are summarized in Table 10:

<table>
<thead>
<tr>
<th>Study</th>
<th>EDURANT® + BR</th>
<th>Efavirenz + BR (Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TMC278-C209</strong></td>
<td>EDURANT®a 25 mg (Oral) once daily BRc, Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC)</td>
<td>Efavirenzb 600 mg (Oral) once daily BRc, Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC)</td>
</tr>
<tr>
<td><strong>(ECHO)</strong></td>
<td>Phase III, randomized, double-blind, active control, multicentre.</td>
<td></td>
</tr>
<tr>
<td><strong>TMC278-C215</strong></td>
<td>EDURANT®a 25 mg (Oral) once daily BRd, Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC), or ● Zidovudine (ZDV) plus Lamivudine (3TC), or ● Abacavir (ABV) plus Lamivudine (3TC).</td>
<td>Efavirenzb 600 mg (Oral) once daily BRd, Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) or ● Zidovudine (ZDV) plus Lamivudine (3TC) or ● Abacavir (ABV) plus Lamivudine (3TC).</td>
</tr>
<tr>
<td><strong>(THRIVE)</strong></td>
<td>Phase III, randomized, double-blind, active control, multicentre.</td>
<td></td>
</tr>
</tbody>
</table>

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

In the pooled analyses of TMC278-C209 and TMC278-C215 the demographic and baseline disease characteristics were balanced between the EDURANT® arm and efavirenz (control) arms (Table 11).
Table 11: Demographic and Baseline Disease Characteristics of Antiretroviral Treatment-Naïve HIV-1 Infected Adult Patients in Studies TMC278-C209 (ECHO) and TMC278-C215 (THRIVE), Pooled Analysis

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>EDURANT® + BR N=686</th>
<th>Efavirenz + BR N=682</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium 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><strong>Baseline Disease Characteristics</strong></th>
<th>EDURANT® + BR N=686</th>
<th>Efavirenz + BR N=682</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Baseline Plasma HIV-1 RNA (range), Log_{10} copies/ml.</td>
<td>5.0 (2-7)</td>
<td>5.0 (3-7)</td>
</tr>
<tr>
<td>Percent 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 (range), cells/mm^3</td>
<td>249 (1-888)</td>
<td>260 (1-1137)</td>
</tr>
<tr>
<td>Percent of Patients with Hepatitis B/C Virus Co-infection</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Percent 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

**Study Results**

Efficacy at Week 48 and Week 96 for subjects in the EDURANT® and efavirenz arms for the pooled data from the TMC278-C209 and TMC278-C215 study populations are shown in Table 12. The response rate (confirmed undetectable viral load < 50 HIV-1 RNA copies/mL) at Week 96 was comparable between the EDURANT® arm and the efavirenz arm. The incidence of virologic failure was higher in the EDURANT® arm than the efavirenz arm at Week 96; however, most of the virologic failures occurred within the first 48 weeks of treatment. Discontinuations due to adverse events were higher in the efavirenz arm than the EDURANT® arm.
Table 12: Virologic Outcome of Randomized Treatment in the TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials in Adults (Pooled Analysis at Week 48 and Week 96; ITT-TLOVR<sup>a</sup>)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Outcome at Week 48</th>
<th>Outcome at Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDURANT&lt;sup&gt;®&lt;/sup&gt; + BR N=686</td>
<td>Efavirenz + BR N=682</td>
</tr>
<tr>
<td>Confirmed Undetectable Viral Load (&lt;50 HIV-1 RNA copies/mL)&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>84.3%</td>
<td>82.3%</td>
</tr>
<tr>
<td>≤ 100,000</td>
<td>90.2%</td>
<td>83.6%</td>
</tr>
<tr>
<td>&gt; 100,000</td>
<td>77.4%</td>
<td>81.0%</td>
</tr>
<tr>
<td>Virologic Failure&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>9.0%</td>
<td>4.8%</td>
</tr>
<tr>
<td>≤ 100,000</td>
<td>3.8%</td>
<td>3.3%</td>
</tr>
<tr>
<td>&gt; 100,000</td>
<td>15.1%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Death</td>
<td>0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Discontinued due to adverse event (AE)</td>
<td>2.0%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Discontinued for non-AE reason&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.5%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

