

## PRODUCT MONOGRAPH

Pr **INTELENCE**<sup>®</sup>\*

etravirine tablets 100 mg, 200 mg

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

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## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>3</b>
SUMMARY PRODUCT INFORMATION .....	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS .....	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	7
DRUG INTERACTIONS .....	13
DOSAGE AND ADMINISTRATION.....	24
OVERDOSAGE .....	25
ACTION AND CLINICAL PHARMACOLOGY .....	25
STORAGE AND STABILITY.....	29
DOSAGE FORMS, COMPOSITION AND PACKAGING .....	29
<b>PART II: SCIENTIFIC INFORMATION .....</b>	<b>30</b>
PHARMACEUTICAL INFORMATION.....	30
CLINICAL TRIALS.....	31
DETAILED PHARMACOLOGY .....	36
MICROBIOLOGY .....	37
TOXICOLOGY .....	40
REFERENCES .....	42
<b>PART III: CONSUMER INFORMATION.....</b>	<b>44</b>

# PrINTELENCE®\*

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	tablet, 100 mg	lactose monohydrate  <i>For a complete listing see <b>DOSAGE FORMS, COMPOSITION AND PACKAGING</b> section.</i>
Oral	tablet, 200 mg	none  <i>For a complete listing see <b>DOSAGE FORMS, COMPOSITION AND PACKAGING</b> section.</i>

### INDICATIONS AND CLINICAL USE

INTELENCE® (etravirine), in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in treatment-experienced adult patients who have failed prior therapy and have HIV-1 strains resistant to multiple antiretroviral agents, including NNRTIs.

This indication is based on safety and efficacy data at 48 weeks from two Phase 3, double-blinded, placebo-controlled trials in treatment-experienced patients who had a least one NNRTI resistance-associated mutation and multiple primary protease inhibitor mutations (see **CLINICAL TRIALS** for description of studies).

The following points should be considered when initiating therapy with INTELENCE®:

- Do not use INTELENCE® with only N[t]RTIs in the setting of previous NNRTI failure. This is based on an analysis of an exploratory Phase 2 clinical trial in patients who had experienced virologic failure on an NNRTI- and N[t]RTI-containing regimen (See Clinical Trials for Description of Studies).

- The use of other active antiretroviral agents with INTELENCE<sup>®</sup> is associated with an increased likelihood of treatment response.
- Treatment history and, when available, resistance testing, should guide the use of INTELENCE<sup>®</sup>.

**Geriatrics (> 65 years of age):**

Clinical studies of INTELENCE<sup>®</sup> did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised when administering INTELENCE<sup>®</sup> in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY**).

**Pediatrics (< 18 years of age):**

Safety and effectiveness of INTELENCE<sup>®</sup> in pediatric patients have not been established. Treatment with INTELENCE<sup>®</sup> is not recommended in children and adolescents (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY**).

**CONTRAINDICATIONS**

INTELENCE<sup>®</sup> (etravirine) is contraindicated in patients who are hypersensitive to etravirine or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

**WARNINGS AND PRECAUTIONS****Skin**

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking INTELENCE<sup>®</sup> (etravirine). These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and infrequently organ dysfunction, including hepatic failure.

Discontinue INTELENCE<sup>®</sup> immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping INTELENCE<sup>®</sup> treatment after the onset of severe rash may result in a life-threatening reaction.

In Phase III clinical trials, Grade 3 and 4 rashes were reported in 1.3% of subjects receiving INTELENCE<sup>®</sup> compared to 0.2% of placebo subjects. A total of 2% of HIV-1-infected patients receiving INTELENCE<sup>®</sup> discontinued from Phase III trials due to rash. Rash occurred most commonly during the first 6 weeks of therapy (see **ADVERSE REACTIONS, Skin Rash**).

## **General**

Patients with hereditary problems of lactose intolerance should not take this medicine.

## **Carcinogenesis and Mutagenesis**

Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. A statistically significant increase in the incidences of hepatocellular adenomas and carcinomas was observed in treated female mice. Administration of etravirine did not cause a statistically significant increase in the incidence of tumors in female or male rats. The relevance of the findings in mice to humans is not known. At the highest tested doses, the systemic exposures (based on AUC) to etravirine were lower than those in humans at the clinical therapeutic dose (200 mg b.i.d) with animal versus human AUC ratios being 0.6 (mice) and between 0.2 and 0.7 (rats) (see ***Product Monograph Part II: TOXICOLOGY, Carcinogenesis and Mutagenesis***).

Etravirine 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 presence and absence of the metabolic activation system. Etravirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice (see ***Product Monograph Part II: TOXICOLOGY, Carcinogenesis and Mutagenesis***).

## **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 “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

## **Hepatic/Biliary/Pancreatic**

### **Hepatic Impairment**

No dose adjustment is required in patients with mild or moderate hepatic impairment. The pharmacokinetics of INTELENCE<sup>®</sup> have not been studied in patients with severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency and DOSAGE AND ADMINISTRATION, Recommended Dosage and Dosage Adjustment, Hepatic Impairment**).

## **Pancreatitis**

Pancreatitis has been reported infrequently (<1%) during clinical trials with INTELENCE<sup>®</sup>. In the placebo-controlled Phase III DUET-1 and DUET-2 trials, the rate of clinical pancreatitis was similar in patients receiving INTELENCE<sup>®</sup> 4/599 (0.7%) and placebo 2/604 (0.3%). Pancreatitis has been reported in one healthy volunteer (1/1093, 0.09%).

In the DUET trials asymptomatic grade 3 or 4 increases in serum amylase levels were observed in a similar number of patients treated with INTELENCE<sup>®</sup> (7.5%) and placebo (7.9%) (see **ADVERSE REACTIONS; Laboratory Abnormalities**). Grade 3 or 4 elevated lipase levels were reported in 2.7% patients receiving INTELENCE<sup>®</sup> compared to 1.7% of patients receiving placebo.

## **Immune**

### **Immune Reconstitution**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including INTELENCE<sup>®</sup>. 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.

## **Renal**

### **Renal Impairment**

Since the renal clearance of etravirine is minimal (<1.2%), a decrease in total body clearance is not expected in patients with renal impairment. No special precautions or dose adjustments are required in patients with renal impairment. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

## **Special Populations**

### **Pregnant Women:**

There are no adequate and well-controlled studies with etravirine in pregnant women. Studies in animals have not shown evidence of developmental toxicity or effect on reproductive function and fertility (see *Product Monograph Part II: TOXICOLOGY, Reproductive and Developmental Toxicity*).

INTELENCE<sup>®</sup> should be used during pregnancy only if the potential benefit justifies the potential risk.

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

### **Nursing Women:**

There were indirect indications of the presence of etravirine in the milk of lactating rats. It is not yet known if etravirine is excreted in human milk and whether there is potential for adverse events in nursing infants. Because of both the potential for HIV transmission and the potential for adverse events in nursing infants, mothers should be instructed not to breast-feed if they are receiving INTELENCE<sup>®</sup> (see *Product Monograph Part II: TOXICOLOGY, Reproductive and Developmental Toxicity*).

### **Pediatrics (<18 years of age):**

The safety and effectiveness of INTELENCE<sup>®</sup> in pediatric patients have not been established.

### **Geriatrics (>65 years of age):**

There were insufficient numbers of subjects aged 65 and over in the clinical studies to determine whether they respond differently from younger subjects. In general, caution should be exercised when administering INTELENCE<sup>®</sup> in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The safety assessment is based on all data from 1203 patients in the ongoing Phase III placebo-controlled trials in antiretroviral treatment-experienced HIV-1-infected adult patients [DUET-1 (TMC125-C206) and DUET-2 (TMC125-C216)], 599 of whom received INTELENCE<sup>®</sup> (etravirine), 200 mg b.i.d. In these pooled trials, the median exposure for subjects in the INTELENCE<sup>®</sup> arm and placebo arm was 52.3 and 51.0 weeks, respectively.

In the pooled DUET trials, 96.0% of both INTELENCE<sup>®</sup>-treated subjects and placebo-treated subjects experienced adverse events. The most frequently reported (>10%) adverse events of all intensities and regardless of causality that occurred at a higher rate in INTELENCE<sup>®</sup>-treated subjects as compared to placebo-treated subjects included rash (any type) in 19.2% and 10.9% of INTELENCE<sup>®</sup>-treated subjects and placebo-treated subjects, respectively. Severe and potentially life-threatening skin reactions including Stevens-Johnson syndrome, hypersensitivity reaction and erythema multiforme occurred in <1% of subjects taking INTELENCE<sup>®</sup> (see **WARNINGS AND PRECAUTIONS** and **ADVERSE DRUG REACTIONS, Skin Rash**).

The other most frequently reported adverse events that occurred at a higher rate in the INTELENCE<sup>®</sup>-treated subjects as compared to placebo-treated subjects were nausea in 14.9% and 12.7%, and nasopharyngitis in 11.0% and in 10.4% of INTELENCE<sup>®</sup>-treated subjects and placebo-treated subjects, respectively.

In total, 79.3% and 73.0% of the subjects experienced adverse drug reactions (ADRs; i.e., adverse events considered related to INTELENCE<sup>®</sup>) with INTELENCE<sup>®</sup> and placebo, respectively. The majority of the ADRs reported during treatment with INTELENCE<sup>®</sup> were grade 1 to 2 in severity. Grade 3 or 4 ADRs were reported in 22.2% and 17.2% of the INTELENCE<sup>®</sup>- and placebo-treated subjects. The most commonly reported Grade 3 or 4 ADRs were hypertriglyceridemia (4.2% in the INTELENCE<sup>®</sup> arm and 2.3% in the placebo arm),

hypercholesterolemia (2.2% in the INTELENCE<sup>®</sup> arm and 2.3% in the placebo arm), renal failure (2.0% in the INTELENCE<sup>®</sup> arm and 1.2% in the placebo arm) and anemia (1.7% in the INTELENCE<sup>®</sup> arm and 1.3% in the placebo arm). ADRs were reported as SAEs in 6.8% and 8.3% of subjects treated with INTELENCE<sup>®</sup> and placebo, respectively. ADRs that led to permanent discontinuation of the investigational medication were reported in 5.2% of the INTELENCE<sup>®</sup>-treated subjects and in 2.6% of the placebo-treated subjects. The most commonly reported ADRs (any grade) with INTELENCE<sup>®</sup> identified from the pooled DUET trials were rash (any type), reported by 19.2% of INTELENCE<sup>®</sup>-treated subjects and by 10.9% of placebo-treated subjects, diarrhea (18.0% and 23.5%), and nausea (14.9% and 12.8%).

### **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.*

ADRs of moderate intensity or greater ( $\geq$  Grade 2) and reported in  $\geq 1\%$  of subjects treated with INTELENCE<sup>®</sup> (200 mg b.i.d.) in the DUET-1 and DUET-2 trials are presented in Table 1. Laboratory abnormalities considered ADRs are included in Table 3.

<b>Table 1: Treatment-Emergent Adverse Reactions* of at Least Moderate Intensity (Grades 2-4) in <math>\geq 1\%</math> of Adult Subjects in the INTELENCE<sup>®</sup> Treatment Groups</b>		
<b>System Organ Class, Preferred Term, %</b>	<b>DUET-1 and DUET-2 Trials</b>	
	<b>INTELENCE<sup>®</sup> + BR N=599</b>	<b>Placebo + BR N=604</b>
<b>Blood and Lymphatic System Disorders</b>		
Anemia	4.0%	3.8%
Thrombocytopenia	1.3%	1.5%
<b>Cardiac Disorders</b>		
Myocardial infarction	1.3%	0.3%
<b>Gastrointestinal Disorders</b>		
Diarrhea	7.0%	11.3%
Nausea	5.2%	4.8%
Abdominal pain	3.5%	3.1%
Vomiting	2.8%	2.8%
Gastroesophageal reflux disease	1.8%	1.0%
Flatulence	1.5%	1.0%
Gastritis	1.5%	1.0%
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	3.5%	4.6%
<b>Metabolism and Nutrition Disorders</b>		
Hypertriglyceridemia	6.3%	4.3%

<b>Table 1: Treatment-Emergent Adverse Reactions* of at Least Moderate Intensity (Grades 2-4) in <math>\geq 1\%</math> of Adult Subjects in the INTELENCE<sup>®</sup> Treatment Groups</b>		
<b>System Organ Class, Preferred Term, %</b>	<b>DUET-1 and DUET-2 Trials</b>	
	<b>INTELENCE<sup>®</sup> + BR N=599</b>	<b>Placebo + BR N=604</b>
Hypercholesterolemia	4.3%	3.6%
Hyperlipidemia	2.5%	1.3%
Hyperglycemia	1.5%	0.7%
Diabetes mellitus	1.3%	0.2%
<b>Nervous System Disorders</b>		
Peripheral neuropathy	3.8%	2.0%
Headache	3.0%	4.5%
<b>Psychiatric Disorders</b>		
Insomnia	2.7%	2.8%
Anxiety	1.7%	2.6%
<b>Renal and Urinary Disorders</b>		
Renal failure	2.7%	2.0%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	10.0%	3.5%
Lipohypertrophy	1.0%	0.3%
Night sweats	1.0%	1.0%
<b>Vascular Disorders</b>		
Hypertension	3.2%	2.5%

\*Includes adverse reactions at least possibly, probably, or very likely related to the drug  
N = total number of subjects per treatment group  
BR = background regimen

### **Skin Rash**

The most frequently reported adverse drug reaction of at least Grade 2 in severity in the Phase III studies was rash (10%). Stevens-Johnson syndrome, severe hypersensitivity reaction, and erythema multiforme were reported in <0.1% of subjects during clinical development with INTELENCE<sup>®</sup>. A total of 2% of HIV-1-infected subjects receiving INTELENCE<sup>®</sup> discontinued from Phase III trials due to rash. In general, rash was mild to moderate, macular to maculopapular or erythematous, occurred primarily in the second week of therapy and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy. In Phase III studies, the incidence of rash was higher in women compared to men in the INTELENCE<sup>®</sup> arm. Patients with a history of NNRTI-related rash did not appear to be at increased risk for the development of INTELENCE<sup>®</sup>-related rash compared to patients without a history of NNRTI-related rash. See Table 2 for a summary of rash events.

