HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INTELENCE™ safely and effectively. See full prescribing information for INTELENCE™.

INTELENCE™ (etravirine) [Tablets]

Initial U.S. Approval – 2008

----------INDICATIONS AND USAGE----------
INTELENCE™ is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated:

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to an NNRTI and other antiretroviral agents. (1)

In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE™ in combination with only N[t]RTIs. (1)

The safety and efficacy of INTELENCE™ have not been established in pediatric patients or treatment-naïve adult patients. (1)

----------DOSAGE AND ADMINISTRATION----------
200 mg (two 100 mg tablets) taken twice daily following a meal. (2)

----------DOSAGE FORMS AND STRENGTHS----------
100 mg tablets (3)

----------CONTRAINDICATIONS----------
None

----------WARNINGS AND PRECAUTIONS----------
Severe and potentially life threatening skin reactions, including cases of Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme, have been reported. Discontinue treatment if severe rash develops. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse events (incidence > 10%) of any intensity that occurred at a higher rate than placebo are rash and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Tibotec Therapeutics at 1-877-REACH-TT or 1-877-732-2488 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
INTELENCE™ should not be co-administered with the following antiretrovirals:

- Tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir
- Protease inhibitors administered without ritonavir
- NNRTIs

Co-administration of INTELENCE™ with drugs that inhibit or induce CYP3A4, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of INTELENCE™. (7)

Co-administration of INTELENCE™ with drugs that are substrates of CYP3A4, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of the co-administered drugs. (7)

Refer to the Full Prescribing Information for other drugs that should not be co-administered with INTELENCE™ and for other drugs that may require a change in dose or regimen. (7)

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

- Pregnancy: *Pregnancy Category B*—Use during pregnancy only if the potential benefit justifies the potential risk. Antiviral Pregnancy Registry available. Register patients by calling 1-800-258-4263. (8.1)
- Nursing Mothers: Mothers should not breastfeed due to the potential for HIV transmission. (8.3)

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

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INTELENCE™*, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents.

This indication is based on Week 24 analyses from 2 randomized, double-blind, placebo-controlled trials of INTELENCE™. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N[t]RTI, PI) treatment-experienced adults.

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

- Treatment history and, when available, resistance testing, should guide the use of INTELENCE™.
- The use of other active antiretroviral agents with INTELENCE™ is associated with an increased likelihood of treatment response.
- In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE™ in combination with only N[t]RTIs [*see Clinical Studies (14)*].
- The risks and benefits of INTELENCE™ have not been established in pediatric patients or in treatment-naïve adult patients.

2 DOSAGE AND ADMINISTRATION

The recommended oral dose of INTELENCE™ tablets is 200 mg (two 100 mg tablets) taken twice daily following a meal [*see Clinical Pharmacology (12.3)*]. The type of food does not affect the exposure to etravirine. Patients who are unable to swallow INTELENCE™ tablets whole may disperse the tablets in a glass of water. Once 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.

3 DOSAGE FORMS AND STRENGTHS

100 mg white to off-white oval tablets debossed with “TMC125” on one side and “100” on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Severe Skin Reactions

Severe and potentially life-threatening skin reactions have occurred in patients taking INTELENCE™, including Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme. These reactions have been reported in < 0.1% of subjects taking INTELENCE™. Treatment with INTELENCE™ should be discontinued and appropriate therapy initiated if severe rash develops.

In general, in clinical trials, rash was mild to moderate, occurred primarily in the second week of therapy and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy [*see Adverse Reactions (6)*]. A total of 2% of HIV-1-infected subjects receiving INTELENCE™ discontinued from Phase 3 trials due to rash.

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5.2 Fat Redistribution

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

5.3 Immune Reconstitution Syndrome

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The safety assessment is based on all data from 1203 subjects in the ongoing Phase 3 placebo-controlled trials, TMC125-C206 and TMC125-C216, conducted in antiretroviral treatment-experienced HIV-1-infected adult subjects, 599 of whom received INTELENCE™ (200 mg b.i.d.). In these pooled trials, the median exposure for subjects in the INTELENCE™ arm and placebo arm was 30.0 and 29.1 weeks, respectively.

The most commonly (> 10%) reported adverse events of all intensities and regardless of causality that occurred at a higher rate in INTELENCE™-treated subjects as compared to placebo-treated subjects are presented in Table 1.

Table 1: Adverse Events of All Intensities and Regardless of Causality at a Higher Rate Compared to Placebo in > 10% of Adult Subjects in the INTELENCE™ Treatment Groups

	Pooled TMC125-C206 and TMC125-C216 Trials	
System Organ Class, Preferred Term, %	**INTELENCE™ + BR N=599**	**Placebo + BR** N=604
Gastrointestinal Disorders		
Nausea	13.9%	11.1%
Skin and Subcutaneous Tissue Disorders		
Rash (any type)	16.9%	9.3%
N=total number of subjects per treatment group, BR=background regimen		

The most frequently reported adverse drug reaction (ADR) at least Grade 2 in severity was rash (9.0%). Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme were reported in < 0.1% of subjects during clinical development with INTELENCE™. A total of 2% of HIV-1-infected subjects in Phase 3 trials receiving INTELENCE™ discontinued due to rash. In general, in clinical trials, rash was mild to moderate, occurred primarily in the second week of therapy, and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy [*see Warnings and Precautions (5.1)*]. The incidence of rash was higher in women compared to men in the INTELENCE™ arm. Patients with a history of NNRTI-related rash did not appear to be at increased risk for the development of INTELENCE™-related rash compared to patients without a history of NNRTI-related rash.

Common Adverse Reactions

ADRs of moderate intensity or greater (≥ Grade 2) and reported in ≥ 2% of subjects treated with INTELENCE™ are presented in Table 2. Laboratory abnormalities considered ADRs are included in Table 3.

Table 2: Treatment-Emergent Adverse Reactions* of at least Moderate Intensity† (Grades 2-4) in ≥ 2% of Adult Subjects in the INTELENCE™ Treatment Groups

System Organ Class, Preferred Term, %	Pooled TMC125-C206 and TMC125-C216 Trials	
	INTELENCE™ + BR N=599	Placebo + BR N=604
Gastrointestinal Disorders		
Diarrhea	5.2%	9.6%
Nausea	4.7%	3.5%
Abdominal pain	3.0%	2.5%
Vomiting	2.3%	2.0%
General Disorders and Administration Site Conditions		
Fatigue	3.3%	4.0%
Nervous System Disorders		
Peripheral neuropathy	2.8%	1.8%
Headache	2.7%	4.1%
Skin and Subcutaneous Tissue Disorders		
Rash	9.0%	3.1%
Vascular Disorders		
Hypertension	2.8%	2.2%

N=total number of subjects per treatment group, BR=background regimen
* Includes adverse reactions at least possibly, probably, or very likely related to the drug.
† Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).