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

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

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

A subgroup analysis of the virological response (<50 HIV-1 RNA copies/mL, TLOVR) at 48 and 96 weeks by background NRTIs, and by CD4+ cell count, and virological failure by CD4+ cell count (pooled data from the TMC278-C209 and TMC278-C215 trials) is presented in Table 13.
### Table 13: Subgroup Outcomes (ITT-TLOVR) at Week 48 (primary) and Week 96 in the Pooled TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) Trials in Adults, by Background NRTI, and Baseline CD4+ Cell Count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week-48 Outcomes HIV-RNA (&lt;50 copies/mL)</th>
<th>Week-96 Outcomes HIV-RNA (&lt;50 copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDURANT® + BR N=686 n/N (%)</td>
<td>Efavirenz + BR N=682 n/N (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virological Response by Background NRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tenofovir disoproxil fumarate plus emtricitabine</td>
<td>459/550 (83.5)</td>
<td>450/546 (82.4)</td>
</tr>
<tr>
<td>zidovudine plus lamivudine</td>
<td>88/101 (87.1)</td>
<td>83/103 (80.6)</td>
</tr>
<tr>
<td>abacavir plus lamivudine</td>
<td>31/35 (88.6)</td>
<td>28/33 (84.8)</td>
</tr>
<tr>
<td>Virological Response by Baseline CD4+ Cell Count (cells/mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>20/34 (58.8)</td>
<td>29/36 (80.6)</td>
</tr>
<tr>
<td>≥50 - &lt;200</td>
<td>156/194 (80.4)</td>
<td>143/175 (81.7)</td>
</tr>
<tr>
<td>≥200 - &lt;350</td>
<td>272/313 (86.9)</td>
<td>253/307 (82.4)</td>
</tr>
<tr>
<td>≥350</td>
<td>130/144 (90.3)</td>
<td>136/164 (82.9)</td>
</tr>
<tr>
<td>Virological Failure by Baseline CD4+ Cell Count (cells/mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>6/34 (17.6)</td>
<td>1/36 (2.8)</td>
</tr>
<tr>
<td>≥50 - &lt;200</td>
<td>27/194 (13.9)</td>
<td>14/175 (8.0)</td>
</tr>
<tr>
<td>≥200 - &lt;350</td>
<td>21/313 (6.7)</td>
<td>14/307 (4.6)</td>
</tr>
<tr>
<td>≥350</td>
<td>8/144 (5.6)</td>
<td>4/164 (2.4)</td>
</tr>
</tbody>
</table>

N = number of subjects per treatment group
n = number of observations
* Imputations according to the TLOVR algorithm.

Virological Failure by Baseline CD4+ Cell Count (cells/mm³)

Trial TMC278-C204

Study TMC278-C204 was a randomized, active-controlled, Phase IIb trial in antiretroviral treatment-naïve HIV-1-infected adult subjects consisting of 2 parts: an initial 96 weeks, partially-blinded dose-finding part (EDURANT® doses blinded) followed by a long-term, open-label part. After Week 96, subjects randomized to one of the 3 doses of EDURANT® were switched to EDURANT® 25 mg once daily. Subjects in the control arm received efavirenz 600 mg once daily in addition to a BR in both parts of the study. The BR consisted of 2 investigator-selected N(t)RTIs: zidovudine plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine.
Study TMC278-C204 enrolled 368 HIV-1-infected treatment-naïve adult subjects who had a plasma HIV-1 RNA ≥5000 copies/ml, previously received ≤2 weeks of treatment with an N(t)RTI or protease inhibitor, had no prior use of NNRTIs, and were screened for susceptibility to N(t)RTI and for absence of specific NNRTI RAMs.

At 96 weeks, the proportion of subjects with <50 HIV-1 RNA copies/mL receiving EDURANT® 25 mg (N = 93) compared to subjects receiving efavirenz (N = 89) was 76% and 71%, respectively. The mean increase from baseline in CD4+ counts was 146 cells/mm³ in subjects receiving EDURANT® 25 mg and 160 cells/mm³ in subjects receiving efavirenz.

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

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

Trial TMC278-C213

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

In the efficacy analysis, most subjects (75%; 28/36) had baseline HIV RNA <100,000 copies/mL. For these 28 subjects the median baseline plasma HIV-1 RNA was 44,250 (range: 2,060-92,600 copies/mL) and the median baseline CD4+ cell count was 445.5 cells/mm³ (range: 123 to 983 cells/mm³).