<b>Table 2: Rash (Any Type) - Week 48 DUET Analysis</b>		
<b>Rash Summary, n (%)</b>	<b>Placebo N=604</b>	<b>Pooled DUET Trials N=599</b>
<b>Rash (any type)</b>	<b>66(10.9)</b>	<b>115 (19.2)</b>
Grade 1	46 (7.6)	61 (10.2)
Grade 2	21 (3.5)	52 (8.7)
Grade 3	0	8 (1.3)
Onset in days, median	50.0	14.0
Duration in days, median	26.0	15.0
<b>Leading to permanent stop</b>	<b>0</b>	<b>13 (2.2)</b>
<b>Vesicular Rash</b>	<b>1 (0.2)</b>	<b>0</b>
N = number of subjects, n = number of subjects with observations		

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

Treatment-emergent adverse drug reactions in the DUET-1 and DUET-2 trials (n=599) occurring in less than 1% of patients receiving INTELENCE<sup>®</sup> (200 mg b.i.d.), and of at least moderate intensity (≥ Grade 2) are listed below by body system:

**Cardiac disorders:** angina pectoris, atrial fibrillation

**Ear and labyrinth disorders:** vertigo

**Eye disorders:** blurred vision

**Gastrointestinal disorders:** abdominal distension, constipation, dry mouth, hematemesis, pancreatitis, retching, stomatitis

**General disorders and administration site conditions:** sluggishness

**Hepatobiliary disorders:** cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly

**Immune system disorders:** drug hypersensitivity, immune reconstitution syndrome

**Metabolism and nutrition disorders:** anorexia, dyslipidemia

**Nervous system disorders:** convulsion, disturbance in attention, hypoesthesia, syncope, amnesia, hypersomnia, paraesthesia, somnolence, tremor

**Psychiatric disorders:** abnormal dreams, confusional state, disorientation, nervousness, nightmares, sleep disorders

**Reproductive system and breast disorders:** gynecomastia

**Respiratory, thoracic and mediastinal disorders:** bronchospasm, exertional dyspnea

**Skin and subcutaneous tissue disorders:** dry skin, hyperhidrosis, prurigo, swelling face

Additional ADRs observed in other trials occurring in less than 1% of patients receiving INTELENCE<sup>®</sup> (200 mg b.i.d.), and of at least moderate intensity ( $\geq$  Grade 2) are listed below by body system:

**Metabolism and nutrition disorders:** acquired lipodystrophy

**Nervous system disorders:** haemorrhagic stroke

**Skin and subcutaneous tissue disorders:** angioneurotic edema, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis

Additional ADRs of at least moderate intensity observed in other trials were acquired lipodystrophy, angioneurotic edema, erythema multiforme and haemorrhagic stroke, each reported in no more than 0.5% of subjects. Stevens-Johnson syndrome has been reported rarely (<0.1%) during clinical development with INTELENCE<sup>®</sup>.

### **Abnormal Hematologic and Clinical Chemistry Findings**

#### **Laboratory Abnormalities**

Treatment-emergent clinical laboratory abnormalities (Grade 3 or 4) observed in patients and reported in greater than or equal to 2% of INTELENCE<sup>®</sup>-treated subjects are presented in the table below. All other grade 3 or 4 abnormal laboratory parameters were observed in less than 2% of the INTELENCE<sup>®</sup>-treated subjects.

<b>Table 3: Treatment Emergent Grade 3 to 4 Laboratory Abnormalities Reported in <math>\geq</math>2% of Subjects</b>		
<b>Pooled DUET-1 and DUET-2 Trials</b>		
<b>Laboratory Parameter Preferred Term, n (%)</b>	<b>INTELENCE<sup>®</sup> + BR N=599</b>	<b>Placebo + BR N=604</b>
<b>GENERAL BIOCHEMISTRY</b>		
<b>Pancreatic amylase</b>	<b>53 (8.9)</b>	<b>57 (9.4)</b>
Grade 3	44 (7.4)	51 (8.4)
Grade 4	9 (1.5)	6 (1.0)
<b>Creatinine</b>	<b>12 (2.0)</b>	<b>10 (1.7)</b>
Grade 3	12 (2.0)	9 (1.5)
Grade 4	0 (0)	1 (0.2)
<b>Lipase</b>	<b>20 (3.4)</b>	<b>16 (2.6)</b>
Grade 3	12 (2.0)	13 (2.2)
Grade 4	8 (1.3)	3 (0.5)
<b>GENERAL HEMATOLOGY</b>		
<b>White blood cell count</b>	<b>12 (2.0)</b>	<b>26 (4.3)</b>
Grade 3	6 (1.0)	22 (3.6)
Grade 4	6 (1.0)	4 (0.7)
<b>HEMATOLOGY DIFFERENTIAL COUNTS</b>		
<b>Neutrophils</b>	<b>30 (5.1)</b>	<b>45 (7.5)</b>
Grade 3	21 (3.5)	26 (4.3)
Grade 4	9 (1.5)	19 (3.1)
<b>LIPIDS AND GLUCOSE</b>		
<b>Total cholesterol</b>	<b>48 (8.1)</b>	<b>32 (5.3)</b>

<b>Table 3: Treatment Emergent Grade 3 to 4 Laboratory Abnormalities Reported in ≥2% of Subjects</b>		
<b>Pooled DUET-1 and DUET-2 Trials</b>		
<b>Laboratory Parameter Preferred Term, n (%)</b>	<b>INTELENCE<sup>®</sup> + BR N=599</b>	<b>Placebo + BR N=604</b>
Grade 3	48 (8.1)	32 (5.3)
<b>Low density lipoprotein</b>	<b>42 (7.2)</b>	<b>39 (6.6)</b>
Grade 3	42 (7.2)	39 (6.6)
<b>Elevated glucose levels</b>	<b>21 (3.5)</b>	<b>14 (2.3)</b>
Grade 3	21 (3.5)	13 (2.2)
Grade 4	0 (0)	1 (0.2)
<b>Triglycerides</b>	<b>55 (9.2)</b>	<b>35 (5.8)</b>
Grade 3	34 (5.7)	24 (4.0)
Grade 4	21 (3.5)	11 (1.8)
<b>HEPATIC PARAMETERS</b>		
<b>Alanine amino transferase</b>	<b>22 (3.7)</b>	<b>12 (2.0)</b>
Grade 3	16 (2.7)	10 (1.7)
Grade 4	6 (1.0)	2 (0.3)
<b>Aspartate amino transferase</b>	<b>19 (3.2)</b>	<b>12 (2.0)</b>
Grade 3	16 (2.7)	10 (1.7)
Grade 4	3 (0.5)	2 (0.3)

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

In the pooled analysis for DUET-1 and DUET-2, the safety profile in co-infected subjects (139) was generally comparable between subjects receiving INTELENCE<sup>®</sup> and subjects receiving placebo. There was a higher incidence of hepatic and biliary system disorders in co-infected subjects treated with INTELENCE<sup>®</sup> (12.5% of 72 subjects) compared to co-infected subjects in the placebo group (9.0% of 67 subjects). No specific pattern or type of event was observed.

Among co-infected subjects:

- Grade 3 or 4 elevations in AST developed in 9.7% of subjects in the INTELENCE<sup>®</sup> arm compared to 6.0% of subjects in the placebo arm;
- Grade 3 or 4 elevations in ALT developed in 11.1% of subjects in the INTELENCE<sup>®</sup> arm compared to 7.5% of subjects in the placebo arm;
- Grade 3 or 4 elevations in bilirubin developed in 5.7% of subjects in the INTELENCE<sup>®</sup> arm compared to 1.5% of subjects in the placebo arm.

#### Post-Marketing Adverse Drug Reactions

##### **Immune system disorders:**

Fatal cases of toxic epidermal necrolysis have been reported. Severe hypersensitivity including cases of hepatic failure have been reported (see **WARNINGS AND PRECAUTIONS**).

##### **Musculoskeletal and connective tissue disorders:**

myopathy, rhabdomyolysis

## DRUG INTERACTIONS

### Overview

Etravirine is metabolized by cytochrome CYP3A4, CYP2C9 and CYP2C19 followed by glucuronidation of the metabolites by uridine diphosphate glucuronosyltransferase (UDPGT). Therefore, co-administration of INTELENCE<sup>®</sup> with drugs that induce or inhibit CYP3A, CYP2C9, or CYP2C19 may result in altered plasma concentrations of etravirine and alter the therapeutic effect or adverse reaction profile of INTELENCE<sup>®</sup>.

Etravirine is an inducer of CYP3A4, and an inhibitor of CYP2C9, CYP2C19 and P-glycoprotein. Therefore, co-administration of drugs that are substrates of CYP3A4, CYP2C9, CYP2C19 or that are transported by the P-glycoprotein with INTELENCE<sup>®</sup> may result in altered plasma concentrations and alter the therapeutic effect or adverse reaction profile of the co-administered drug(s).

### Drug-Drug Interactions

Drugs that are not recommended for co-administration with INTELENCE<sup>®</sup> are included in Table 4. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

<b>Table 4: Drugs That Should Not Be Co-administered With INTELENCE<sup>®</sup></b>	
<b>Concomitant Drug Class: Drug Name</b>	<b>Clinical Comment</b>
<b>HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>	
efavirenz nevirapine delavirdine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE <sup>®</sup> with efavirenz or nevirapine may cause a decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE <sup>®</sup> . INTELENCE <sup>®</sup> and other NNRTIs should not be co-administered.  Combining two NNRTIs has not been shown to be beneficial. INTELENCE <sup>®</sup> and delavirdine should not be co-administered.
<b>HIV-Antiviral Agents: Protease Inhibitors (PIs)—Unboosted (i.e., without co-administration of low-dose ritonavir)</b>	
ritonavir	Concomitant use of INTELENCE <sup>®</sup> with full-dose ritonavir (600 mg b.i.d.) may cause a significant decrease in the plasma concentration of etravirine. This may result in loss of therapeutic effect of INTELENCE <sup>®</sup> . It is not recommended to co-administer full-dose ritonavir (600 mg b.i.d.) with INTELENCE <sup>®</sup> .
atazanavir nelfinavir indinavir	Concomitant use of INTELENCE <sup>®</sup> without co-administration of low-dose ritonavir may cause a significant alteration in the plasma concentrations of the PI. INTELENCE <sup>®</sup> should not be co-administered with PIs without low-dose ritonavir.

<b>Table 4: Drugs That Should Not Be Co-administered With INTELENCE<sup>®</sup></b>	
<b>Concomitant Drug Class: Drug Name</b>	<b>Clinical Comment</b>
<b>HIV-Antiviral Agents: Protease Inhibitors (PIs)—Boosted (with co-administration of low-dose ritonavir)</b>	
atazanavir/ritonavir	Concomitant use of INTELENCE <sup>®</sup> with atazanavir/ritonavir may cause a significant decrease in atazanavir C <sub>min</sub> by about 38%. INTELENCE <sup>®</sup> and atazanavir/ritonavir should not be co-administered.
fosamprenavir/ritonavir	An increase of 69% for amprenavir exposure was observed when fosamprenavir/ritonavir was co-administered in the presence of etravirine. Appropriate doses of the combination of INTELENCE <sup>®</sup> and fosamprenavir/ritonavir have not been established. INTELENCE <sup>®</sup> and fosamprenavir/ritonavir should not be co-administered.
tipranavir/ritonavir	Concomitant use of INTELENCE <sup>®</sup> with tipranavir/low-dose ritonavir may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of INTELENCE <sup>®</sup> . Tipranavir/low-dose ritonavir and INTELENCE <sup>®</sup> should not be co-administered.
<b>Anticonvulsants:</b> carbamazepine phenobarbital phenytoin	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE <sup>®</sup> should not be used in combination with carbamazepine, phenobarbital, or phenytoin as co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE <sup>®</sup> .
<b>Antimycobacterials:</b> rifampin	Rifampin is a potent inducer of CYP450 enzymes. INTELENCE <sup>®</sup> should not be used in combination with rifampin as co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE <sup>®</sup> .
<b>Herbal Products:</b> St. John's Wort ( <i>Hypericum perforatum</i> )	INTELENCE <sup>®</sup> should not be used concomitantly with products containing St. John's Wort because co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE <sup>®</sup> .