Less Common Adverse Reactions

Treatment-emergent ADRs occurring in less than 2% of subjects (n=599) receiving INTELENCE™ and of at least moderate intensity (≥ Grade 2) are listed below by body system:

Cardiac Disorders: myocardial infarction, angina pectoris, atrial fibrillation
Ear and Labyrinth Disorders: vertigo
Eye Disorders: blurred vision
Gastrointestinal Disorders: gastroesophageal reflux disease, flatulence, gastritis, abdominal distension, pancreatitis, constipation, dry mouth, hematemesis, retching, stomatitis
General Disorders and Administration Site Conditions: sluggishness
Hematologic Disorders: anemia, hemolytic anemia
Hepatobiliary Disorders: cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly
Immune System Disorders: drug hypersensitivity, immune reconstitution syndrome
Metabolism and Nutrition Disorders: diabetes mellitus, dyslipidemia, anorexia
Nervous System Disorders: paraesthesia, somnolence, convulsion, hypoesthesia, syncope, amnesia, hypersomnia, tremor
Psychiatric Disorders: insomnia, anxiety, sleep disorders, abnormal dreams, confusional state, disorientation, nervousness, nightmares
Renal and Urinary Disorders: renal failure
Reproductive System and Breast Disorders: gynecomastia

Respiratory,Thoracic and Mediastinal Disorders: exertional dyspnea, bronchospasm
Skin and Subcutaneous Tissue Disorders: night sweats, hyperhidrosis, prurigo, dry skin, lipohypertrophy, swelling face

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.

Laboratory Abnormalities in Treatment-Experienced Patients

Selected Grade 2 to Grade 4 laboratory abnormalities that represent a worsening from baseline observed in adult subjects treated with INTELENCE™ are presented in Table 3.

Table 3: Selected Grade 2 to 4 Laboratory Abnormalities Observed in Treatment-Experienced Subjects

		Pooled TMC125-C206 and TMC125-C216 Trials	
Laboratory Parameter Preferred Term, %	**DAIDS Toxicity Range**	**INTELENCE™ + BR N=599**	**Placebo + BR N=604**
GENERAL BIOCHEMISTRY			
Pancreatic amylase			
Grade 2	> 1.5-2 x ULN	5.9%	7.3%
Grade 3	> 2-5 x ULN	6.3%	7.0%
Grade 4	> 5 x ULN	1.2%	1.0%
Lipase			
Grade 2	> 1.5-3 x ULN	3.4%	4.8%
Grade 3	> 3-5 x ULN	1.7%	1.2%
Grade 4	> 5xULN	1.0%	0.5%
Creatinine			
Grade 2	> 1.4-1.8 x ULN	4.7%	4.0%
Grade 3	> 1.9-3.4 x ULN	1.9%	1.2%
Grade 4	> 3.4 x ULN	0%	0.2%
HEMATOLOGY			
Decreased hemoglobin			
Grade 2	90-99 g/L	1.9%	3.5%
Grade 3	70-89 g/L	1.0%	0.7%
Grade 4	< 70 g/L	0.7%	0.7%
Neutrophils			
Grade 2	750-999/mm^3	4.4%	5.3%
Grade 3	500-749/mm^3	2.7%	3.5%
Grade 4	< 500/mm^3	1.0%	2.8%
Platelet count			
Grade 2	50,000-99,999/mm^3	2.9%	4.5%
Grade 3	25,000-49,999/mm^3	1.2%	0.8%
Grade 4	< 25,000/mm^3	0.2%	0.2%
LIPIDS AND GLUCOSE			
Total cholesterol			
Grade 2	> 6.20-7.77 mmol/L 240-300 mg/dL	18.0%	12.6%
Grade 3	> 7.77 mmol/L > 300 mg/dL	5.8%	4.1%
Low density lipoprotein			
Grade 2	4.13-4.9 mmol/L 160-190 mg/dL	11.5%	9.1%
Grade 3	> 4.9 mmol/L	5.2%	5.4%

	> 190 mg/dL		
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500 –750 mg/dL	7.1%	6.5%
Grade 3	8.49-13.56 mmol/L 751 - 1200 mg/dL	4.1%	3.0%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	2.9%	1.3%
Elevated glucose levels			
Grade 2	6.95-13.88 mmol/L 161-250 mg/dL	13.1%	10.8%
Grade 3	13.89-27.75 mmol/L 251 – 500 mg/dL	2.5%	1.8%
Grade 4	> 27.75 mmol/L > 500 mg/dL	0%	0.2%
HEPATIC PARAMETERS			
Alanine amino transferase			
Grade 2	2.6-5 x ULN	5.4%	4.0%
Grade 3	5.1-10 x ULN	1.9%	1.3%
Grade 4	> 10 x ULN	0.7%	0.3%
Aspartate amino transferase			
Grade 2	2.6-5 x ULN	5.1%	6.5%
Grade 3	5.1-10 x ULN	2.0%	1.3%
Grade 4	> 10 x ULN	0.5%	0.3%
ULN=Upper Limit of Normal, BR=background regimen			

Patients co-infected with hepatitis B and/or hepatitis C virus

In Phase 3 trials TMC125-C206 and TMC125-C216, 140 subjects (12.4%) with chronic hepatitis B and/or hepatitis C virus co-infection out of 1130 subjects were permitted to enroll. AST and ALT abnormalities occurred more frequently in hepatitis B and/or hepatitis C virus co-infected subjects for both treatment groups. Grade 2 or higher laboratory abnormalities that represent a worsening from baseline of AST, ALT or total bilirubin occurred in 22.8%, 21.4% and 5.7% respectively, of INTELENCE™-treated co-infected subjects as compared to 5.5%, 6.1% and 1.2% of non-co-infected INTELENCE™-treated subjects. In general, adverse events reported by INTELENCE™-treated subjects with hepatitis B and/or hepatitis C virus co-infection were similar to INTELENCE™-treated subjects without hepatitis B and/or hepatitis C virus co-infection.

7 DRUG INTERACTIONS

Etravirine is a substrate of CYP3A4, CYP2C9, and CYP2C19. Therefore, co-administration of INTELENCE™ with drugs that induce or inhibit CYP3A4, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse reaction profile of INTELENCE™ (see Table 4). [*See also Clinical Pharmacology (12.3)*.]

Etravirine is an inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19. Therefore, co-administration of drugs that are substrates of CYP3A4, CYP2C9 and CYP2C19 with INTELENCE™ may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s) (see Table 4). *[See also Drug Interactions (7) and Clinical Pharmacology (12.3)*.]

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

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

Concomitant Drug Class: Drug Name	**Effect on Concentration of Etravirine or Concomitant Drug**	**Clinical Comment**
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz* nevirapine*	↓ etravirine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE™ with efavirenz or nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and other NNRTIs should not be co-administered.
delavirdine	↑ etravirine	Combining two NNRTIs has not been shown to be beneficial. INTELENCE™ and delavirdine should not be co-administered.
HIV-Antiviral Agents: Protease Inhibitors (PIs)—Unboosted (i.e., without co-administration of low-dose ritonavir)		
atazanavir* fosamprenavir nelfinavir indinavir* (without ritonavir)	↓ atazanavir ↑ amprenavir ↑ nelfinavir ↓ indinavir	Concomitant use of INTELENCE™ with PIs without co-administration of low-dose ritonavir may cause a significant alteration in the plasma concentrations of the PI. INTELENCE™ should not be co-administered with PIs without low-dose ritonavir.
ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with ritonavir 600 mg b.i.d. may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and ritonavir 600 mg b.i.d. should not be co-administered.
HIV-Antiviral Agents: Protease Inhibitors (PIs)—Boosted (with co-administration of low-dose ritonavir)		
tipranavir/ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with tipranavir/ritonavir may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and tipranavir/ritonavir should not be co-administered.
fosamprenavir/ritonavir*	↑ amprenavir	Due to a significant increase in the systemic exposure of amprenavir, the appropriate doses of the combination of INTELENCE™ and fosamprenavir/ritonavir have not been established. INTELENCE™ and fosamprenavir/ritonavir should not be co-administered.
atazanavir/ritonavir*	↓ atazanavir ↑ etravirine	Concomitant use of INTELENCE™ with atazanavir/ritonavir may cause a significant decrease in atazanavir C_{min} by about 38% and loss of therapeutic effect of atazanavir. In addition, the mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with atazanavir/ritonavir is anticipated to be about 100% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. INTELENCE™ and