Among the subjects who had baseline HIV RNA ≤ 100,000, the proportion with HIV-1 RNA <50 copies/mL at Week 48 (TLOVR) was 79% (22/28), versus 50.0% (4/8) in those with >100,000 copies/mL. The proportion of virologic failures among subjects with a baseline viral load ≤100,000 copies/mL was 17.9% (5/28), versus 37.5% (3/8) in those with >100,000 copies/mL. One subject discontinued due to an adverse event and one subject discontinued due to reasons other than an adverse event or virological failure. At Week 48, the mean increase in CD4+ cell count from baseline was 201.2 cells/mm³.

DETAILED PHARMACOLOGY

Pharmacodynamics

Electrocardiogram
See Product Monograph Part 1: ACTION AND CLINICAL PHARMACOLOGY; Special Populations and Conditions; Effect on Electrocardiogram
Pharmacokinetics

Absorption
After oral administration of single or multiple doses, maximum rilpivirine plasma concentrations are generally achieved within 4-5 hours after dosing. Steady-state plasma concentrations are reached in approximately 11 days.

The population pharmacokinetics derived mean (SD) C₀h and AUC₂₄h for rilpivirine in HIV-1 infected patients (pooled Phase III trials) receiving EDURANT® is 80 (37) ng/mL and 2397 (1032) ng.h/mL, respectively.

Effect of food on oral absorption
The exposure to rilpivirine is similar when taken following a standard normal caloric meal (561 kcal) or high-fat, high caloric meal (928 kcal). When compared to administration following a standard normal caloric meal, the exposure to rilpivirine was decreased by approximately 40% in fasted conditions. When EDURANT® was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal. Therefore, to achieve optimal exposure, EDURANT® should be taken with a meal (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Distribution
Rilpivirine is approximately 99.7% bound to plasma proteins, primarily to albumin in vitro. 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 CYP3A system.

Elimination
The terminal elimination half-life of rilpivirine is approximately 45 hours. After single-dose oral administration of $^{14}$C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in feces and urine, respectively. In feces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (<1% of dose) were detected in urine.

Demographics
Population pharmacokinetic analysis in HIV-infected patients treated with EDURANT® indicated that there was no clinically relevant effect of race on the pharmacokinetics of rilpivirine, and no clinically relevant difference between the pharmacokinetics in men and women, or across the age range of 18–78 years (the analysis included only two subjects above 65 years).

The multiple dose exposure of rilpivirine was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment, as compared to healthy matched controls. EDURANT® has not been studied in subjects with severe hepatic impairment. Population pharmacokinetic analysis indicated that hepatitis B and/or C virus co-infection had no clinically relevant effect on the exposure to rilpivirine.
The pharmacokinetics of rilpivirine has not been investigated in patients with renal insufficiency.

The pharmacokinetics of rilpivirine in children less than 12 years of age are under investigation.

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

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

**MICROBIOLOGY**

**Antiviral Activity *In Vitro***

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

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

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

**Resistance**

**Resistance *In Vitro***
Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1. The most commonly observed amino acid substitutions that emerged included: L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

Resistance to rilpivirine was determined as a fold change in EC$_{50}$ value (FC) above the biological cut-off (BCO) of the assay.
Resistance in Treatment-Naïve Adult Subjects


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

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

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

Cross-resistance

Site-Directed NNRTI Mutant Virus

In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96%) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V. The K103N substitution did not show reduced susceptibility to rilpivirine by itself, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine.

Recombinant Clinical Isolates

Rilpivirine retained sensitivity (FC \leq BCO) against 62% of 4786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine. Clinical isolates resistant to rilpivirine (FC>BCO) were usually also resistant to etravirine.