Established and other potentially significant drug interactions with INTELENCE<sup>®</sup> are included in Table 5. These recommendations are based on either drug interaction studies or predicated interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

<b>Table 5: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction</b>		
<b>Concomitant Drug Class: Drug Name</b>	<b>Effect on Concentration of Etravirine or Concomitant Drug</b>	<b>Clinical Comment</b>
<b>HIV-Antiviral Agents: Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)</b>		
didanosine*	↔ etravirine ↔ didanosine	The combination of INTELENCE <sup>®</sup> and didanosine can be used without dose adjustments. As didanosine is administered on an empty stomach, didanosine should be administered one hour before or two hours after INTELENCE <sup>®</sup> (which should be administered following a meal).
tenofovir disoproxil fumarate*	↓ etravirine ↔ tenofovir	The combination of INTELENCE <sup>®</sup> and tenofovir disoproxil fumarate can be used without dose adjustments.
Other NRTIs: Based on the primarily renal elimination route for other NRTIs (e.g., abacavir, emtricitabine, lamivudine, stavudine, and zidovudine), no drug interactions are expected between these drugs and INTELENCE <sup>®</sup> .		
<b>HIV-Antiviral Agents: Protease Inhibitors (PIs)—Boosted (with co-administration of low-dose ritonavir)</b>		
darunavir/ritonavir*	↓ etravirine ↔ darunavir	The mean systemic exposure (AUC) of etravirine was reduced by 37% when INTELENCE <sup>®</sup> was co-administered with darunavir/ritonavir. However, the combination of darunavir/ritonavir and etravirine was used safely and effectively in the Phase 3 trials, therefore, INTELENCE <sup>®</sup> and darunavir/ritonavir can be co-administered without any dose adjustments.
lopinavir/ritonavir (soft gel capsule)*	↑ etravirine ↓ lopinavir	The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE <sup>®</sup> with lopinavir/ritonavir is anticipated to be about 85% higher than the mean AUC of etravirine observed in the Phase 3 trials**. The amount of safety data at these increased etravirine exposures is limited, therefore, INTELENCE <sup>®</sup> and lopinavir/ritonavir should be co-administered with caution.
lopinavir/ritonavir (tablet)*	↔ lopinavir ↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced by approximately 35% after co-administration with lopinavir/ritonavir. This reduction is similar to the reduction in the mean systemic exposure of etravirine in the presence of darunavir/ritonavir observed in Phase 3 trials, therefore INTELENCE <sup>®</sup> can be co-administered with the tablet formulation of lopinavir/ritonavir without dose adjustments.
saquinavir/ritonavir*	↓ etravirine ↔ saquinavir	The mean systemic exposure (AUC) of etravirine was reduced by about 33% after co-administration of INTELENCE <sup>®</sup> and saquinavir/ritonavir. The reduction in the mean systemic exposures of etravirine in the presence of saquinavir/ritonavir is similar to the reduction in mean systemic exposures of etravirine in the presence of darunavir/ritonavir, therefore, INTELENCE <sup>®</sup> and saquinavir/ritonavir can be co-administered without any dose adjustments.

<b>Table 5: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction</b>		
<b>Concomitant Drug Class: Drug Name</b>	<b>Effect on Concentration of Etravirine or Concomitant Drug</b>	<b>Clinical Comment</b>
<b>HIV-Antiviral Agents: Dual Boosted Protease Inhibitors</b>		
lopinavir/saquinavir/ritonavir*	↔ etravirine ↓ lopinavir ↓ saquinavir	The combination of INTELENCE <sup>®</sup> and lopinavir/saquinavir/ritonavir can be used without dose adjustments.
<b>CCR5 Antagonists</b>		
maraviroc	↔ etravirine ↓ maraviroc	Concomitant use of INTELENCE <sup>®</sup> with maraviroc may cause a significant decrease (53%) in the plasma concentration of maraviroc. When INTELENCE <sup>®</sup> is co-administered with maraviroc in the absence of a potent CYP3A4 inhibitor (e.g., a boosted PI), the recommended dose of maraviroc is 600 mg b.i.d. No dose adjustment for INTELENCE <sup>®</sup> is needed.
maraviroc/darunavir/ritonavir	↔ etravirine ↑ maraviroc	When INTELENCE <sup>®</sup> is co-administered with maraviroc in the presence of a potent CYP3A inhibitor (e.g., a boosted PI), the recommended dose of maraviroc is 150 mg b.i.d. No dose adjustment of INTELENCE <sup>®</sup> is needed.
<b>HIV-Antiviral Agents: Fusion Inhibitors</b>		
enfuvirtide	↔ etravirine ↔ enfuvirtide	No interaction is expected for either INTELENCE <sup>®</sup> or enfuvirtide when co-administered.
<b>HIV-Antiviral Agents: Integrase Strand Transfer Inhibitors</b>		
raltegravir*	↔ etravirine ↓ raltegravir	The combination of INTELENCE <sup>®</sup> and raltegravir can be used without dose adjustments.
<b>Other Agents</b>		
<b>Antiarrhythmics:</b> amiodarone bepidil disopyramide flecainide lidocaine (systemic) mexiletine propafenone quinidine	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE <sup>®</sup> . Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with INTELENCE <sup>®</sup> .
digoxin	↑ digoxin ↔ etravirine	The combination of INTELENCE <sup>®</sup> and digoxin can be used without dose adjustments. It is recommended that digoxin levels be monitored when digoxin is combined with INTELENCE <sup>®</sup> .

**Table 5: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction**

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
<b>Anticoagulants:</b> warfarin	↑ warfarin	Warfarin concentrations may be affected when co-administered with INTELENCE®. Co-administration of INTELENCE® and warfarin is anticipated to cause an increase in warfarin exposures, while etravirine exposures are not expected to change. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with INTELENCE®.
<b>Anti-infectives:</b> azithromycin  clarithromycin*	↔ etravirine ↔ azithromycin  ↑ etravirine ↓ clarithromycin ↑ 14-OH-clarithromycin	Based on the renal elimination pathway of azithromycin, no drug interactions are expected between azithromycin and INTELENCE®.  Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against <i>Mycobacterium avium</i> complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.
<b>Antifungals:</b> fluconazole	↔ fluconazole ↑ etravirine ↑ voriconazole	The plasma concentrations of INTELENCE® are increased when co-administered with fluconazole (a potent inhibitor of CYP2C9) or with voriconazole, (a substrate and inhibitor of CYP3A, CYP2C9 and CYP2C19). The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE® with fluconazole or voriconazole in the absence of a boosted HIV protease inhibitor is anticipated to be about 194% and 114% higher, respectively, as compared to the mean AUC of etravirine observed in Phase III trials**. There is limited safety data on these increased etravirine exposures. Therefore INTELENCE® and either fluconazole or voriconazole should be co-administered with caution. Dose adjustments for voriconazole may be necessary depending on other co-administered drugs.
Itraconazole posaconazole ketoconazole	↑ etravirine ↓ itraconazole ↔ posaconazole ↓ ketoconazole	Posaconazole is a potent inhibitor of CYP3A and may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE® may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE®. Dose adjustments for itraconazole or ketoconazole may be necessary depending on other co-administered drugs.

<b>Table 5: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction</b>		
<b>Concomitant Drug Class: Drug Name</b>	<b>Effect on Concentration of Etravirine or Concomitant Drug</b>	<b>Clinical Comment</b>
<b>Antimycobacterials:</b> rifabutin*	↓ etravirine ↓ rifabutin ↓ 25-O-desacetyl-rifabutin	The combination of INTELENCE <sup>®</sup> and rifabutin should be used with caution due to the risk of decrease in etravirine and rifabutin exposures.  If INTELENCE <sup>®</sup> is co-administered with darunavir/ritonavir, saquinavir/ritonavir or the tablet formulation of lopinavir/ritonavir, then rifabutin should not be co-administered due to the potential for significant reductions in etravirine exposure.
<b>Antivirals:</b> ribavirin	↔ etravirine ↔ ribavirin	Based on the renal elimination pathway of ribavirin, no drug interactions are expected between ribavirin and INTELENCE <sup>®</sup> .
<b>Benzodiazepines:</b> diazepam	↑ diazepam	Concomitant use of INTELENCE <sup>®</sup> with diazepam may increase plasma concentrations of diazepam. A decrease in diazepam dose may be needed.
<b>Corticosteroids:</b> dexamethasone (systemic)	↓ etravirine	Systemic dexamethasone induces CYP3A and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE <sup>®</sup> . Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use.
<b>Estrogen-based Contraceptives:</b> ethinylestradiol* norethindrone*	↔ etravirine ↑ ethinylestradiol ↔ norethindrone	The combination of estrogen-and/or progesterone-based contraceptives and INTELENCE <sup>®</sup> can be used without dose adjustment.
<b>HMG-CoA Reductase Inhibitors:</b> atorvastatin*	↔ etravirine ↓ atorvastatin ↑ 2-OH-atorvastatin	Atorvastatin plasma concentrations are decreased 37% and plasma concentrations of the active metabolite, 2-hydroxy-atorvastatin, are increased by 27% when combined with INTELENCE <sup>®</sup> . Dose adjustment of atorvastatin may be necessary to tailor the clinical response when combined with INTELENCE <sup>®</sup> .
fluvastatin lovastatin pravastatin rosuvastatin simvastatin	↔ etravirine ↑ fluvastatin ↓ lovastatin ↔ pravastatin ↔ rosuvastatin ↓ simvastatin	No interaction between pravastatin and INTELENCE <sup>®</sup> is expected.  Lovastatin, rosuvastatin, and simvastatin are CYP3A substrates and co-administration with INTELENCE <sup>®</sup> may result in lower plasma concentrations of the HMG-CoA reductase inhibitor.

<b>Table 5: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interaction</b>		
<b>Concomitant Drug Class: Drug Name</b>	<b>Effect on Concentration of Etravirine or Concomitant Drug</b>	<b>Clinical Comment</b>
		Fluvastatin and rosuvastatin are metabolized by CYP2C9. Co-administration of fluvastatin with INTELENCE® may result in higher plasma concentrations of the HMG-CoA reductase inhibitor. Dose adjustments for fluvastatin may be necessary. No interaction between rosuvastatin and INTELENCE® is expected.
<b>H<sub>2</sub>-Receptor Antagonists:</b> ranitidine*	↓ etravirine	INTELENCE® can be co-administered with H <sub>2</sub> -receptor antagonists without dose adjustments.
<b>Immunosuppressants:</b> cyclosporine sirolimus tacrolimus	↓ cyclosporine ↓ sirolimus ↓ tacrolimus	Co-administration with systemic immunosuppressants should be done with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected when co-administered with INTELENCE®.
<b>Narcotic Analgesics:</b> methadone*	↔ etravirine ↔ R(-) methadone ↔ S(+) methadone	INTELENCE® and methadone may be co-administered without dose adjustments, however, clinical monitoring for withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.
<b>Phosphodiesterase Type 5 (PDE-5) Inhibitors:</b> sildenafil* vardenafil tadalafil	↓ sildenafil ↓ N-desmethyl-sildenafil	Sildenafil plasma concentrations are decreased by 57% and plasma concentrations of the active metabolite, N-desmethyl-sildenafil, are decreased by 41% when combined with INTELENCE®. Concomitant use of PDE-5 inhibitors with INTELENCE® may require dose adjustment of the PDE-5 inhibitor to attain the desired clinical effect.
<b>Platelet Aggregation Inhibitors:</b> clopidogrel		Activation of clopidogrel to its active metabolite may be decreased when clopidogrel is co-administered with INTELENCE®. Alternatives to clopidogrel should be considered.
<b>Proton Pump Inhibitors:</b> omeprazole*	↑ etravirine	INTELENCE® can be co-administered with proton pump inhibitors without dose adjustments.
<b>Selective Serotonin Reuptake Inhibitors (SSRIs):</b> paroxetine*	↔ etravirine ↔ paroxetine	INTELENCE® can be co-administered with paroxetine without dose adjustments.
↑ = increases, ↓ = decreases, ↔ = no change		
* The interaction between INTELENCE® and the drug was evaluated in a clinical trial. All other drug interactions shown are predicted.		
**The expected increase in systemic exposure of etravirine when co-administered with either lopinavir/ritonavir tablet (~85%), fluconazole (~194%) or voriconazole (~114%) is theoretical and is based on comparisons of etravirine exposures from drug-drug interaction studies to those in the pivotal Phase III trials (in which darunavir/ritonavir was co-administered as part of the background regimen).		

Drug interaction studies were performed with etravirine and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of etravirine on the AUC, C<sub>max</sub>, and C<sub>min</sub> values are summarized

in Table 6 and Table 7. Different formulations and/or doses were used which led to similar exposures and, therefore, interactions relevant for one formulation are relevant for the other.