		atazanavir/ritonavir should not be co-administered.
darunavir/ritonavir	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced by about 37% when INTELENCE™ was co-administered with darunavir/ritonavir. Because all subjects in the Phase 3 trials received darunavir/ritonavir as part of the background regimen and etravirine exposures from these trials were determined to be safe and effective, INTELENCE™ and darunavir/ritonavir can be co-administered without any dose adjustments.
lopinavir/ritonavir	↑ etravirine	The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with lopinavir/ritonavir is anticipated to be about 85% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. The amount of safety data at these increased etravirine exposures is limited, therefore, INTELENCE™ and lopinavir/ritonavir should be co-administered with caution.
saquinavir/ritonavir	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced by about 33% when INTELENCE™ was co-administered with saquinavir/ritonavir. Because 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, INTELENCE™ and saquinavir/ritonavir can be co-administered without any dose adjustments.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE™. INTELENCE™ and antiarrhythmics should be co-administered with caution. Drug concentration monitoring is recommended, if available.
Anticoagulants: warfarin	↑ anticoagulants	Warfarin concentrations may be increased when co-administered with INTELENCE™. The international normalized ratio (INR) should be monitored when warfarin is combined with INTELENCE™.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ etravirine	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE™ 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™.
Antifungals: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	↑ etravirine ↔ fluconazole ↓ itraconazole ↓ ketoconazole ↔ posaconazole ↑ voriconazole	Posaconazole is a potent inhibitor of CYP3A4 and fluconazole is a potent inhibitor of CYP2C9; both may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A4. 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™. Voriconazole is a CYP2C19 substrate and CYP3A4, CYP2C9 and CYP2C19 inhibitor.

		Concomitant use of voriconazole and INTELENCE™ may increase plasma concentrations of both drugs. Dose adjustments for itraconazole, ketoconazole or voriconazole may be necessary depending on other co-administered drugs.
Antiinfectives: clarithromycin*	↑ etravirine ↓ clarithromycin ↑ 14-OH-clarithromycin	Clarithromycin exposure was decreased by INTELENCE™; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.
Antimycobacterials: rifampin, rifapentine	↓ etravirine	Rifampin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE™ should not be used with rifampin or rifapentine as co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™.
Antimycobacterials: rifabutin*	↓ etravirine ↓ rifabutin ↓ 25-*O*-desacetylrifabutin	If INTELENCE™ is NOT co-administered with a protease inhibitor/ritonavir, then rifabutin at a dose of 300 mg q.d. is recommended. If INTELENCE™ is co-administered with darunavir/ritonavir or saquinavir/ritonavir, then rifabutin should not be co-administered due to the potential for significant reductions in etravirine exposure.
Benzodiazepines: diazepam	↑ diazepam	Concomitant use of INTELENCE™ with diazepam may increase plasma concentrations of diazepam. A decrease in diazepam dose may be needed.
Corticosteroids: dexamethasone (systemic)	↓ etravirine	Systemic dexamethasone induces CYP3A4 and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE™. Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use.
Herbal Products: St. John's wort (*Hypericum perforatum*)	↓ etravirine	Concomitant use of INTELENCE™ with products containing St. John's wort may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™. INTELENCE™ and products containing St. John's wort should not be co-administered.
HMG-CoA Reductase Inhibitors: atorvastatin* fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	↔ etravirine ↓ atorvastatin ↑ 2-OH-atorvastatin ↔ etravirine ↑ fluvastatin, ↓ lovastatin, ↔ pravastatin, ↔ rosuvastatin, ↓ simvastatin	The combination of INTELENCE™ and atorvastatin can be given without any dose adjustments, however, the dose of atorvastatin may need to be altered based on clinical response. No interaction between pravastatin, rosuvastatin and INTELENCE™ is expected. Lovastatin and simvastatin are CYP3A4 substrates and co-administration with INTELENCE™ may result in lower plasma concentrations of the HMG-CoA reductase inhibitor. Fluvastatin is metabolized by CYP2C9 and co-administration with INTELENCE™ may result in higher plasma concentrations of the HMG-CoA reductase inhibitor. Dose adjustments for these HMG-CoA reductase inhibitors may be necessary.
Immunosuppressants:	↓	INTELENCE™ and systemic immunosuppressants should be co-

cyclosporine, sirolimus, tacrolimus	immunosuppressant	administered with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected.
Narcotic Analgesics: methadone*	↔ etravirine ↔ methadone	INTELENCE™ and methadone can 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.
Phosphodiesterase Type 5 (PDE-5) Inhibitors: sildenafil*, vardenafil, tadalafil	↓ sildenafil ↓ N-desmethyl-sildenafil	INTELENCE™ and sildenafil can be co-administered without dose adjustments, however, the dose of sildenafil may need to be altered based on clinical effect.
↑ = increase, ↓ = decrease, ↔ = no change * The interaction between INTELENCE™ and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.		

In addition to the drugs included in Table 4, the interaction between INTELENCE™ and the following drugs were evaluated in clinical studies and no dose adjustment is needed for either drug [*see Clinical Pharmacology (12.3)*]: didanosine, enfuvirtide, ethinylestradiol/norethindrone, omeprazole, paroxetine, raltegravir, ranitidine, and tenofovir disoproxil fumarate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

No adequate and well-controlled studies of INTELENCE™ use in pregnant women have been conducted. In addition, no pharmacokinetic studies have been conducted in pregnant patients. Animal reproduction studies in rats and rabbits at systemic exposures equivalent to those at the recommended human dose of 400 mg/day revealed no evidence of fetal harm. INTELENCE™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry

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

8.3 Nursing mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. It is not known whether etravirine is secreted in human milk. Because of both the potential for HIV transmission and the potential for adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving INTELENCE™**.

8.4 Pediatric use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric use

Clinical studies of INTELENCE™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

No dose adjustment of INTELENCE™ is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The pharmacokinetics of INTELENCE™ have not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C).

8.7 Renal Impairment

Since the renal clearance of etravirine is negligible (< 1.2%), a decrease in total body clearance is not expected in patients with renal impairment. No 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 hemodialysis or peritoneal dialysis.

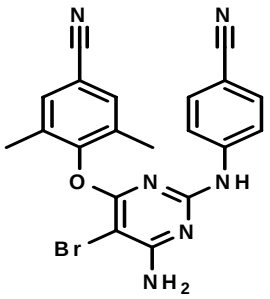
10 OVERDOSAGE

There is no specific antidote for overdose with INTELENCE™. Human experience of overdose with INTELENCE™ is limited. The highest dose studied in healthy volunteers was 400 mg once daily. Treatment of overdose with INTELENCE™ consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Because etravirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

11 DESCRIPTION

INTELENCE™ (etravirine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1).