Cross-Resistance in Treatment-Naïve Adult Subjects

In the Week 48 pooled analysis of the two Phase III trials, of the 62 subjects with virologic failure on EDURANT® for whom phenotypic resistance data was available, 31 (50%) lost susceptibility to rilpivirine and within that subset 28 (90%) were resistant to etravirine, 27 (87%) to efavirenz, and 14 (45%) to nevirapine. Of the 28 subjects with virologic failure on efavirenz (control) for whom phenotypic resistance data was available, 12 (43%) lost susceptibility to efavirenz and within that subset none were resistant to etravirine or to rilpivirine, and 12 (100%) to nevirapine.
In the Week 96 pooled analysis of the two Phase III trials, of the 81 subjects with virologic failure on EDURANT® for whom phenotypic resistance data was available, 35 (43%) lost susceptibility to rilpivirine and within that subset 32 (91%) were resistant to etravirine, 30 (86%) to efavirenz, and 16 (45%) to nevirapine. Of the 41 subjects with virologic failure on efavirenz (control) for whom phenotypic resistance data was available, 17 (41%) lost susceptibility to efavirenz and within that subset 1 (6%) were resistant to etravirine, none to rilpivirine, and 15 (38%) to nevirapine.

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

TOXICOLOGY

General Toxicology

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

Carcinogenesis and Mutagenesis

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice, and doses of 40, 200, 500 and 1500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in both mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of rilpivirine did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats may be rodent-specific, associated with liver enzyme induction. The follicular cell findings may be rat-specific, associated with increased clearance of thyroxine. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg q.d.).

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

In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day, a dose of rilpivirine that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function at exposures relevant for human administration.

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

Impairment of Fertility

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


PART III: CONSUMER INFORMATION

EDURANT®
rilpivirine tablets
25 mg rilpivirine as rilpivirine hydrochloride

This leaflet is Part III of a three-part “Product Monograph” published when EDURANT® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about EDURANT®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What is EDURANT®?

- EDURANT® is a prescription anti-HIV medicine that helps to control HIV (Human Immunodeficiency Virus) infection in adults and children (12 years to less than 18 years of age and weighing at least 35 kg). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- EDURANT® is a type of anti-HIV drug called a non-nucleoside reverse transcriptase inhibitor (NNRTI).
- EDURANT® is used in adults and children (12 years to less than 18 years of age and weighing at least 35 kg) who have not taken anti-HIV medicines before.
- EDURANT® must be taken in combination with other anti-HIV medicines.
- It is very important for you to remain under the care of your doctor during treatment with EDURANT®.
- The safety and effectiveness of EDURANT® in children less than 12 years of age has not been determined.

How does EDURANT® work?

- EDURANT® blocks an enzyme which the virus (HIV) needs in order to make more virus. The enzyme that EDURANT® blocks is called HIV reverse transcriptase.
- When used with other anti-HIV medicines, EDURANT® may help:
  - reduce the amount of HIV in your blood. This is called “viral load.”
  - increase the number of white blood cells called CD4+ (T) cells that help fight off other infections.
- Reducing the amount of HIV and increasing the CD4+ (T) cell count may improve your immune system and, as a result, reduce the risk of death or infections that can happen when your immune system is weak (opportunistic infections).

Does EDURANT® cure HIV or AIDS?

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

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

Does EDURANT® reduce the risk of passing HIV to others?

No. EDURANT® does not reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood.
- Always practice safer sex.
- Use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- Never re-use or share needles.

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

When it should not be used:

Do not take EDURANT® if you are allergic to rilpivirine or any of the other ingredients in EDURANT® (See “What the nonmedicinal ingredients are”).

Do not take EDURANT® with the following drugs:

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Examples of Generic Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>carbamazepine, oxcarbazepine, phenytoin, phenobarbital</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Systemic dexamethasone (more than a single dose)</td>
</tr>
<tr>
<td>Herbal products</td>
<td>St. John’s wort (Hypericum perforatum)</td>
</tr>
<tr>
<td>Proton Pump Inhibitors</td>
<td>omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole</td>
</tr>
</tbody>
</table>

What the medicinal ingredient is:

Each tablet contains 25 mg of rilpivirine in the form of rilpivirine hydrochloride.

What the nonmedicinal ingredients are:

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

**What dosage forms it comes in:**
25 mg tablets

**WARNINGS AND PRECAUTIONS**

**What should I tell my doctor before I take EDURANT®?**
Together with your doctor, you need to decide whether taking EDURANT® is right for you.

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

**INTERACTIONS WITH THIS MEDICATION**

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription (e.g., over-the-counter herbal products).