<b>Table 6: Drug Interactions: Pharmacokinetic Parameters for Etravirine in the Presence of Co-administered Drugs<sup>a</sup></b>						
Co-administered Drug	Dose/Schedule of Co-administered Drug	N	PK	Mean Ratio of Etravirine Pharmacokinetic Parameters 90% CI; No Effect = 1.00		
				C <sub>max</sub>	AUC	C <sub>min</sub>
<b>Co-Administration With Protease Inhibitors (PIs)</b>						
atazanavir	400 mg q.d.	14	↑	1.47 (1.36-1.59)	1.50 (1.41-1.59)	1.58 (1.46-1.70)
atazanavir/ ritonavir	300/100 mg q.d.	14	↑	1.30 (1.17-1.44)	1.30 (1.18-1.44)	1.26 (1.12-1.42)
darunavir/ ritonavir	600/100 mg b.i.d.	14	↓	0.68 (0.57-0.82)	0.63 (0.54-0.73)	0.51 (0.44-0.61)
fosamprenavir/ ritonavir	700/100 mg b.i.d.	8	↔	N.A.	N.A.	N.A.
lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	13	↑	1.15 (0.94-1.41)	1.17 (0.96-1.43)	1.23 (0.98-1.53)
lopinavir/ritonavir (tablet)	400/100 mg b.i.d.	16	↓	0.70 (0.64-0.78)	0.65 (0.59-0.71)	0.55 (0.49-0.62)
ritonavir	100 mg single dose	18	↔	1.00 (0.89-1.12)	1.03 (0.91-1.17)	N.A.
ritonavir	600 mg b.i.d.	11	↓	0.68 (0.55-0.85)	0.54 (0.41-0.73)	N.A.
saquinavir/ ritonavir	1000/100 mg b.i.d.	14	↓	0.63 (0.53-0.75)	0.67 (0.56-0.80)	0.71 (0.58-0.87)
tipranavir/ ritonavir	500/200 mg b.i.d.	19	↓	0.29 (0.22-0.40)	0.24 (0.18-0.33)	0.18 (0.13-0.25)
<b>Co-Administration with Dual Boosted Protease Inhibitors (PIs)</b>						
lopinavir/ saquinavir/ ritonavir	400 mg/800- 1000 mg/100 mg b.i.d.	11	↔	N.A.	N.A.	N.A.
<b>Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</b>						
didanosine	400 mg q.d.	15	↔	1.16 (1.02-1.32)	1.11 (0.99-1.25)	1.05 (0.93-1.18)
tenofovir disoproxil fumarate	300 mg q.d.	23	↓	0.81 (0.75-0.88)	0.81 (0.75-0.88)	0.82 (0.73-0.91)
<b>Co-Administration With CCR5 Antagonists</b>						
maraviroc	300 mg b.i.d.	14	↔	1.05 (0.97-1.17)	1.06 (0.99-1.14)	1.08 (0.98-1.19)
<b>Co-Administration With Fusion Inhibitors</b>						
enfuvirtide	90 mg b.i.d.	261	↔ <sup>b</sup>	N.A.	N.A.	N.A.
<b>Co-Administration With Integrase Strand Transfer Inhibitors</b>						
raltegravir	400 mg b.i.d.	19	↔	1.04 (0.97-1.12)	1.10 (1.03-1.16)	1.17 (1.10-1.26)
<b>Co-Administration With Other Drugs</b>						
atorvastatin	40 mg q.d.	16	↔	0.97 (0.93-1.02)	1.02 (0.97-1.07)	1.10 (1.02-1.19)
clarithromycin	500 mg b.i.d.	15	↑	1.46 (1.38-1.56)	1.42 (1.34-1.50)	1.46 (1.36-1.58)

<b>Table 6: Drug Interactions: Pharmacokinetic Parameters for <u>Etravirine</u> in the Presence of Co-administered Drugs<sup>a</sup></b>						
<b>Co-administered Drug</b>	<b>Dose/Schedule of Co-administered Drug</b>	<b>N</b>	<b>PK</b>	<b>Mean Ratio of <u>Etravirine</u> Pharmacokinetic Parameters 90% CI; No Effect = 1.00</b>		
				<b>C<sub>max</sub></b>	<b>AUC</b>	<b>C<sub>min</sub></b>
ethinylestradiol/ norethindrone	0.035 mg q.d./ 1 mg q.d.	16	↔	N.A.	N.A.	N.A.
fluconazole	200 mg q.a.m.	16	↑	1.75 (1.60-1.91)	1.86 (1.73-2.00)	2.09 (1.90-2.31)
methadone	Individual dose regimen ranging from 60 to 130 mg/day	16	↔	N.A.	N.A.	N.A.
omeprazole	40 mg q.d.	18	↑	1.17 (0.96-1.43)	1.41 (1.22-1.62)	N.A.
paroxetine	20 mg q.d.	16	↔	1.05 (0.96-1.15)	1.01 (0.93-1.10)	1.07 (0.98-1.17)
Ranitidine	150 mg b.i.d.	18	↓	0.94 (0.75-1.17)	0.86 (0.76-0.97)	N.A.
Rifabutin	300 mg q.d.	12	↓	0.63 (0.53-0.74)	0.63 (0.54-0.74)	0.65 (0.56-0.74)
voriconazole	200 mg b.i.d.	16	↑	1.26 (1.16-1.38)	1.36 (1.25-1.47)	1.52 (1.41-1.64)

CI = Confidence Interval; N = maximum number of subjects with data; N.A. = not available; ↑ = increases; ↓ = decreases; ↔ = no change; q.d. = once daily; b.i.d. = twice daily; q.a.m. = once daily in the morning

<sup>a</sup>In drug-drug interaction studies, different formulations and/or doses of INTELENCE<sup>®</sup> were used which led to similar exposures, and, therefore, interactions relevant for one formulation are relevant for the other.

<sup>b</sup>Based on population pharmacokinetic analysis

<b>Table 7: Drug Interactions: Pharmacokinetic Parameters for <u>Co-administered Drugs</u> in the Presence of <u>Etravirine</u><sup>a</sup></b>						
<b>Co-administered Drug</b>	<b>Dose/Schedule of Co-administered Drug</b>	<b>N</b>	<b>PK</b>	<b>Mean Ratio of <u>Co-administered Drug</u> Pharmacokinetic Parameters 90% CI; No effect = 1.00</b>		
				<b>C<sub>max</sub></b>	<b>AUC</b>	<b>C<sub>min</sub></b>
<b>Co-Administration With Protease Inhibitors (PIs)</b>						
atazanavir	400 mg q.d.	14	↓	0.97 (0.73-1.29)	0.83 (0.63-1.09)	0.53 (0.38-0.73)
atazanavir/ ritonavir	300/100 mg q.d.	13	↓	0.97 (0.89-1.05)	0.86 (0.79-0.93)	0.62 (0.55-0.71)
darunavir/ ritonavir	600/100 mg b.i.d.	15	↔	1.11 (1.01-1.22)	1.15 (1.05-1.26)	1.02 (0.90-1.17)
fosamprenavir/ ritonavir	700/100 mg b.i.d.	8	↑	1.62 (1.47-1.79)	1.69 (1.53-1.86)	1.77 (1.39-2.25)
lopinavir/ ritonavir (soft gel capsule)	400/100 mg b.i.d.	14	↓	0.85 (0.62-1.05)	0.80 (0.49-1.07)	0.92 (0.15-1.68)
lopinavir/ritonavir (tablet)	400/100 mg b.i.d.	16	↔	0.89 (0.82-0.96)	0.87 (0.83-0.92)	0.80 (0.73-0.88)

<b>Table 7: Drug Interactions: Pharmacokinetic Parameters for <u>Co-administered Drugs</u> in the Presence of Etravirine<sup>a</sup></b>						
<b>Co-administered Drug</b>	<b>Dose/Schedule of Co-administered Drug</b>	<b>N</b>	<b>PK</b>	<b>Mean Ratio of Co-administered Drug Pharmacokinetic Parameters 90% CI; No effect = 1.00</b>		
				<b>C<sub>max</sub></b>	<b>AUC</b>	<b>C<sub>min</sub></b>
lopinavir/ saquinavir/ ritonavir	400 mg b.i.d./ 800-1000 mg b.i.d./ 100 mg b.i.d.	11	↓ LPV	0.84 (0.74-0.95)	0.82 (0.70-0.96)	0.76 (0.54-1.08)
		11	↓ SQV	0.85 (0.61-1.19)	0.87 (0.62-1.21)	0.87 (0.60-1.28)
saquinavir/ ritonavir	1000/100 mg b.i.d.	15	↔	1.00 (0.70-1.42)	0.95 (0.64-1.42)	0.80 (0.46-1.38)
tipranavir/ ritonavir	500/200 mg b.i.d.	19	↑	1.14 (1.02-1.27)	1.18 (1.03-1.36)	1.24 (0.96-1.59)
<b>Co-Administration With CCR5 Antagonists</b>						
maraviroc	300 mg b.i.d.	10	↓	0.40 (0.28-0.57)	0.47 (0.38-0.58)	0.61 (0.53-0.71)
maraviroc/darunavir/ ritonavir	150 mg/600 mg/100 mg b.i.d.	10	↑	1.77 <sup>§</sup> (1.20-2.60)	3.10 <sup>§</sup> (2.57-3.74)	5.27 <sup>§</sup> (4.51-6.15)
§compared to maraviroc 150 mg b.i.d.						
<b>Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</b>						
didanosine	400 mg q.d.	14	↔	0.91 (0.58-1.42)	0.99 (0.79-1.25)	N.A.
tenofovir disoproxil fumarate	300 mg q.d.	19	↔	1.15 (1.04-1.27)	1.15 (1.09-1.21)	1.19 (1.13-1.26)
<b>Co-Administration With Integrase Strand Transfer Inhibitors</b>						
raltegravir	400 mg b.i.d.	19	↓	0.89 (0.68-1.15)	0.90 (0.68-1.18)	0.66 (0.34-1.26)
<b>Co-Administration With Other Drugs</b>						
atorvastatin	40 mg q.d.	16	↓	1.04 (0.84-1.30)	0.63 (0.58-0.68)	N.A.
2-hydroxy- atorvastatin		16	↑	1.76 (1.60-1.94)	1.27 (1.19-1.36)	N.A.
clarithromycin	500 mg b.i.d.	15	↓	0.66 (0.57-0.77)	0.61 (0.53-0.69)	0.47 (0.38-0.57)
14-hydroxy- clarithromycin		15	↑	1.33 (1.13-1.56)	1.21 (1.05-1.39)	1.05 (0.90-1.22)
digoxin	0.5 mg single dose	16	↑	1.19 (0.96-1.49)	1.18 (0.90-1.56)	N.A.
ethinyl estradiol	0.035 mg q.d.	16	↑	1.33 (1.21-1.46)	1.22 (1.13-1.31)	1.09 (1.01-1.18)
norethindrone	1 mg q.d.	16	↔	1.05 (0.98-1.12)	0.95 (0.90-0.99)	0.78 (0.68-0.90)

<b>Table 7: Drug Interactions: Pharmacokinetic Parameters for <u>Co-administered Drugs</u> in the Presence of Etravirine<sup>a</sup></b>						
<b>Co-administered Drug</b>	<b>Dose/Schedule of Co-administered Drug</b>	<b>N</b>	<b>PK</b>	<b>Mean Ratio of Co-administered Drug Pharmacokinetic Parameters 90% CI; No effect = 1.00</b>		
				<b>C<sub>max</sub></b>	<b>AUC</b>	<b>C<sub>min</sub></b>
fluconazole	200 mg q.a.m.	15	↔	0.92 (0.85-1.00)	0.94 (0.88-1.01)	0.91 (0.84-0.98)
R(-) methadone	Individual dose regimen ranging from 60 to 130 mg/day	16	↔	1.02 (0.96-1.09)	1.06 (0.99-1.13)	1.10 (1.02-1.19)
S(+) methadone		16	↔	0.89 (0.83-0.97)	0.89 (0.82-0.96)	0.89 (0.81-0.98)
paroxetine	20 mg q.d.	16	↔	1.06 (0.95-1.20)	1.03 (0.90-1.18)	0.87 (0.75-1.02)
rifabutin	300 mg q.d.	12	↓	0.90 (0.78-1.03)	0.83 (0.75-0.94)	0.76 (0.66-0.87)
25- <i>O</i> -desacetyl-rifabutin	300 mg q.d.	12	↓	0.85 (0.72-1.00)	0.83 (0.74-0.92)	0.78 (0.70-0.87)
sildenafil	50 mg single dose	15	↓	0.55 (0.40-0.75)	0.43 (0.36-0.51)	N.A.
N-desmethyl-sildenafil		15	↓	0.75 (0.59-0.96)	0.59 (0.52-0.68)	N.A.
voriconazole	200 mg b.i.d.	14	↑	0.95 (0.75-1.21)	1.14 (0.88-1.47)	1.23 (0.87-1.75)

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increases; ↓ = decreases; ↔ = no change; q.d. = once daily; b.i.d. = twice daily; q.a.m. = once daily in the morning

<sup>a</sup>In drug-drug interaction studies, different formulations and/or doses of INTELENCE<sup>®</sup> were used which led to similar exposures, and, therefore, interactions relevant for one formulation are relevant for the other.

### **Drug-Food Interactions**

The systemic exposure (AUC) to etravirine was decreased by about 50% when INTELENCE<sup>®</sup> was administered under fasting conditions, as compared to when INTELENCE<sup>®</sup> was administered following a meal. Therefore, INTELENCE<sup>®</sup> should always be taken following a meal. The caloric and fat content of the meal is irrelevant.