The chemical name for etravirine is 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile. Its molecular formula is $C_{20}H_{15}BrN_6O$ and its molecular weight is 435.28. Etravirine has the following structural formula:



Etravirine is a white to slightly yellowish brown powder. Etravirine is practically insoluble in water over a wide pH range. It is very slightly soluble in propylene glycol and slightly soluble in ethanol. Etravirine is soluble in polyethylene glycol (PEG)400 and freely soluble in some organic solvents (e.g., N,N-dimethylformamide and tetrahydrofuran).

INTELENCE™ is available as a white to off-white, oval tablet for oral administration containing 100 mg of etravirine. Each tablet contains the inactive ingredients hypromellose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and lactose monohydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Etravirine is an antiviral drug [*see Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

Effects on Electrocardiogram

In a randomized, double-blind, active, and placebo-controlled crossover study, 41 healthy subjects were administered INTELENCE™ 200 mg b.i.d., INTELENCE™ 400 mg q.d., placebo, and moxifloxacin 400 mg. After 8 days of dosing, etravirine did not prolong the QT interval. The maximum mean (upper 1-sided 95% CI) baseline and placebo-adjusted QTcF were 0.6 ms (3.3 ms) for 200 mg b.i.d. and -1.0 ms (2.5 ms) for 400 mg q.d. dosing regimens.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

The pharmacokinetic properties of INTELENCE™ were determined in healthy adult subjects and in treatment-experienced HIV-1-infected adult subjects. The systemic exposures (AUC) to etravirine were lower in HIV-1-infected subjects than in healthy subjects.

Table 5: Population Pharmacokinetic Estimates of Etravirine 200 mg b.i.d. in HIV-1-Infected Subjects (Integrated Data from Phase 3 Trials at Week 24)*

Parameter	Etravirine 200 mg b.i.d. N = 574
AUC_{12h} (ng•h/mL)	
Geometric Mean ± Standard Deviation	4531.53 ± 4543.69
Median (Interquartile Range)	4450.7 (3091.3 - 6315.0)
C_{0h} (ng/mL)	
Geometric Mean ± Standard Deviation	296.74 ± 377.52
Median (Interquartile Range)	298.8 (188.5 - 462.3)

* All HIV-1-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 shown in Table 5 account for reductions in the pharmacokinetic parameters of etravirine due to co-administration of INTELENCE™ with darunavir/ritonavir.

Note: The median protein binding adjusted EC50 for MT4 cells infected with HIV-1/IIIB in vitro = 4 ng/mL.

Absorption and Bioavailability

Following oral administration, etravirine was absorbed with a T_{max} of about 2.5 to 4 hours. The absolute oral bioavailability of INTELENCE™ is unknown.

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

Effects of Food on Oral Absorption

The systemic exposure (AUC) to etravirine was decreased by about 50% when INTELENCE™ was administered under fasting conditions, as compared to when INTELENCE™ was administered following a meal. Therefore, INTELENCE™ should always be taken following a meal. Within the range of meals studied, the systemic exposures to etravirine were similar. The total caloric content of the various meals evaluated ranged from 345 kilocalories (17 grams fat) to 1160 kilocalories (70 grams fat). [*see Dosage and Administration (2)*].

Distribution

Etravirine is about 99.9% bound to plasma proteins, primarily to albumin (99.6%) and alpha 1-acid glycoprotein (97.66%-99.02%) *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 metabolism by CYP3A4, CYP2C9, and CYP2C19 enzymes. The major metabolites, formed by methyl hydroxylation of the dimethylbenzonitrile moiety, were at least 90% less active than etravirine against wild-type HIV in cell culture.

Elimination

After single dose oral administration of 800 mg ^{14}C-etravirine, 93.7% and 1.2% of the administered dose of ^{14}C-etravirine was recovered in the 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 mean (± standard deviation) terminal elimination half-life of etravirine was about 41 (± 20) hours.

Special Populations

Hepatic Impairment

Etravirine is primarily metabolized by the liver. The steady state pharmacokinetic parameters of etravirine were similar after multiple dose administration of INTELENCE™ to subjects with normal hepatic function (n = 16), mild hepatic impairment (Child-Pugh Class A, n = 8), and moderate hepatic impairment (Child-Pugh Class B, n = 8). The effect of severe hepatic impairment on the pharmacokinetics of etravirine has not been evaluated.

Hepatitis B and/or Hepatitis C Virus Co-infection

Population pharmacokinetic analysis of the TMC125-C206 and TMC125-C216 trials showed reduced clearance for etravirine in HIV-1-infected subjects with hepatitis B and/or C virus co-infection. Based upon the safety profile [*see Adverse Reactions (6)*], no dose adjustment is necessary in patients co-infected with hepatitis B and/or C virus.

Renal Impairment

The pharmacokinetics of etravirine have not been studied in patients with renal impairment. The results from a mass balance study with ^{14}C-etravirine showed that <1.2% of the administered dose of etravirine is excreted in the urine as metabolites. No unchanged drug was detected in the urine. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis.

Gender

No significant pharmacokinetic differences have been observed between men and women. A limited number of women were included in clinical studies.

Race

Population pharmacokinetic analysis of etravirine in HIV-infected subjects did not show an effect of race on exposure to etravirine.

Geriatric Patients

Population pharmacokinetic analysis in HIV-infected subjects showed that etravirine pharmacokinetics are not considerably different within the age range (18 to 77 years) evaluated [*see Use in Specific Populations (8.5)*].

Pediatric Patients

The pharmacokinetics of etravirine in pediatric patients have not been evaluated. Dosing recommendations for pediatric patients cannot be made due to insufficient data.

Drug Interactions

[*See also Drug Interactions (7).*]

Etravirine is a substrate of CYP3A4, CYP2C9, and CYP2C19. Therefore, co-administration of INTELENCE™ with drugs that induce or inhibit CYP3A4, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse reaction profile of INTELENCE™.

Etravirine is an inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19. Therefore, co-administration of drugs that are substrates of CYP3A4, CYP2C9 and CYP2C19 with INTELENCE™ may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s).

Drug interaction studies were performed with INTELENCE™ and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of other drugs on the AUC, C_{max}, and C_{min} values of etravirine are summarized in Table 6 (effect of other drugs on INTELENCE™). The effect of co-administration of INTELENCE™ on the AUC, C_{max}, and C_{min} values of other drugs are summarized in Table 7 (effect of INTELENCE™ on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7)*.