Some medicines may affect the levels of EDURANT® in the body when they are taken at the same time as EDURANT®.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine. Your doctor and your pharmacist can tell you if you can take these medicines with EDURANT®.

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

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

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

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

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Examples of Generic Names (Brand Names)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>Aluminum, magnesium hydroxide, calcium carbonate</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>rifabutin</td>
</tr>
</tbody>
</table>
## Type of Drug

### Azole Antifungal Agents
- ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole

### Corticosteroids
- (to treat inflammation or asthma)
  - dexamethasone (Decadron®)

### H2-Receptor Antagonists
- (to treat stomach ulcers or used to relieve heartburn from acid reflux)
  - cimetidine (Tagamet®), famotidine (Pepcid®), nizatidine (Axid AR®), ranitidine (Zantac®)

### Macrolide Antibiotics
- (to treat bacterial infections)
  - clarithromycin (Biaxin®), erythromycin (Benzamycin®, AK Mycin®, EES*-200/400, EES-600, ERYC®, Erythro-S®, Erythro-ES®, Erybid®, PCE®)

### Narcotic Analgesics
- methadone (Methadol®, Metadol-D®, Cophylac® drops)

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

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### PROPER USE OF THIS MEDICATION

- **Take EDURANT® tablets every day exactly as prescribed by your doctor.** The recommended dose is one tablet of EDURANT® one time each day.

- **Always take EDURANT® with a meal.** A meal is important to get the right drug levels in your body. A protein drink alone does not replace a meal.

- **Swallow EDURANT® tablets whole with water.**

- **Do not change your dose or stop taking EDURANT® without first talking with your doctor.** See your doctor regularly while taking EDURANT®.

- **When your supply of EDURANT® starts to run low, get more from your doctor or pharmacy.** It is important not to run out of EDURANT®. The amount of HIV in your blood may increase if the medicine is stopped even for a short time.

- **If you take rifabutin** (a medicine to treat some bacterial infections), take two tablets of EDURANT® once a day. When you stop taking rifabutin, take one tablet of EDURANT® once a day. Talk to your doctor or pharmacist if you are not sure. **If you take an H2-receptor antagonist** (medicines used to treat stomach ulcers, heartburn or acid reflux disease such as cimetidine, famotidine, nizatidine or ranitidine), take the H2-receptor antagonist at least 12 hours before or at least 4 hours after EDURANT®.
  - Importantly, proton pump inhibitors (such as omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole) should not be taken with EDURANT®.

### Overdose:
- In case of drug overdose, contact a health care practitioner (doctor), hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

### Missed dose:
- If you miss a dose of EDURANT® within 12 hours of the time you usually take it, take your dose of EDURANT® with a meal as soon as possible. Then, take your next dose of EDURANT® at the regularly scheduled time.

- If you miss a dose of EDURANT® by more than 12 hours of the time you usually take it, wait and then take the next dose of EDURANT® at the regularly scheduled time.

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

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, EDURANT® may cause side effects including:

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

**Uncommon side effects** (affects less than 1 in 100 people)
- depressed mood
- drowsiness
- stomach discomfort
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

Other side effects include:

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

- Feeling depressed, and thoughts of self-harm or suicide while taking EDURANT®. If you experience any of these symptoms, contact your doctor.

- Changes in body shape or body fat. These changes can happen in patients taking anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck, breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.

- Changes in your immune system (Immune Reconstitution Inflammatory 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, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling, or fatigue or any new symptoms contact your doctor straight away.

- 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®. If you suffer symptoms such as abdominal pain, vomiting, nausea, yellowing of the eyes or skin or fatigue, contact your doctor.

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

This is not a complete list of side effects. For any unexpected effects while taking EDURANT®, contact your doctor or pharmacist.

Tell your doctor right away about these or any other unusual symptoms. If the condition does not go away or worsens, get medical help.

**HOW TO STORE IT**

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

Keep EDURANT® and all medications out of reach and sight of children.

**General advice 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 provides a summary of the most important information about EDURANT®. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about EDURANT® that is written for health professionals.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 1908C
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

**NOTE:** Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.
MORE INFORMATION

For questions, concerns, or the full product monograph go to:
http://www.janssen.com/canada
or contact the manufacturer, Janssen Inc., at:
1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by
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