### **Drug-Herb Interactions**

Concomitant use of INTELENCE<sup>®</sup> and St. John's Wort (*Hypericum perforatum*), or products containing St. John's Wort, is not recommended. Co-administration of etravirine with St. John's Wort may cause significant decreases in etravirine plasma concentrations, which may result in loss of therapeutic effect of INTELENCE<sup>®</sup> (see **Drug-Drug Interactions**, Table 4).

Interactions with other herbal products have not been established.

## **Drug-Laboratory Test Interactions**

Interactions with laboratory tests have not been established.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

- INTELENCE<sup>®</sup> must always be given in combination with other antiretroviral medicinal products.
- It is recommended that the dosage of INTELENCE<sup>®</sup> be taken following a meal. The type of food does not affect the exposure to etravirine.
- Patients should be instructed to swallow the tablet(s) as a whole with a liquid such as water. Patients who are unable to swallow the INTELENCE<sup>®</sup> tablet(s) whole may disperse the tablets in a glass of water. Once the tablet(s) is (are) dispersed, patients should stir the dispersion well, and drink it immediately. The glass should be rinsed with water several times, and each rinse completely swallowed to ensure the entire dose is consumed.

### **Recommended Dose and Dosage Adjustment**

#### **Adults:**

The recommended oral dose of INTELENCE<sup>®</sup> tablets is 200 mg (one 200 mg tablet or two 100 mg tablets) taken twice daily (b.i.d.) following a meal (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

#### **Geriatric Patients:**

In general, caution should be exercised in the administration of INTELENCE<sup>®</sup> in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy (see **INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

#### **Pediatric Patients:**

The safety and efficacy of INTELENCE<sup>®</sup> in pediatric patients have not yet been established. Treatment with INTELENCE<sup>®</sup> is not recommended in children and adolescents (see **INDICATIONS AND CLINICAL USE, WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

#### **Hepatic Impairment:**

No dose adjustment is required in patients with mild or moderate hepatic impairment. The pharmacokinetics of INTELENCE<sup>®</sup> has not been studied in patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**, and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic insufficiency**).

**Renal Impairment:**

No dose adjustment is required in patients with renal impairment (see **WARNINGS AND PRECAUTIONS**, **Renal** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

**Missed Dose**

If the patient misses a dose of INTELENCE<sup>®</sup> within 6 hours of the time it is usually taken, the patient should be told to take INTELENCE<sup>®</sup> following a meal as soon as possible, and then take the next dose of INTELENCE<sup>®</sup> at the regularly scheduled time.

If a patient misses a dose of INTELENCE<sup>®</sup> by more than 6 hours of the time it is usually taken, the patient should be told not to take the missed dose and simply resume the usual dosing schedule.

**OVERDOSAGE**

There is no specific antidote for overdose with INTELENCE<sup>®</sup>. Human experience of overdose with INTELENCE<sup>®</sup> is limited. Treatment of overdose with INTELENCE<sup>®</sup> consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Administration of activated charcoal may be used to aid in removal of unabsorbed active substance. Since etravirine is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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**ACTION AND CLINICAL PHARMACOLOGY****Mechanism of Action**

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Etravirine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Etravirine can bind in at least 2 conformationally distinct modes. Within a given binding mode, torsional flexibility of etravirine permits access to numerous conformational variants, while the compact design of etravirine permits significant repositioning and reorientation (translation and rotation) within the pocket. Etravirine does not inhibit the human DNA polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ .

Decreases in plasma viral load were typically observed as early as 1-2 days after the start of INTELENCE<sup>®</sup> administration in monotherapy trials.

## **Resistance**

Development of resistance against etravirine *in vitro* typically required multiple NNRTI-resistance associated mutations (RAMs) of which the following were observed most frequently: L100I, E138K, E138G, V179I, Y181C and M230I.

In the Phase 3 trials, DUET-1 and DUET-2, mutations that developed most commonly in subjects with virologic failure to the INTELENCE<sup>®</sup>-containing regimen were V179F, V179I and Y181C, generally within a background of other NNRTI RAMs (see **MICROBIOLOGY**).

## **Cross-Resistance**

Limited cross-resistance between etravirine and efavirenz was observed *in vitro* in 3 of the 65 site-directed HIV-1 mutant strains containing an NNRTI resistance-associated mutation. Cross-resistance to delavirdine, efavirenz and/or nevirapine is expected after virologic failure with an etravirine-containing regimen for the virologic failure isolates. Therefore, the treatment of patients with delavirdine, efavirenz or nevirapine following virologic failure of an etravirine-containing regimen is not recommended (see **MICROBIOLOGY**).

## **Pharmacokinetics**

The pharmacokinetic properties of etravirine have been evaluated in adult healthy subjects and in adult treatment-experienced HIV-1-infected patients. Exposure to etravirine was slightly lower in HIV-1-infected patients than in healthy subjects.

<b>Parameter</b>	<b>Etravirine 200 mg b.i.d. N=575</b>
AUC <sub>12h</sub> (ng•h/mL)	
Geometric Mean ± Standard Deviation	4552 ± 4710
Median (Range)	4380 (458-59084)
C <sub>0h</sub> (ng/mL)	
Geometric Mean ± Standard Deviation	297±391
Median (Range)	298 (2-4852)

\*PK values are about 30% higher in healthy volunteers  
All HIV-infected subjects enrolled in Phase 3 clinical trials received darunavir/ritonavir 600/100 mg b.i.d. as part of their background regimen. Therefore, the pharmacokinetic parameter estimates in Table 8 account for reductions in the pharmacokinetic parameters of etravirine due to co-administration of INTELENCE<sup>®</sup> with darunavir/ritonavir.

When INTELENCE<sup>®</sup> was administered for 8 days to healthy volunteers, the increase in exposure to etravirine was generally dose proportional between total daily doses of 200 and 400 mg, and the total exposure to etravirine was similar irrespective of whether the total daily dose was administered in a once-daily or twice-daily regimen.

### **Absorption:**

An intravenous formulation of etravirine is unavailable: thus, the absolute bioavailability of INTELENCE<sup>®</sup> is unknown. After oral administration with food, the maximum plasma concentration of etravirine is generally achieved within 4 hours.

In healthy subjects, the absorption of etravirine is not affected by co-administration of oral ranitidine or omeprazole, drugs that are known to increase gastric pH.

#### Effect of food on absorption:

The exposure to etravirine is similar when taken after a standard normal caloric meal (561 kcal) or high-fat high caloric meal (1160 kcal). When compared to administration following a standard normal caloric meal, exposures decreased when etravirine was taken before a standard normal caloric meal (17%), following a croissant (20%), or fasted (51%). Therefore, to achieve optimal exposure, INTELENCE<sup>®</sup> should be taken following a meal.

#### **Distribution:**

Etravirine is about 99.9% bound to plasma proteins, primarily to albumin (99.6%) and  $\alpha_1$ -acid glycoprotein (94.48%-97.66%) *in vitro*.

In rats, the highest concentrations of radiolabelled etravirine and its metabolites were measured in the gastrointestinal tract, liver and adrenal gland and the lowest levels were associated with blood, plasma, brain, lung and bone. There was no evidence of undue retention or accumulation. The elimination of radioactivity was complete in rats within 96 hours of etravirine oral administration.

In pregnant rats, there was distribution of radiolabelled etravirine and its metabolites to the placenta, vagina, uterus, mammary glands and fetus. Total radioactivity levels in placenta and fetus were about twice the levels observed in maternal blood.

#### **Metabolism:**

*In vitro* experiments with human liver microsomes (HLMs) indicate that etravirine primarily undergoes oxidative metabolism by CYP3A, CYP2C9 and CYP2C19 enzymes. The major metabolites, formed by methyl hydroxylation of the dimethylbenzotrile moiety, were at least 90% less active than etravirine against wild-type HIV in cell culture.

Etravirine is not a substrate for P-glycoprotein in *in vitro* studies. Etravirine is an inhibitor of P-glycoprotein *in vitro* with a 50% inhibitory concentration (IC<sub>50</sub>) value of 10,500 ng/mL for the probe paclitaxel. This value is approximately 20-fold higher than the average maximum plasma concentration observed in HIV-1 infected patients and is unlikely to have a clinically relevant impact. The extent of first-pass metabolism of etravirine has not been evaluated due to the absence of a suitable intravenous formulation. Etravirine has no pharmacologically active metabolites in the presence of NNRTI-resistant strains of HIV. No dose-dependent changes in metabolism have been observed for etravirine over the daily dose range of 200-400 mg.

#### **Excretion:**

After administration of a radiolabelled <sup>14</sup>C-etravirine dose in human subjects, 93.7% and 1.2% of the administered dose of <sup>14</sup>C-etravirine could be retrieved in feces and urine, respectively. Unchanged etravirine accounted for 81.2% to 86.4% of the administered dose in feces. Unchanged etravirine was not detected in urine. The terminal elimination half-life of etravirine was approximately 30-40 hours.

**Effects on Electrocardiogram:**

In a randomized, double-blind, active- and placebo-controlled crossover study, 41 healthy male and female volunteers were administered INTELENCE<sup>®</sup> 200 mg b.i.d., INTELENCE<sup>®</sup> 400 mg q.d., placebo and moxifloxacin 400 mg. After 8 days of dosing, etravirine did not prolong the QT interval. The placebo-adjusted mean maximum increases in QTcF from baseline after 200 mg b.i.d. and 400 mg q.d. of etravirine were 0.1 msec and -0.2 msec, respectively, and 10.1 msec for moxifloxacin 400 mg q.d. No subject in any group had an increase in QTcF of  $\geq 60$  msec. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec.

**Special Populations and Conditions****Pediatrics:**

The pharmacokinetics of etravirine in paediatric patients are under investigation. There are insufficient data at this time to recommend a dose.

**Geriatrics:**

Population pharmacokinetic analysis in HIV-infected subjects showed that etravirine pharmacokinetics are not considerably different in the age range (18 to 77 years) evaluated (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

**Gender:**

A limited number of women were included in studies.

**Race:**

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

**Hepatic Insufficiency:****Hepatic Impairment:**

Etravirine is primarily metabolized and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment to 8 matched controls and 8 patients with moderate hepatic impairment to 8 matched controls, the multiple dose pharmacokinetic disposition of etravirine was not altered in patients with mild to moderate hepatic impairment. No dosing adjustment is required in patients with mild or moderate hepatic impairment. INTELENCE<sup>®</sup> has not been studied in patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

**Hepatitis B or Hepatitis C Virus Co-infection:**

Population pharmacokinetic analysis of the DUET-1 and DUET-2 trials showed reduced clearance for INTELENCE<sup>®</sup> in HIV-1-infected subjects with hepatitis B and/or C virus co-infection. Based upon the safety profile, no dose adjustment is necessary in patients co-infected with hepatitis B and/or C virus.

**Renal Insufficiency:**

The pharmacokinetics of etravirine have not been studied in patients with renal insufficiency. Results from a mass balance study with radioactive <sup>14</sup>C-etravirine showed that <1.2% of the

administered dose of etravirine is excreted in the urine. No unchanged drug was detected in urine so the impact of renal impairment on etravirine elimination is expected to be minimal. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis (see **WARNINGS AND PRECAUTIONS, Renal** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Renal Impairment**).

## **STORAGE AND STABILITY**

Store INTELENCE<sup>®</sup> tablets between 15–30°C. Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **INTELENCE<sup>®</sup> 100 mg tablets**

INTELENCE<sup>®</sup> tablets are supplied as white to off-white oval tablets containing 100 mg of etravirine. Each tablet contains the inactive ingredients hypromellose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and lactose monohydrate.

Each tablet is debossed with “T125” on one side and “100” on the other side. INTELENCE<sup>®</sup> 100 mg tablets are packaged in bottles in the following configuration: 100 mg tablets—bottles of 120. Each bottle contains 3 desiccant pouches.

### **INTELENCE<sup>®</sup> 200 mg tablets**

INTELENCE<sup>®</sup> 200 mg tablets are available as white to off-white, biconvex, oblong tablets containing 200 mg of etravirine. Each tablet contains the inactive ingredients hypromellose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, silicified microcrystalline cellulose and microcrystalline cellulose.

Each tablet is debossed with “T200” on one side. INTELENCE<sup>®</sup> 200 mg tablets are packaged in bottles in the following configuration: 200 mg tablets—bottles of 60. Each bottle contains 3 desiccant pouches.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name:

etravirine

Chemical name:

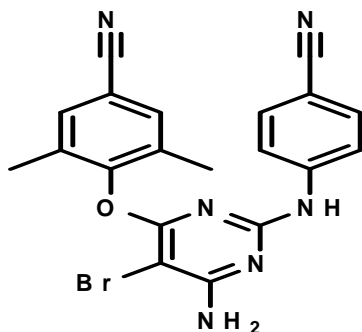
4-[[6-amino-5-bromo-2-[(4-cyanophenyl)-amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile

Molecular formula and molecular mass:

Molecular formula:  $C_{20}H_{15}BrN_6O$

Molecular mass: 435.28

Structural formula:



Physicochemical properties:

Etravirine is a white to slightly yellowish-brown powder with a solubility in water of <math><0.001\text{ g}/100\text{ mL}</math> at

## CLINICAL TRIALS

### Study demographics and trial design

#### **Treatment-Experienced Patients**

The evidence of efficacy of INTELENCE<sup>®</sup> is based on the analyses of 48-week data from 2 ongoing, randomized, double-blinded, placebo-controlled, Phase 3 trials DUET-1 and DUET-2. These trials were identical in design, and similar efficacy for INTELENCE<sup>®</sup> was seen in each trial. The results below are pooled data from the two trials.