Table 6: Drug Interactions: Pharmacokinetic Parameters for Etravirine in the Presence of Co-administered Drugs

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	Exposure	Mean Ratio of Etravirine Pharmacokinetic Parameters 90% CI; No Effect = 1.00		
				C_{max}	AUC	C_{min}
Co-Administration With Protease Inhibitors (PIs)						
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)
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)
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)
Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
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)
Co-Administration With Integrase Strand Transfer Inhibitors						
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)
Co-Administration With Other Drugs						
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)
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)

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increase; ↓ = decrease; ↔ = no change; q.d. = once daily; b.i.d. = twice daily

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

Co-administered Drug	Dose/Schedule of Co-administered Drug	N	Exposure	Mean Ratio of Co-administered Drug Pharmacokinetic Parameters 90% CI; No effect = 1.00		
				C_{max}	AUC	C_{min}
Co-Administration With Protease Inhibitors (PIs)						
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)
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)
Co-Administration With Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
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)
Co-Administration With Integrase Strand Transfer Inhibitors						
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)

Co-Administration With Other Drugs						
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)
Ethinylestradiol	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)
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-*O*-desacetylrifabutin	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.

CI = Confidence Interval; N = number of subjects with data; N.A. = not available; ↑ = increase; ↓ = decrease; ↔ = no change; q.d. = once daily ; b.i.d. = twice daily

12.4 Microbiology

Mechanism of Action

Etravirine is an 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 does not inhibit the human DNA polymerases α, β, and γ.

Antiviral Activity in Cell Culture

Etravirine exhibited 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_{50} 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_{50} values ranging from 0.29 to 1.65 nM and EC_{50} values ranging from 11.5 to 21.7 nM against group O primary isolates. Etravirine did not show antagonism when studied in combination with the following antiretroviral drugs—the NNRTIs delavirdine, efavirenz, and nevirapine; the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir; and the fusion inhibitor enfuvirtide (ENF).

Resistance

In Cell Culture

Etravirine-resistant strains were selected in cell culture originating from wild-type HIV-1 of different origins and subtypes, as well as NNRTI resistant HIV-1. Development of reduced susceptibility to etravirine typically required more than one substitution in reverse transcriptase of which the following were observed most frequently: L100I, E138K, E138G, V179I, Y181C, and M230I.

In Treatment-Experienced Subjects

In the Phase 3 trials TMC125-C206 and TMC125-C216, substitutions that developed most commonly in subjects with virologic failure at Week 24 to the INTELENCE™-containing regimen were V179F, V179I, Y181C, and Y181I which usually emerged in a background of multiple other NNRTI resistance-associated substitutions. In all the trials conducted with INTELENCE™ in HIV-1 infected subjects, the following substitutions emerged most commonly: L100I, E138G, V179F, V179I, Y181C and H221Y. Other NNRTI-resistance associated substitutions which emerged on etravirine treatment in < 10% of the virologic failure isolates included K101E, K103N, V106I/M, V108I, Y188L, V189I, G190S/C and R356K. The emergence of NNRTI substitutions on etravirine treatment contributed to decreased susceptibility to etravirine with a median fold-change in etravirine susceptibility of 40-fold from reference and a median fold-change of 6-fold from baseline.

Cross-Resistance

Site-Directed NNRTI Mutant Virus

Etravirine showed antiviral activity against 55 of 65 HIV-1 strains (85%) with single amino acid substitutions at RT positions associated with NNRTI resistance, including the most commonly found K103N. 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_{50} value) and Y181V (17-fold change in EC_{50} 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 harboring a combination of substitutions V179F + Y181C (187 fold-change), V179F + Y181I (123 fold-change), or V179F + Y181C + F227C (888 fold-change).

Clinical Isolates

Etravirine retained a fold-change ≤ 3 against 60% of 6171 NNRTI-resistant clinical isolates. In the same panel, the proportion of clinical isolates resistant to delavirdine, efavirenz and/or nevirapine (defined as a fold-change above their respective biological cutoff values in the assay) was 79%, 87%, and 95%, respectively. In TMC125-C206 and TMC125-C216, 35% of the baseline isolates had decreased susceptibility to etravirine (fold-change > 3) and 61%, 71%, and 79% of these isolates were resistant to delavirdine, efavirenz, and nevirapine, respectively. Cross-resistance to delavirdine, efavirenz, and/or nevirapine is expected after virologic failure with an etravirine-containing regimen for the virologic failure isolates.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

In TMC125-C206 and TMC125-C216, the presence at baseline of the substitutions V179D, V179F, V179T, Y181V, or G190S was associated with a decreased virologic response to etravirine. The presence of K103N, which was the most prevalent NNRTI substitution in TMC125-C206 and TMC125-C216 at baseline, did not affect the response in the INTELENCE™ arm. Response rates to etravirine decreased as the number of baseline NNRTI mutations increased. The presence at baseline of 3 or more IAS-USA-defined NNRTI substitutions (2007) resulted in a decreased virologic response to INTELENCE™ (shown as the proportion of subjects achieving viral load < 50 plasma HIV RNA copies/mL at Week 24) (Table 8).

Table 8: Proportion of Subjects with < 50 HIV-1 RNA copies/mL at Week 24 by Baseline Number of IAS-USA-Defined NNRTI Mutations in the As-Treated Population of Pooled TMC125-C206 and TMC125-C216 Trials

# IAS-USA-Defined NNRTI*	**Etravirine Arms N = 565**	
	Re-Used/Not Used ENF	**De Novo ENF**
All ranges	60% (251/420)	70% (102/145)
0 - 2	66% (213/322)	76% (80/105)
≥ 3	39% (38/98)	55% (22/40)
	Placebo Arms N = 593	
All ranges	34% (149/434)	62% (99/159)

* 2007 IAS-USA defined mutations = V90I, A98G, L100I, K101E/P, K103N, V106A/I/M, V108I, V179D/F, Y181C/I/V, Y188C/H/L, G190A/S, P225H

Response rates assessed by baseline etravirine phenotype are shown in Table 9. These baseline phenotype groups are based on the select subject populations in TMC125-C206 and TMC125-C216 and are not meant to represent definitive clinical susceptibility breakpoints for INTELENCE™. 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.

Table 9: Proportion of Subjects with < 50 HIV-1 RNA copies/mL at Week 24 by Baseline Phenotype and ENF Use in the Pooled TMC125-C206 and TMC125-C216 Trials*

Etravirine Fold Change	**Etravirine Arms N = 561**		
	Re-Used/Not Used ENF	**De Novo ENF**	**Clinical Response Range**
All ranges	60% (249/416)	70% (102/145)	Overall Response
0 - 3	70% (190/273)	82% (75/92)	Higher than Overall Response
> 3 - 13	47% (37/78)	50% (19/38)	Lower than Overall Response
> 13	34% (22/65)	53% (8/15)	Lower than Overall Response
	Placebo Arms N = 593		
All ranges	34% (149/434)	62% (99/159)	

* As-treated analysis

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity studies of etravirine in rodents are ongoing. 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 absence and presence of a metabolic activation system. Etravirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice. [*See Nonclinical Toxicology (13.2).*]

Impairment of Fertility

No effects on fertility and early embryonic development were observed when etravirine was tested in rats at maternal doses up to 500 mg/kg/day, resulting in systemic drug exposure up to the recommended human dose (400 mg/day).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Developmental toxicity studies were performed in rabbits (at oral doses up to 375 mg/kg/day) and rats (at oral doses up to 1000 mg/kg/day). In both species, no treatment-related embryo-fetal effects including malformations were observed. In addition, no treatment-related effects were observed in a separate pre- and postnatal study performed in rats at oral doses up to 500 mg/kg/day. The systemic drug exposures achieved in these animal studies were equivalent to those at the recommended human dose (400 mg/day).