Treatment-experienced HIV-1-infected subjects who had plasma HIV-1 RNA >5000 copies/mL and had 1 or more NNRTI resistance-associated mutations at screening or from prior genotypic analysis (i.e., archived resistance) were enrolled. These subjects also had 3 or more of the following primary PI mutations: D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, V82A/F/L/S/T, I84V, N88S, or L90M at screening, and were on a stable antiretroviral regimen for at least 8 weeks. Randomization was stratified by the intended use of enfuvirtide in the background regimen (BR), previous use of darunavir/ritonavir, and screening viral load. This analysis included 612 subjects in DUET-1 and 591 subjects in DUET-2 who had completed 48 weeks of treatment or discontinued earlier.

At 48 weeks, the virologic response rate was evaluated in subjects receiving INTELENCE<sup>®</sup> (200 mg b.i.d.) in addition to a BR versus subjects receiving placebo in addition to a BR. The BR consisted of darunavir/ritonavir 600/100 mg b.i.d. and at least 2 other investigator-selected antiretroviral drugs (N[t]RTIs with or without enfuvirtide).

45.6% of subjects in the INTELENCE<sup>®</sup> arm and 46.9% of subjects in the placebo arm used enfuvirtide in the underlying antiretroviral therapy. 25.5% of subjects in the INTELENCE<sup>®</sup> arm used enfuvirtide for the first time (*de novo*), compared with 26.5% of subjects in the placebo arm. 20.0% of subjects in the INTELENCE<sup>®</sup> arm re-used enfuvirtide, compared with 20.4% of subjects in the placebo arm. Virologic response was defined as achieving a confirmed undetectable viral load (<50 HIV-1 RNA copies/mL).

In the pooled analysis for DUET-1 and DUET-2, demographics and baseline characteristics were balanced between the INTELENCE<sup>®</sup> arm and the placebo arm. Table 9 describes the demographic and baseline disease characteristics of the subjects in the INTELENCE<sup>®</sup> arm and subjects in the placebo arm.

<b>Table 9: Demographic and Baseline Disease Characteristics of Subjects in the DUET-1 and DUET-2 Trials (Pooled Analysis)</b>						
	<b>Pooled DUET Trials</b>		<b>DUET-1</b>		<b>DUET-2</b>	
	<b>Placebo N = 604</b>	<b>INTELENCE® N = 599</b>	<b>Placebo N = 308</b>	<b>INTELENCE® N = 304</b>	<b>Placebo N = 296</b>	<b>INTELENCE® N = 295</b>
<b>Demographic Characteristics</b>						
Median Age, years (range)	45 (18-72)	46 (18-77)	45 (18-72)	45 (18-67)	45 (20-69)	46 (31-77)
<b>Sex</b>						
Male	89%	90%	86%	87%	92%	94%
Female	11%	10%	14%	13%	8%	6%
<b>Race</b>						
White	70%	70%	65%	65%	76%	77%
Black	13%	13%	12%	13%	14%	13%
Hispanic	12%	11%	14%	14%	10%	8%
Asian	1%	1%	1%	1%	0%	2%
Other	4%	4%	8%	7%	0%	1%
<b>Baseline Disease Characteristics</b>						
Median Baseline Plasma HIV-1 RNA (range), log <sub>10</sub> copies/mL	4.8 (2.2-6.5)	4.8 (2.7-6.8)	4.9 (2.4-6.5)	4.8 (2.7-6.2)	4.8 (2.2-6.3)	4.8 (3.0-6.8)
<b>Percentage of Subjects with Baseline Viral Load:</b>						
<30,000 copies/mL	28.8%	27.5%	27.3%	26.6%	30.4%	28.5%
≥30,000 and <100,000 copies/mL	35.3%	34.4%	31.8%	34.2%	38.9%	34.6%
≥100,000 copies/mL	35.9%	38.1%	40.9%	39.1%	30.7%	36.9%
Median Baseline CD4+ Cell Count (range), 10 <sup>6</sup> cells/L	109 (0-912)	99 (1-789)	109 (1-694)	99 (1-789)	108 (0-912)	100 (1-708)
<b>Percentage of Subjects with Baseline CD4+ Cell Count:</b>						
<50 cells/mm <sup>3</sup>	34.7%	35.6%	36.5%	34.7%	32.8%	36.6%
≥50 and <200 cells/mm <sup>3</sup>	34.5%	34.8%	33.9%	34.0%	35.1%	35.6%
≥200 cells/mm <sup>3</sup>	30.8%	29.6%	29.7%	31.4%	32.1%	27.8%
Median (range) Number of PI Mutations <sup>a</sup>	4 (8)	4 (0-7)	4 (8)	4 (0-7)	4 (0-8)	4 (0-7)
<b>Percentage of Subjects with Previous Use of NNRTIs:</b>						
0	7.9%	8.2%	6.5%	6.9%	9.5%	9.5%
1	46.7%	46.9%	48.4%	50.0%	44.9%	43.7%
>1	45.4%	44.9%	45.1%	43.1%	45.6%	46.8%

<b>Table 9: Demographic and Baseline Disease Characteristics of Subjects in the DUET-1 and DUET-2 Trials (Pooled Analysis)</b>						
	<b>Pooled DUET Trials</b>		<b>DUET-1</b>		<b>DUET-2</b>	
	<b>Placebo N = 604</b>	<b>INTELENCE® N = 599</b>	<b>Placebo N = 308</b>	<b>INTELENCE® N = 304</b>	<b>Placebo N = 296</b>	<b>INTELENCE® N = 295</b>
Percentage of Subjects with Previous Use of the Following NNRTIs:						
Efavirenz	72.5%	70.3%	73.7%	72.4%	71.3%	68.1%
Nevirapine	58.6%	57.1%	58.4%	56.9%	58.8%	57.3%
Delavirdine	12.6%	13.7%	13.0%	8.2%	12.5%	19.3%
Median (range) Number of NNRTI RAMs <sup>b</sup> :	2 (0-7)	2 (0-7)	2 (0-7)	2 (0-7)	2 (0-6)	2 (0-6)
Median Fold Change of the Virus for the Following NNRTIs:						
Delavirdine	26.1	27.3	32.3	27.1	23.0	27.5
Efavirenz	45.4	63.9	72.8	99.8	25.0	39.9
Etravirine	1.5	1.6	1.4	1.6	1.7	1.6
Nevirapine	74.0	74.3	73.7	74.3	74.3	77.3
Percentage of Subjects with Previous Use of Enfuvirtide	42.2%	39.6%	34.4%	30.6%	50.3%	48.8%
Percentage of Subjects with a Phenotypic Sensitivity Score (PSS) for the background therapy <sup>c</sup> of:						
0	16.2%	17.0%	16.4%	17.3%	16.1%	16.7%
1	38.7%	36.5%	35.1%	38.2%	42.5%	34.7%
2	27.8%	26.9%	31.8%	23.6%	23.6%	30.3%
≥3	17.3%	19.7%	16.8%	20.9%	17.7%	18.4%
RAMs = Resistance-Associated Mutations FC = fold change in EC <sub>50</sub> <sup>a</sup> IAS-USA primary PI mutations [August/September 2007], D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, L90M <sup>b</sup> Tibotec NNRTI RAMs [June 2008]: A98G, V90I, L100I, K101E/H/P/Q, K103H/N/S/T, V106A/M/I, V108I, E138A/G/K/Q, V179D/E/F/G/I/T, Y181C/I/V, Y188C/H/L, V189I, G190A/C/E/Q/S, H221Y, P255H, F227C/L, M230I/L, P236L, K238N/T, Y318F <sup>c</sup> The PSS was calculated for the background therapy (as determined on Day 7). Percentages are based on the number of subjects with available phenotype data. For fusion inhibitors (enfuvirtide), subjects were considered resistant if the drug was used in previous therapy up to baseline. INTELENCE® is not included in this calculation.						

## **Study results**

Table 10 below presents the efficacy results at 48 weeks for patients in the INTELENCE® arm and patients in the placebo arm from the pooled DUET-1 and DUET-2 trials.

At week 24 a statistically significant interaction (p=0.0064, Breslow-Day test) between treatment and enfuvirtide use was seen. The interaction effect was still significant at Week 48 (p=0.1279).

Therefore, the primary analysis at Week 48 was performed for each enfuvirtide stratum: “Re-Used/Not Used Enfuvirtide” [patients re-using or not using enfuvirtide] and “De novo Enfuvirtide use”.

Outcomes	De Novo Enfuvirtide use		Re-Used/Not Used Enfuvirtide	
	Placebo + BR N=159	INTELENCE <sup>®</sup> + BR N=153	Placebo + BR N=445	INTELENCE <sup>®</sup> + BR N=446
Virologic Responders				
Viral Load <50 HIV-1 RNA copies/mL <sup>1</sup>	93 (58.5%)	109 (71.2%) <sup>a</sup>	147 (33.0%)	254 (57.0%) <sup>a</sup>
Viral Load <400 HIV-1 RNA copies/mL <sup>1</sup>	110 (69.2%)	125 (81.7%)	176 (39.6%)	303 (67.9%)
Mean change from baseline in log <sub>10</sub> HIV-1 RNA	-2.22 (0.11)	-2.60 (0.10)	-1.23 (0.07)	-2.13 (0.07)*
Mean change from baseline in CD4 cell count	111.4 (9.3)	134.5 (10.0)	59.2 (5.0)	85.7 (5.0)
Virologic Failures	52 (32.7)	30 (19.6)	248 (55.7)	147 (33.0)
Viral Load ≥50 HIV-1 RNA copies/mL	17 (10.7%)	16 (10.5%)	30 (6.7%)	50 (11.2%)
Death	4 (2.5%)	4 (2.6%)	16 (3.6%)	7 (1.6%)
Discontinuation due to Adverse Event	3 (1.9%)	7 (4.6%)	11 (2.5%)	24 (5.4%)
Discontinuation due to Other Reasons	7 (4.4%)	3 (2.0%)	23 (5.2%)	14 (3.1%)

<sup>1</sup>Imputations according to the TLOVR algorithm  
NS: p>0.05, \*: p<0.0001; p-values INTELENCE<sup>®</sup> vs placebo  
BR – background regimen consisting of DRV/rtv + minimum of 2 commercially available ARVs consisting of NRTI(s) with or without ENFUVIRTIDE  
<sup>a</sup> p-value vs placebo from CMH test controlling for previous DRV use and baseline viral load  
<sup>b</sup>DUET 1 & 2 are ongoing 96-week clinical trials.

At week 48, AIDS-defining illness or death occurred in 5.8% of INTELENCE<sup>®</sup>-treated subjects and 9.8% of placebo-treated subjects.

The proportion of virologic responders (viral load <50 HIV-1 RNA copies/mL) by the Phenotypic Sensitivity Score (PSS) of the background therapy, including enfuvirtide, is shown in Table 11.

<b>Table 11: Virologic Response (Viral Load &lt;50 HIV-1 RNA copies/mL) at Week 48 by Phenotypic Sensitivity Score (PSS) in the Non-Viral Failure Excluded Population of TMC125-C206 and TMC125-C216 Trials (Pooled Analysis)</b>		
	<b>INTELENCE<sup>®</sup> + BR N=539</b>	<b>Placebo + BR N=536</b>
<b>PSS*</b>		
0	46% (40/87)	6% (5/83)
1	63% (125/200)	32% (64/201)
2	79% (114/145)	62% (97/156)
≥ 3	78% (83/107)	75% (72/96)
* In the calculation of the PSS, darunavir was counted as a sensitive antiretroviral if the FC ≤ 10; enfuvirtide was counted as a sensitive antiretroviral if it had not been used previously. INTELENCE <sup>®</sup> was not included in this calculation.		

### **Trial TMC125-C227**

Trial TMC125-C227 was a randomized, exploratory, active-controlled, open-label, Phase 2b trial. Eligible subjects were treatment-experienced, PI-naïve HIV-1-infected patients with genotypic evidence of NNRTI resistance at screening or from prior genotypic analysis. The virologic response was evaluated in 116 subjects who were randomized to INTELENCE<sup>®</sup> (n=59) or an investigator-selected PI (n=57), each given with 2 investigator-selected N(t)RTIs. Compared to the control PI-treated subjects, INTELENCE<sup>®</sup>-treated subjects had lower antiviral responses associated with reduced susceptibility to the N(t)RTIs and to INTELENCE<sup>®</sup>.

### **Pivotal Comparative Bioavailability Study**

In a Phase I, open-label, randomized, 4-period crossover bioavailability trial, the relative oral bioavailability of etravirine administered as either two INTELENCE<sup>®</sup> (etravirine) 100 mg non-coated tablets (Treatment A; F060), two etravirine 100 mg coated tablets (Treatment B; F069), one etravirine 200 mg non-coated tablet (Treatment C; F068), or one etravirine 200 mg coated tablet (Treatment D; F070) under fed conditions (21 g fat; 533 kcal) was assessed in 24 healthy male and female subjects

A summary of the results based on the comparison between the current marketed INTELENCE<sup>®</sup> (etravirine) 100 mg non-coated tablets (F060; Treatment A [n=24] and the proposed for marketed etravirine 200 mg non-coated tablets (F068); Treatment C [n=23]) is presented in Table 12.