14 CLINICAL STUDIES

14.1 Treatment-Experienced Subjects

The clinical efficacy of INTELENCE™ is derived from the analyses of 24-week data from 2 ongoing, randomized, double-blinded, placebo-controlled, Phase 3 trials, TMC125-C206 and TMC125-C216 (DUET-1 and DUET-2). These trials are identical in design and the results below are pooled data from the two trials.

TMC125-C206 and TMC125-C216 are Phase 3 studies designed to evaluate the safety and antiretroviral activity of INTELENCE™ in combination with a background regimen (BR) as compared to placebo in combination with a BR. Eligible subjects were treatment-experienced HIV-1-infected patients with plasma HIV-1 RNA > 5000 copies/mL while on a stable antiretroviral regimen for at least 8 weeks. In addition, subjects had 1 or more NNRTI resistance-associated mutations at screening or from prior genotypic analysis, and 3 or more of the following primary PI mutations at screening: D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, V82A/F/L/S/T, I84V, N88S, or L90M. Randomization was stratified by the intended use of enfuvirtide (ENF) in the BR, previous use of darunavir/ritonavir (DRV/rtv), and screening viral load. Virologic response was defined as undetectable viral load (< 50 HIV-1 RNA copies/mL) at 24 weeks.

All study subjects received DRV/rtv as part of their BR, and at least 2 other investigator-selected antiretroviral drugs (N[t]RTIs with or without ENF). Of INTELENCE™-treated subjects, 25.5% used ENF for the first time (*de novo*) and 20.0% re-used ENF. Of placebo-treated subjects, 26.5% used *de novo* ENF and 20.4% re-used ENF.

In the pooled analysis for TMC125-C206 and TMC125-C216, demographics and baseline characteristics were balanced between the INTELENCE™ arm and the placebo arm. Table 10 displays selected demographic and baseline disease characteristics of the subjects in the INTELENCE™ and placebo arms.

Table 10: Demographic and Baseline Disease Characteristics of Subjects in the TMC125-C206 and TMC125-C216 Trials (Pooled Analysis)		
	Pooled TMC125-C206 and TMC125-C216 Trials	
	INTELENCE™ + BR N=599	**Placebo + BR N=604**
Demographic Characteristics		
Median Age, years (range)	46 (18-77)	45 (18-72)
Sex		
Male	90.0%	88.6%
Female	10.0%	11.4%
Race		
White	70.1%	69.8%
Black	13.2%	13.0%
Hispanic	11.3%	12.2%
Asian	1.3%	0.6%
Other	4.1%	4.5%
Baseline Disease Characteristics		
Median Baseline Plasma HIV-1 RNA (range), $\log_{10}$ copies/mL	4.8 (2.7-6.8)	4.8 (2.2-6.5)
Percentage of Subjects with Baseline Viral Load:		
< 30,000 copies/mL	27.5%	28.8%
≥ 30,000 copies/mL and < 100,000 copies/mL	34.4%	35.3%
≥ 100,000 copies/mL	38.1%	35.9%
Median Baseline CD4+ Cell Count (range), cells/mm^3	99 (1-789)	109 (0-912)
Percentage of Subjects with Baseline CD4+ Cell Count:		
< 50 cells/mm^3	35.6%	34.7%
≥ 50 cells/mm^3 and < 200 cells/mm^3	34.8%	34.5%
≥ 200 cells/mm^3	29.6%	30.8%
Median (range) Number of Primary PI Mutations*	4 (0-7)	4 (0-7)
Percentage of Subjects with Previous Use of NNRTIs:		
0	8.2%	7.9%
1	46.9%	46.7%
>1	44.9%	45.4%
Percentage of Subjects with Previous Use of the following NNRTIs:		
Efavirenz	70.3%	72.5%
Nevirapine	57.1%	58.6%
Delavirdine	13.7%	12.7%
Median (range) Number of NNRTI RAMs†	2 (0-5)	2 (0-4)
Median Fold Change of the Virus for the Following NNRTIs:		
Delavirdine	27.4	26.4
Efavirenz	63.9	46.1
Etravirine	1.6	1.5
Nevirapine	74.3	74.3
Percentage of Subjects with Previous		

Use of Enfuvirtide	39.6%	41.9%

RAMs = Resistance-Associated Mutations, BR=background regimen
FC = fold change in EC_{50}
*IAS-USA primary PI mutations [November 2005]: D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, V82A/F/L/S/T, I84V, N88S, L90M
†Tibotec NNRTI RAMs [March 2007]: A98G, L100I, K101E/P/Q, K103H/N/S/T, V106A/M, V108I, E138G/K/Q, V179D/E/F/G/I, Y181C/I/V, Y188C/H/L, G190A/C/E/Q/S, H221Y, P225H, F227C/L, M230I/L, P236L, K238N/T, Y318F

Efficacy at Week 24 for subjects in the INTELENCE™ and placebo arms for the pooled TMC125-C206 and TMC125-C216 study populations are shown in Table 11.

Table 11: Outcomes of Treatment at Week 24 of the TMC125-C206 and TMC125-C216 Trials (Pooled Analysis)

	Pooled TMC125-C206 and TMC125-C216 Trials	
	INTELENCE™ + BR N=599	**Placebo + BR N=604**
Virologic Responders at Week 24 Viral Load < 50 HIV-1 RNA copies/mL	358 (59.8%)	243 (40.2%)
Virologic Failures (VF) at Week 24 Viral Load ≥ 50 HIV-1 RNA copies/mL	190 (31.7%)	320 (53.0%)
Death*	9 (1.5%)	16 (2.6%)
Discontinuations before Week 24†:		
due to VF	2 (0.3%)	3 (0.5%)
due to Adverse Events	28 (4.7%)	11 (1.8%)
due to other reasons	12 (2.0%)	11 (1.8%)

* all deaths, including the follow-up period
† all discontinuations up to and including day 154 of the treatment period
BR=background regimen

At Week 24, 74.0% of INTELENCE™-treated subjects achieved HIV-1 RNA < 400 copies/mL as compared to 51.5% of placebo-treated subjects. The mean decrease in plasma HIV-1 RNA from baseline to Week 24 was –2.37 $\log_{10}$ copies/mL for INTELENCE™-treated subjects and –1.68 $\log_{10}$ copies/mL for placebo-treated subjects. The mean CD4+ cell count increase from baseline for INTELENCE™-treated subjects was 81 cells/mm^3 and 64 cells/mm^3 for placebo-treated subjects.

Of the study population who either re-used or did not use ENF, 56.7% of INTELENCE™-treated subjects and 32.7% of placebo-treated subjects achieved HIV-1 RNA < 50 copies/mL. Of the study population using ENF *de novo,* 68.6% of INTELENCE™-treated subjects and 61.3% of placebo-treated subjects achieved HIV-1 RNA < 50 copies/mL.

Study 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™ (n=59) or an investigator-selected PI (n=57), each given with 2 investigator-selected N(t)RTIs. INTELENCE™-treated subjects had lower antiviral responses associated with reduced susceptibility to the N(t)RTIs and to INTELENCE™ as compared to the control PI-treated subjects.

16 HOW SUPPLIED/STORAGE AND HANDLING

INTELENCE™ tablets are supplied as white to off-white, oval tablets containing 100 mg of etravirine. Each tablet is debossed with "TMC125" on one side and "100" on the other side.

INTELENCE™ tablets are packaged in bottles in the following configuration: 100 mg tablets—bottles of 120 (NDC 59676-570-01). Each bottle contains 3 desiccant pouches.

Store INTELENCE™ tablets at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature]. Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.

17 PATIENT COUNSELING INFORMATION

[See FDA-approved patient labeling].

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

Patients should be informed that INTELENCE™ is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of INTELENCE™ are unknown at this time. Patients should be informed that INTELENCE™ does not reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to blood. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should also be advised to never re-use or share needles. Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using INTELENCE™.

Patients should be advised to take INTELENCE™ following a meal twice a day as prescribed. The type of food does not affect the exposure to etravirine. Patients should be instructed to swallow the tablets as a whole with a liquid such as water. Patients who are unable to swallow the INTELENCE™ tablets whole may disperse the tablets in a glass of water. Once 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. INTELENCE™ must always be used in combination with other antiretroviral drugs. Patients should not alter the dose of INTELENCE™ or discontinue therapy with INTELENCE™ without consulting their physician. If the patient misses a dose of INTELENCE™ within 6 hours of the time it is usually taken, the patient should be told to take INTELENCE™ following a meal as soon as possible, and then take the next dose of INTELENCE™ at the regularly scheduled time. If a patient misses a dose of INTELENCE™ 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. Inform the patient that he or she should not take more or less than the prescribed dose of INTELENCE™ at any one time.

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

Severe and potentially life-threatening rash has been reported with INTELENCE™. Treatment with INTELENCE™ should be discontinued if severe rash develops. Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including INTELENCE™, and that the cause and long-term health effects of these conditions are not known at this time.

Manufactured for Tibotec, Inc. by:
Janssen Cilag S.p.A., Latina, Italy
Distributed by:
Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

Patent Numbers: 6,878,717 and 7,037,917; and other U.S. patents pending.

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10095300

Patient Information
INTELENCE™* (in-tel-ence)
etravirine (et-ra-vir-een)
Tablets

Important: Ask your doctor or pharmacist about medicines that should NOT be taken with INTELENCE™. For more information, read the section "Can INTELENCE™ be taken with other medicines?".

Read this information carefully before you start taking INTELENCE™ and each time you renew your prescription, as new information may be available. This leaflet does not take the place of talking with your doctor. You and your doctor should discuss your treatment with INTELENCE™ when you start taking it and at regular checkups. You should not change or stop treatment without first talking with your doctor.

What is INTELENCE™?

- **INTELENCE™ is a prescription anti-HIV medicine that helps to control 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 medicine called a non-nucleoside reverse transcriptase inhibitor (NNRTI).
- INTELENCE™ is used with other anti-HIV medicines in patients who are already taking or have taken anti-HIV medicines and the medicines are not controlling their HIV infection.
- The long-term effects of INTELENCE™ are not known at this time. It is important that you remain under the care of your doctor during treatment with INTELENCE™.
- The safety and effectiveness of INTELENCE™ have not been studied in children.

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

How does INTELENCE™ work?

- INTELENCE™ blocks an enzyme which the virus (HIV) needs in order to make more virus. The enzyme that INTELENCE™ blocks is called HIV reverse transcriptase.
- When used with other anti-HIV medicines, INTELENCE™ may:
  - reduce the amount of HIV in your blood. This is called your "viral load".
  - increase the number of white blood cells called CD4+ (T) cells that help fight off other infections.

  Reducing the amount of HIV and increasing the CD4+ (T) cell count may improve your immune system and, as a result, reduce the risk of death or infections that can happen when your immune system is weak (opportunistic infections).

* Trademark of Tibotec Pharmaceuticals Ltd.

Does INTELENCE™ cure HIV or AIDS?

No. INTELENCE™ does not cure HIV infection or AIDS. Right now, there is no cure for HIV infection. People taking INTELENCE™ may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of the other conditions that can happen with HIV are: pneumonia, herpes virus infection, *Mycobacterium avium* complex (MAC) infections.

Does INTELENCE™ reduce the risk of passing HIV to others?

No. INTELENCE™ does **not** reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood.

- Always practice safer sex.
- Use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- Never re-use or share needles.

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

What should I tell my doctor before I take INTELENCE™?

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

Tell your doctor about all of your medical conditions, including if you:

- have had or currently have liver problems, including hepatitis B 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 breastfeeding. Do not breastfeed if you are taking INTELENCE™. You should not breastfeed 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.

Can INTELENCE™ be taken with other medicines?**

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*). **Some medicines may interact with INTELENCE™.**

- Sometimes serious side effects happen if INTELENCE™ is taken with some medicines.
- INTELENCE™ should not be taken with some medicines which may lower the amount of INTELENCE™ in your blood. This may lead to an increased HIV viral load. Resistance to INTELENCE™ or cross resistance to other HIV medicines may develop.

** The brands listed are the registered trademarks of their respective owners and are not trademarks of Tibotec Pharmaceuticals Ltd.

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

Tell your doctor if you take other HIV medicines. INTELENCE™ can be combined with most HIV medicines while some HIV medicines are not recommended.

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

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics (to treat abnormal heart rhythms)	amiodarone (Cordarone®) bepridil (Vascor®) disopyramide (Norpace®) flecainide (Tambocor™) lidocaine (Xylocaine®) mexiletine (Mexitil®) propafenone (Rythmol SR®) quinidine (Quinidex®)
Anticoagulants (to prevent blood clots)	warfarin (Coumadin®)
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine (Tegretol®, Carbatrol®) phenobarbital (Luminal®) phenytoin (Dilantin®, Phenytek®)
Antifungals (to treat fungal infections)	fluconazole (Diflucan®) itraconazole (Sporanox®) ketoconazole (Nizoral®) posaconazole (Noxafil®) voriconazole (Vfend®)
Anti-infectives (to treat bacterial infections)	clarithromycin (Biaxin®)
Antimycobacterials (to treat bacterial infections, including tuberculosis (TB))	rifabutin (Mycobutin®) rifampin (Rifadin®, Rifater®, Rifamate®) rifapentine (Priftin®)
Benzodiazepines (to treat trouble with sleeping and/or anxiety)	diazepam (Valium®)
Corticosteroids	dexamethasone (Decadron®)

Type of Drug (to treat inflammation or asthma)	Examples of Generic Names (Brand Names)
HMG-CoA Reductase Inhibitors (to lower cholesterol levels)	atorvastatin (Lipitor®) fluvastatin (Lescol®) lovastatin (Advicor®, Altoprev®, Mevacor®) rosuvastatin (Crestor®) simvastatin (Vytorin®, Zocor®)
Immunosuppressants	cyclosporine (Sandimmune®, Neoral®) sirolimus (Rapamune®) tacrolimus (Prograf®)
Narcotic Analgesic	methadone (Dolophine®)
PDE-5 Inhibitors (to treat erectile dysfunction)	sildenafil (Viagra®) vardenafil (Levitra®) tadalafil (Cialis®)

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

How should I take INTELENCE™?