**Table 12: Summary Table of the Comparative Bioavailability Data Under Fed Conditions**

Etravirine (TMC125) 1 x 200 mg tablet (F068) and 2 x 100 mg tablets(F060) From measured data				
Geometric Mean Arithmetic Mean (CV%)				
Parameter <sup>&amp;</sup>	Test*	Reference <sup>†</sup>	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>0-72</sub> (ng.h/mL)	3741 4247 (50.81)	3697 4037 (42.95)	98.26	90.61 – 106.6
C <sub>max</sub> (ng/mL)	389 425(46.62)	369 392 (37.59)	103.3	94.42 – 113.0
T <sub>max</sub> <sup>§</sup> (h)	4.0 (2.0 – 6.0)	5.0 (2.0- 6.0)		

<sup>&</sup> Due to the design of the study AUC<sub>1</sub> and T<sub>1/2</sub> parameters could not be accurately estimated

\* Etravirine 200 mg non-coated tablets (F068) (Janssen Inc.)

<sup>†</sup> INTELENCE<sup>®</sup> (etravirine) 100 mg non-coated tablets (F060) (Janssen Inc.)

<sup>§</sup> Expressed as the median (range) only

## DETAILED PHARMACOLOGY

### Pharmacokinetics

#### Absorption

Maximum etravirine plasma concentrations are generally attained by 4 hours following single or multiple oral doses of 100 mg to 400 mg. Dose-proportional pharmacokinetics were observed for daily doses from 200-400 mg and steady-state plasma concentrations were reached in approximately 7 days.

The population pharmacokinetics derived geometric mean (SD) C<sub>0h</sub> and AUC<sub>12h</sub> for etravirine in 574 HIV-1-infected patients receiving INTELENCE<sup>®</sup> is 4531.53 (±4543.69) ng.h/mL and 296.74 (±377.52) ng/mL, respectively.

#### Effect of food on oral absorption

The exposure to etravirine is similar when taken following a standard normal caloric meal (561 kcal) or high-fat high caloric meal (1160 kcal). When compared to administration following a standard normal caloric meal, exposure to etravirine was decreased by 51% in fasted conditions. Therefore, to achieve optimal exposure, INTELENCE<sup>®</sup> should be taken following a meal. The caloric and fat content of the meal is irrelevant. (See **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS; Drug-Food Interactions**).

#### Distribution

Etravirine is approximately 99.9% bound to plasma proteins, primarily to albumin (99.6%) and alpha1-acid glycoprotein (94.48-97.66%) *in vitro*. The distribution of etravirine into compartments other than plasma (e.g. cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

## **Metabolism**

*In vitro* experiments with human liver microsomes (HLMs) indicate that etravirine primarily undergoes oxidative metabolism by CYP3A, CYP2C9 and CYP2C19 enzymes. The major metabolites, formed by methyl hydroxylation of the dimethylbenzotrile moiety, were at least 90% less active than etravirine against wild-type HIV in cell culture.

## **Elimination**

The terminal elimination half-life of etravirine is approximately 30-40 hours. After administration of a radiolabelled <sup>14</sup>C-etravirine dose, 93.7% and 1.2% of the administered radioactivity could be retrieved in feces and urine, respectively. Unchanged etravirine accounted for 81.2%-86.4% of the administered dose in feces while no unchanged etravirine could be detected in urine.

## **Demographics**

The pharmacokinetics of etravirine in HIV-1-infected patients appears to be similar between men and women, among the ethnic groups studied and for patients in the age range 18-77 years. The pharmacokinetics of etravirine in children and adolescents are under investigation. Population pharmacokinetic analysis showed reduced clearance of etravirine in subjects with hepatitis B and/or C infection. Based on the safety data, no dose adjustment is required in patients co-infected with hepatitis B and/or C virus.

The pharmacokinetics of etravirine were not significantly changed in subjects with mild or moderate hepatic impairment. INTELENCE<sup>®</sup> has not been studied in subjects with severe hepatic impairment.

The pharmacokinetics of etravirine has not been investigated in patients with renal insufficiency. Less than 1.2% of the dose is excreted in the urine and the impact of renal impairment on etravirine elimination is expected to be minimal.

## **MICROBIOLOGY**

### **Antiviral Activity *In Vitro***

Etravirine exhibits activity against laboratory strains and clinical isolates of wild-type HIV-1 in acutely infected T-cell lines, human peripheral blood mononuclear cells, and human monocytes/macrophages with median EC<sub>50</sub> values ranging from 0.9 to 5.5 nM (i.e., 0.4 to 2.4 ng/mL).

Etravirine demonstrated antiviral activity in cell culture against a broad panel of HIV-1 group M isolates (subtype A, B, C, D, E, F, G) with EC<sub>50</sub> values ranging from 0.29 to 1.65 nM and EC<sub>50</sub> values ranging from 11.5 to 21.7 nM against group O primary isolates. These EC<sub>50</sub> values are well below the 50% cellular toxicity concentration range of 15 to >100 μM.

The EC<sub>50</sub> value of etravirine for HIV-1 increases by a median factor of 5.8 in the presence of human serum.

No antagonism is observed between etravirine and any of the studied antiretrovirals. Etravirine shows additive antiviral activity in combination with the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and saquinavir; the N(t)RTIs zalcitabine, didanosine, stavudine, abacavir, and tenofovir; the NNRTIs efavirenz, delavirdine, and nevirapine; the fusion inhibitor enfuvirtide; the integrase inhibitor raltegravir and the CCR5 antagonist maraviroc. Etravirine shows additive to synergistic antiviral activity in combination with the NRTIs emtricitabine, lamivudine, and zidovudine.

### **Resistance *In Vitro***

Etravirine showed antiviral activity against 55 of 65 HIV-1 strains with single amino acid substitutions at RT positions associated with NNRTI resistance, including the K103N. The amino acid substitutions which led to the highest resistance to etravirine in cell culture are Y181I (13-fold change in EC<sub>50</sub> value) and Y181V (17-fold change in EC<sub>50</sub> value). The antiviral activity of etravirine in cell culture against 24 HIV-1 strains with multiple amino acid substitutions associated with resistance to N(t)RTIs and/or PIs is comparable to that observed against wild type HIV-1.

*In vitro* selection of etravirine-resistant strains originating from wild type HIV-1 of different origins and subtypes as well as NNRTI-resistant HIV-1 was performed at high and low virus inoculum. At high virus inoculum, emergence of resistant strains from wild type HIV-1 was delayed or prevented at concentrations of 40 nM or 200 nM. Regardless of the experimental design and the original HIV-1 strain, development of resistance against etravirine typically required multiple mutations in the RT of which the following were observed most frequently: L100I, E138K, E138G, V179I, Y181C, and M230I.

### **Resistance in treatment-experienced subjects**

In the Phase 3 trials DUET-1 and DUET-2, mutations that developed most commonly in subjects with virologic failure to the INTELENCE<sup>®</sup>-containing regimen were V179F, V179I and Y181C which usually emerged in a background of multiple other NNRTI resistance-associated mutations (RAMs). In all the trials conducted with INTELENCE<sup>®</sup> in HIV-1 infected subjects, the following mutations emerged most commonly: L100I, E138G, V179F, V179I, Y181C and H221Y.

### **Cross-Resistance *In Vitro***

The single amino acid substitutions associated with an etravirine reduction in susceptibility >3-fold were K101A, K101P, K101Q, E138G, E138Q, Y181C, Y181I, Y181T, Y181V, and M230L, and of these, the greatest reductions were Y181I (13-fold change in EC<sub>50</sub> values) and Y181V (17-fold change in EC<sub>50</sub> value). Mutant strains containing a single NNRTI resistance associated substitution (K101P, K101Q, E138Q, or M230L) had cross-resistance between etravirine and efavirenz. The majority (39 of 61; 64%) of the NNRTI mutant viruses with 2 or 3 amino acid substitutions associated with NNRTI resistance had decreased susceptibility to etravirine (fold-change >3). The highest levels of resistance to etravirine were observed for HIV-1 harbouring a combination of substitutions V179F + Y181C (181 fold-change), V179 + Y181I (123 fold-change), or V179F + Y181C + F227C (888 fold-change). Etravirine retains an EC<sub>50</sub> value <10 nM against 83% of 6171 clinical isolates resistant to delavirdine, efavirenz

and/or nevirapine. The treatment of patients with delavirdine, efavirenz or nevirapine following virologic failure of an etravirine-containing regimen is not recommended.

### **Baseline Genotype/Phenotype and Virologic Outcome Analyses**

In DUET-1 and DUET-2, the presence at baseline of 3 or more of the following mutations: V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, Y181C, Y181I, Y181V, G190A, and G190S (INTELENCE<sup>®</sup>-RAMs) was associated with a decreased virologic response to INTELENCE<sup>®</sup> (see Table 13). These individual mutations mainly occurred in the presence of other NNRTI RAMs. V179F was never present without Y181C.

K103N, which was the most prevalent NNRTI mutation in DUET-1 and DUET-2 at baseline, was not identified as a mutation associated with resistance to INTELENCE<sup>®</sup>. The presence of this mutation did not affect the response in the INTELENCE<sup>®</sup> arm.

Number of TMC125 RAMs*	Etravirine Arms N=540		Placebo Arms N= 541	
	Re-Used/Not Used Enfuvirtide	De Novo Enfuvirtide	Re-Used/Not Used Enfuvirtide	De Novo Enfuvirtide
<b>All ranges</b>	63.3% (254/401)	78.4% (109/139)	37.1% (147/396)	64.1% (93/145)
<b>0</b>	74.1% (117/158)	91.3% (42/46)	42.7% (61/143)	73.6% (39/53)
<b>1</b>	61.3% (73/119)	80.4% (41/51)	38.6% (59/153)	64.7% (33/51)
<b>2</b>	64.1% (41/64)	66.7% (18/27)	26.2% (16/61)	52.6% (10/19)
<b>≥3</b>	38.3 (23/60)	53.3% (8/15)	28.2% (11/39)	50.0% (11/22)

\*TMC125 RAMs = V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change pending additional data.

Response rates assessed by baseline etravirine phenotype are shown in Table 14. These baseline phenotype groups are based on the select subject populations in DUET-1 and DUET-2 and are not meant to represent definitive clinical susceptibility breakpoints for INTELENCE<sup>®</sup>. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to etravirine in treatment-experienced patients.

<b>Table 14: Proportion of Subjects with &lt;50 HIV-1 RNA copies/mL at Week 48 by Baseline Phenotype and Enfuvirtide Use in the Pooled DUET studies*</b>				
<b>Etravirine Fold Change</b>	<b>Etravirine Arms N= 539</b>		<b>Placebo Arms N=534</b>	
	<b>Re-Used/Not Used Enfuvirtide</b>	<b>De Novo Enfuvirtide</b>	<b>Re-Used/Not Used Enfuvirtide</b>	<b>De Novo Enfuvirtide</b>
<b>All ranges</b>	63% (253/400)	78% (109/139)	37% (145/391)	64% (92/143)
<b>0 – ≤3</b>	70% (188/267)	85% (78/88)	43% (112/262)	64% (61/95)
<b>&gt; 3 – ≤13</b>	53% (39/74)	68% (25/37)	29% (22/77)	69% (18/26)
<b>&gt; 13</b>	44% (26/59)	64% (9/14)	21% (11/52)	59% (13/22)
*non-VF Excluded Population				

In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the treatment history and to resistance testing results where available.

## **TOXICOLOGY**

### **Acute Toxicity**

In mice and rats, there were no relevant effects following oral or subcutaneous administration of etravirine at doses up to 1000 and 320 mg/kg, respectively. Similarly, in dogs there was no effect of etravirine treatment following oral administration at doses up to 160 mg/kg.

### **Chronic Toxicity**

Chronic repeat dose toxicity studies were conducted in mice (3 month duration), rats (6 month duration) and dogs (12 month duration). In mice the key target organs identified were the liver and the coagulation system. Haemorrhagic cardiomyopathy was only observed in male mice and was considered to be secondary to severe coagulopathy mediated via the vitamin K pathway. This is considered not relevant to humans. In the rat, the key target organs identified were the liver, the thyroid, and the coagulation system. Exposure in mice was equivalent to human exposure while in rats it was below the clinical exposure at the recommended dose (200 mg b.i.d.).

In the dog, changes in the liver and gall bladder were seen at exposures approximately 8-fold higher than human exposure observed at the recommended dose (200 mg b.i.d.).

### **Carcinogenesis and Mutagenesis**

Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. A statistically significant increase in the incidences of hepatocellular adenomas and carcinomas was observed in treated female mice. Administration of etravirine did not cause a statistically significant increase in the incidence of tumors in female or male rats. The

relevance of the findings in mice to humans is not known. At the highest tested doses, the systemic exposures (based on AUC) to etravirine were lower than those in humans at the clinical therapeutic dose (200 mg b.i.d.) with animal versus human AUC ratios being 0.6 (mice) and between 0.2 and 0.7 (rats).

In a range of mutagenicity studies, etravirine tested negative in the *in vitro* Ames reverse mutation assay, *in vitro* chromosomal aberration assay in human lymphocytes, and *in vitro* clastogenicity mouse lymphoma assay, in the absence and presence of a metabolic activation system. Etravirine 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 etravirine treatment up to 500 mg/kg/day and exposure levels equivalent to those in humans at the clinically recommended dose.

There was no teratogenicity with etravirine in rats (1000 mg/kg) and rabbits (375 mg/kg) at exposures equivalent to those observed in humans at the recommended clinical dose. In a pre- and postnatal development assessment in rats, etravirine had no effect on offspring development during lactation or post-weaning when the mother was dosed up to 500 mg/kg and at exposures equivalent to those observed at the recommended clinical dose.

### **Local Tolerance**

Etravirine was classified as “nonsensitizing” based on an *in vivo* guinea pig skin sensitization study and was also found to be unlikely to cause skin sensitization in a mouse local lymph node assay. Etravirine was also classified as “nonirritant” based on an *in vivo* rabbit skin irritation study. In an *in vitro* eye irritation assay, etravirine was considered as a “mild” eye irritant. No effects were observed in an *in vitro* phototoxicity study.

### **Immunotoxicity**

Immunotoxicity has been evaluated in rats. Etravirine was administered at a dose of 600 mg/kg/day for 4 weeks and effects on lymphoid organs (lymph nodes, spleen and thymus) were evaluated. There were no relevant effects of treatment with etravirine, and the immune response, as measured by IgM production, was not affected by treatment.

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**PART III: CONSUMER INFORMATION****INTELENCE®\***  
etravirine tablets

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

**ABOUT THIS MEDICATION****What the medication is used for:**

INTELENCE® is an oral tablet used for the treatment of HIV (Human Immunodeficiency Virus) infection in adults. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). INTELENCE® is a type of anti-HIV drug called a non-nucleoside reverse transcriptase inhibitor (NNRTI), otherwise known as a "non-nuke".

INTELENCE® does not reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Never use or share dirty needles.

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

**What it does:**

INTELENCE® blocks HIV reverse transcriptase, an enzyme which the virus needs to multiply. When used with other anti-HIV medicines, INTELENCE® reduces the amount of HIV in your blood (called "viral load") and increases your CD4 (T) cell count. HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. Reducing the amount of HIV and increasing the CD4 (T) cell count can improve your immune system and, thus, reduce the risk of death or infections that can happen when your immune system is weak (opportunistic infections).

INTELENCE® must be taken in combination with other anti-HIV medicines.

INTELENCE® does **not** cure HIV infection or AIDS. At present, there is no cure for HIV infection. People taking INTELENCE® may still develop infections or other conditions associated with HIV infection. Because of this, it is very important for you to remain under the care of a doctor. Although INTELENCE® is not a cure for HIV or AIDS, INTELENCE® can help reduce your risks of getting illnesses associated with HIV infection (AIDS and

opportunistic infection) and eventually dying from these conditions.

**When it should not be used:**

Together with your doctor, you need to decide whether taking INTELENCE® is right for you.

**Do not take INTELENCE®:**

- If you are allergic to etravirine or any of the other ingredients in INTELENCE® (see "**What the nonmedicinal ingredients are**").

**What the medicinal ingredient is:**

The active substance is etravirine. Each 100 mg tablet contains 100 mg of etravirine. Each 200 mg tablet contains 200 mg of etravirine.

**What the nonmedicinal ingredients are:****INTELENCE® 100 mg tablets**

Patients with hereditary problems of lactose intolerance should not take this medicine. The other ingredients are hypromellose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate and lactose monohydrate.

**INTELENCE® 200 mg tablets**

The other ingredients are hypromellose, silicified microcrystalline cellulose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium and magnesium stearate.

**What dosage forms it comes in:**

100 mg tablets  
200 mg tablets

**WARNINGS AND PRECAUTIONS**

BEFORE you use INTELENCE® talk to your doctor or pharmacist if you:

- have had or currently have liver problems, including hepatitis B and/or C.
- are pregnant or planning to become pregnant. It is not known if INTELENCE® can harm your unborn baby. You and your doctor will need to decide if taking INTELENCE® is right for you. If you take INTELENCE® while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- are breast-feeding. Do not breast-feed if you are taking INTELENCE®. You should not breast-feed if you have HIV because of the chance of passing HIV to your baby. Talk with your doctor about the best way to feed your baby.

**INTERACTIONS WITH THIS MEDICATION**

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements, including St. John’s Wort (*Hypericum perforatum*). INTELENCE® and many other medicines can interact. Sometimes serious side effects will happen if INTELENCE® is taken with certain other medicines.

Tell your doctor if you take other anti-HIV medicines, particularly atazanavir, didanosine, fosamprenavir, maraviroc, nelfinavir, ritonavir, indinavir, saquinavir, tipranavir, nevirapine, efavirenz and delavirdine or any combinations of these medications. INTELENCE® can be combined with some other anti-HIV medicines while other combinations are not recommended.

Do not take the following medications while taking INTELENCE® as these medications will reduce the levels of INTELENCE® and may make this medication ineffective:

- Do not take anticonvulsants (to treat epilepsy and prevent seizures) such as carbamazepine (Tegretol®), phenobarbital and phenytoin (Dilantin®) while on an INTELENCE® treatment regimen.
- Do not take rifampin (Rifadin®, Rifater®) (to treat bacterial infections) while on an INTELENCE® treatment regimen.

Tell your doctor if you are taking any of the following medicines:

<u>Type of Drug</u>	<u>Examples of Generic Names (Brand Names)</u>
<b>Antiarrhythmics</b> (to treat abnormal heart rhythms)	bepidil disopyramide digoxin (Lanoxin®) flecainide lidocaine mexiletine propafenone quinidine amiodarone (Cordarone®)
<b>Anticoagulants</b> (to prevent the clotting of red blood cells)	warfarin (Coumadin®)
<b>Anti-infectives</b> (to treat bacterial infections)	clarithromycin (Biaxin®)
<b>Antifungals</b> (to treat fungal infections)	ketoconazole (Nizoral®) itraconazole (Sporanox®) voriconazole (Vfend®)

Type of Drug

Examples of Generic Names (Brand Names)

<b>Antimycobacterials</b> (to treat bacterial infections)	rifabutin (Mycobutin®)
<b>Benzodiazepines</b> (to treat anxiety)	Diazepam®
<b>Corticosteroids</b> (to treat inflammation or asthma)	dexamethasone (Decadron®) fluticasone propionate (Advair Diskus®, Cutivate®, Flonase®, Flovent Diskus®)
<b>HMG-CoA Reductase Inhibitors</b> (to lower cholesterol)	atorvastatin (Lipitor®) lovastatin (Mevacor®) pravastatin (Pravachol®) simvastatin (Zocor®)
<b>Immunosuppressants</b> (to prevent organ transplant rejection)	cyclosporine (Sandimmune®, Neoral®) tacrolimus (Prograf®) sirolimus (Rapamune®)
<b>Platelet Aggregation Inhibitors</b> (to prevent blood clots)	clopidogrel (Plavix®)
<b>PDE-5 Inhibitors</b> (to treat erectile dysfunction)	sildenafil (Viagra®) vardenafil (Levitra®) tadalafil (Cialis®)

Tell your doctor if you are taking any medicines that you obtained without a prescription.

This is **not** a complete list of medicines that you should tell your doctor that you are taking. Know and keep track of all the medicines you take and have a list of them with you. Show this list to all of your doctors and pharmacists any time you get a new medicine. Both your doctor and your pharmacist can tell you if you can take these other medicines with INTELENCE®. Do not start any new medicines while you are taking INTELENCE® without first talking with your doctor or pharmacist. You can ask your doctor or pharmacist for a list of medicines that can interact with INTELENCE®.

**PROPER USE OF THIS MEDICATION**

Always use INTELENCE® exactly as your doctor has told you. You must check with your doctor if you are not sure.

Usual adult dose:

**Take INTELENCE® tablets every day exactly as prescribed by your doctor.** The usual dose is 200 mg (one 200 mg tablet or two 100 mg tablets) of INTELENCE®, twice daily *every day*. It may be easier to remember to take

INTELENCE<sup>®</sup> if you take them at the same time every day. If you have questions about when to take INTELENCE<sup>®</sup>, your doctor can help you decide which schedule works for you.

**You should always take INTELENCE<sup>®</sup> following a meal.** You should not take INTELENCE<sup>®</sup> on an empty stomach. Taking INTELENCE<sup>®</sup> on an empty stomach may lessen the effect of INTELENCE<sup>®</sup>. Follow your doctor's advice on the type of meal you should be taking with INTELENCE<sup>®</sup>.

Swallow the tablets whole with a liquid such as water. Do not chew the tablets. If you are unable to swallow the INTELENCE<sup>®</sup> tablets whole, you may place the tablets in a glass of water. Stir well until the water looks milky, then drink it immediately. Rinse the glass with water several times, and completely swallow the rinse each time to make sure you take the entire dose.

Continue taking INTELENCE<sup>®</sup> unless your doctor tells you to stop. Take the exact amount of INTELENCE<sup>®</sup> that your doctor tells you to take, right from the very start. To help make sure you will benefit from INTELENCE<sup>®</sup>, you must not skip doses or interrupt therapy. If you do not take INTELENCE<sup>®</sup> as prescribed, the beneficial effects of INTELENCE<sup>®</sup> may be reduced or even lost.

**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 INTELENCE<sup>®</sup> by more than 6 hours, wait and then take the next dose of INTELENCE<sup>®</sup> at the regularly scheduled time.** If you miss a dose of INTELENCE<sup>®</sup> by less than 6 hours, take your missed dose of INTELENCE<sup>®</sup> immediately. Then take your next dose of INTELENCE<sup>®</sup> at the regularly scheduled time.

If a dose of INTELENCE<sup>®</sup> is skipped, do not double the next dose. Do not take more or less than your prescribed dose of INTELENCE<sup>®</sup> at any one time.

**Do not stop using INTELENCE<sup>®</sup> without talking to your doctor first.**

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like all prescription drugs, INTELENCE<sup>®</sup> can cause side effects. The following is **not** a complete list of side effects reported with INTELENCE<sup>®</sup> when taken either alone or with other anti-HIV medicines. Do not rely on this leaflet alone for information about side effects. Your doctor can discuss with you a more complete list of side effects.

The most common side effects include the following:

- Skin rash: The rash is usually mild to moderate. In rare instances, rash can be potentially life-threatening. It is therefore important to contact your doctor immediately if you develop a rash. Your doctor will advise you how to deal with your symptoms and decide whether INTELENCE<sup>®</sup> must be stopped.
- diarrhea, nausea, abdominal pain, vomiting, heartburn, gas, and inflammation of the stomach
- fatigue, tingling or pain in hands or feet, numbness, headache, sleeplessness, and anxiety
- kidney failure, high blood pressure, heart attack, and diabetes
- night sweats
- changes in some values of your blood cells or chemistry. These can be seen in the results from blood tests. Your doctor will explain these to you. Examples are low red blood cell count, low blood platelet count, high or abnormal blood fat levels, high cholesterol levels, and high sugar levels.

Other side effects of INTELENCE<sup>®</sup> which can be serious, include muscle pain, tenderness or weakness.

As with other anti-HIV medicines, INTELENCE<sup>®</sup> may cause side effects, including:

- 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.
- immune reconstitution syndrome. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

Do not be alarmed by the following list of possible side effects. You may not experience any of them. If any of these side effects are experienced, they are usually mild and temporary. However, do not hesitate to report undesired side effects to your doctor.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
<b>Uncommon</b> <u>Serious skin rash</u> with blistering, mouth ulcers, fever, swelling of face or lips, tongue or parts of the body, shortness of breath			✓
		✓	
<b>Uncommon</b> <u>Liver problems</u> such as hepatitis (liver inflammation) and symptoms such as abdominal pain, persistent vomiting, feeling unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine.		✓	
		✓	
		✓	
<b>Uncommon</b> <u>Diabetes</u> and symptoms such as excessive thirst, excessive urination, excessive eating, unexplained weight loss, poor wound healing, infections		✓	
		✓	
<b>Uncommon</b> <u>Kidney failure</u> and symptoms such as nausea, loss of appetite and weakness, pass little or no urine, breathlessness		✓	
		✓	
<b>Uncommon</b> <u>High blood pressure</u> and symptoms such as headache, dizziness, blurred vision, nausea	✓		

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

Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

**HOW TO STORE IT**

Keep out of the reach and sight of children.

Store INTELENCE® tablets at room temperature between 15-30°C. Keep INTELENCE® in the bottle given to you by your pharmacist. Keep the bottle tightly closed in order to protect from moisture.

The bottle contains 3 little pouches of drying agent (desiccants) to keep the tablets dry. Keep the pouches in the bottle. Do not eat the pouches. Ask your doctor or pharmacist if you have any questions about storing your tablets.

**This medication is prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep INTELENCE® and all of your medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control centre or emergency room immediately.**

This leaflet provides a summary of information about INTELENCE®. If you have any questions or concerns about either INTELENCE® or HIV, talk to your doctor.

**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](http://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 0701E  
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](http://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**

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.janssen.ca>

or by contacting the sponsor, Janssen Inc., at:  
1-800-567-3331

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