- **Take INTELENCE™ tablets every day exactly as prescribed by your doctor.** The usual dose is two tablets of INTELENCE™ two times each day (a total of four tablets each day). It may be easier to remember to take INTELENCE™ if you take it at the same time every day. If you have questions about when to take INTELENCE™, your doctor can help you decide which schedule works for you.

- **Take INTELENCE following a meal**. Do not take INTELENCE™ on an empty stomach. INTELENCE™ may not work as well if you take it on an empty stomach. The type of food is not important.

- Swallow INTELENCE™ tablets whole, with a liquid such as water. **Do not chew the tablets.** If you are unable to swallow the INTELENCE™ 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.

- Do not change your dose or stop taking INTELENCE™ without first talking with your doctor. See your doctor regularly while taking INTELENCE™.

- Take all your anti-HIV medicines as prescribed and at the right times of day. This can help your medicines work better and lowers the chance that your medicines will stop working to fight HIV (drug resistance).

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

- If you miss a dose of INTELENCE™ within 6 hours of the time you usually take it, take your dose of INTELENCE™ following a meal as soon as possible. Then, take your next dose of INTELENCE™ at the regularly scheduled time. If you miss a dose of INTELENCE™ by more than 6 hours of the time you usually take it, wait and then take the next dose of INTELENCE™ at the regularly scheduled time.

- Do not double the next dose to make up for a missed dose. Do not take more or less than your prescribed dose of INTELENCE™ at any one time. Always take INTELENCE™ following a meal.

- If you take too much INTELENCE™, contact your local poison control center or emergency room right away.

What are the possible side effects of INTELENCE™?

Skin rash is a common side effect of INTELENCE™. Rash can be serious and potentially life-threatening, and sometimes INTELENCE™ must be stopped. Tell your doctor right away if you get a rash.

Other common side effects of INTELENCE™ include diarrhea, nausea, abdominal pain, vomiting, tiredness, tingling or pain in hands or feet, numbness, headache, and high blood pressure.

As with other anti-HIV medicines, INTELENCE™ may cause side effects, including:

- changes in body shape or body fat. These changes can happen in patients taking anti-HIV medicine. 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. A condition called Immune Reconstitution Syndrome can happen in some patients with advanced HIV infection (AIDS) when HIV treatment is started. Signs and symptoms of inflammation from opportunistic infections that a person has or had may occur as the medicines work to control the HIV infection and strengthen the immune system. Call your doctor right away if you notice any signs or symptoms of an infection after starting INTELENCE™ with other anti-HIV medicines.

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

These are not all of the possible side effects with INTELENCE™. For more information, ask your doctor or pharmacist.

How should I store INTELENCE™ tablets?

- Store INTELENCE™ tablets at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep INTELENCE™ in the bottle given to you by your pharmacist.

Keep the bottle tightly closed to protect INTELENCE™ 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. Keep INTELENCE™ and all medicines out of the reach of children.**

General Advice about INTELENCE™

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

This leaflet provides a summary of the most important information about INTELENCE™. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about INTELENCE™ that is written for health professionals. For more information, you may also call Tibotec Therapeutics at 1-877-REACH-TT or 1-877-732-2488.

What are the ingredients in INTELENCE™?

Active ingredient: Each tablet contains 100 mg of etravirine.

Inactive ingredients: hypromellose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and lactose monohydrate

Manufactured for Tibotec, Inc. by:
Janssen Cilag S.p.A., Latina, IT
Distributed by:
Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

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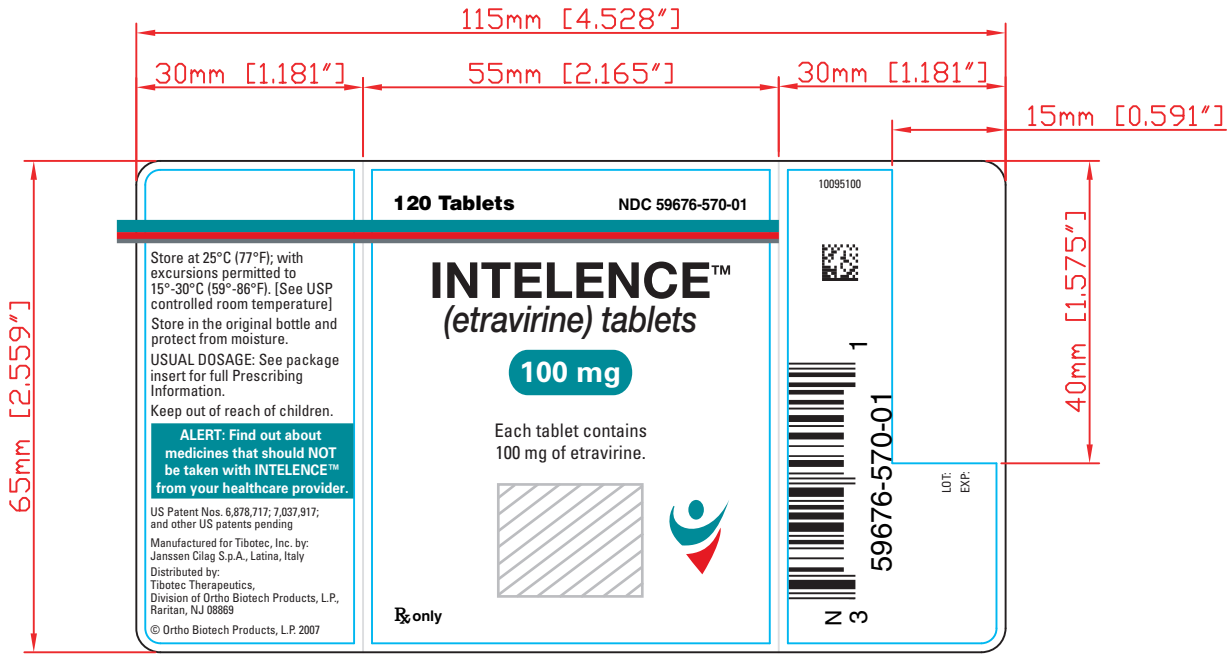
10095300



GPSG Global Pharmaceutical Supply Group

PRODUCT NAME	Intelence	COMPONENT TYPE	label
COMP. NUMBER	10095100	ARTWORK VERSION	6
SOFTWARE USED	Illustrator	VERS. CS	UPGRADE ❑
MODIFIED DATE	12/18/07	DESIGNER	Colleen Miller
Date/Comment:		TITLE BLOCK PROOFED	❑ NO ■ YES

COLORS USED IN FILE: BLACK, PMS 1797, PMS 321, PMS 431, PMS, LPI-1013, COATING

DIMENSIONS 115 mm x 65 mm

DWG # NA OUTPUT % 100%

SPEC # NA ePM Order # Number

Date/Comment: 06/20/07: V1: CR created label from TMC 125 Label MU. Named new # 10095100. Made changes per manuscript. Created new barcodes.
06/29/07: V2: KT added new line and relocated component code.
10/29/07: V3: KT changed product name to Helv Neu and other revs per TG markup.
10/29/07: V4: KT moved added # between 120 Tabs and NDC number and made product subhead ital per TG markup.
11/05/07: V5: KT replaced AC name with LPI-1013 in slug per TG markup.
12/19/07: V6: CM added "...from your healthcare provider." to the end of the Alert statement, adjusted text size to fit