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

* The expected increase in systemic exposure of etravirine when co-administered with either atazanavir/ritonavir (~100%) or lopinavir/ritonavir (~85%) as outlined in Table 3 is theoretical and based on comparing exposures of etravirine in drug-drug interaction studies with exposure in the pivotal Phase 3 trials (in which darunavir/ritonavir was part of the background regimen).

† The reference for etravirine exposure is the pharmacokinetic parameters of etravirine in the presence of darunavir/ritonavir.

Table 6: 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 CCR5 Antagonists						
Maraviroc	300 mg b.i.d.	14	↓	0.40 (0.28-0.57)	0.47 (0.38-0.58)	0.61 (0.53-0.71)
Maraviroc (when co-administered with darunavir/ ritonavir)*	150/600/100 mg b.i.d.	10	↑	1.77 (1.20-2.60)	3.10 (2.57-3.74)	5.27 (4.51-6.15)
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)
Digoxin	0.5 mg single dose	16	↑	1.19 (0.96-1.49)	1.18 (0.90-1.56)	N.A.
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
* compared to maraviroc 150 mg b.i.d.

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; the fusion inhibitor enfuvirtide; the integrase strand transfer inhibitor raltegravir and the CCR5 co-receptor antagonist maraviroc.

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 48 to the INTELENCE®-containing regimen were V179F, V179I, and Y181C 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/H/P, K103N/R, V106I/M, V108I, Y181I, Y188L, V189I, G190S/C, N348I 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, 34% of the baseline isolates had decreased susceptibility to etravirine (fold-change > 3) and 60%, 69%, and 78% of all baseline isolates were resistant to delavirdine, efavirenz, and nevirapine, respectively. Of subjects who received etravirine and were virologic failures in TMC125-C206 and TMC125-C216, 90%, 84%, and 96% of viral isolates obtained at the time of treatment failure were resistant to delavirdine, efavirenz, and nevirapine, respectively. Therefore, 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 L100I, E138A, I167V, V179D, V179F, Y181I, Y181V, or G190S was associated with a decreased virologic response to etravirine. Additional substitutions associated with a decreased virologic response to etravirine when in the presence of 3 or more additional 2008 IAS-USA defined NNRTI substitutions include A98G, K101H, K103R, V106I, V179T, and Y181C. 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. Overall, response rates to etravirine decreased as the number of baseline NNRTI substitutions increased (shown as the proportion of subjects achieving viral load < 50 plasma HIV RNA copies/mL at Week 48) (Table 7).

Table 7: Proportion of Subjects with < 50 HIV-1 RNA copies/mL at Week 48 by Baseline Number of IAS-USA-Defined NNRTI Substitutions in the Non-VF Excluded Population of the Pooled TMC125-C206 and TMC125-C216 Trials

# IAS-USA-Defined NNRTI substitutions*	Etravirine Arms N = 561	
	Re-Used/Not Used Enfuvirtide	De Novo Enfuvirtide
All ranges	61% (254/418)	76% (109/143)
0	68% (52/76)	95% (20/21)
1	67% (72/107)	77% (24/31)
2	64% (75/118)	86% (38/44)
3	55% (36/65)	62% (16/26)
≥ 4	37% (19/52)	52% (11/21)
	Placebo Arms N = 592	
All ranges	34% (147/435)	59% (93/157)

* 2008 IAS-USA defined substitutions = V90I, A98G, L100I, K101E/H/P, K103N, V106A/I/M, V108I, E138A, V179D/F/T, Y181C/I/V, Y188C/H/L, G190A/S, P225H, M230L

Response rates assessed by baseline etravirine phenotype are shown in Table 8. 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 8: Proportion of Subjects with < 50 HIV-1 RNA copies/mL at Week 48 by Baseline Phenotype and Enfuvirtide Use in the Pooled TMC125-C206 and TMC125-C216 Trials*

Etravirine Fold Change	Etravirine Arms N = 559		
	Re-Used/Not Used Enfuvirtide	De Novo Enfuvirtide	Clinical Response Range
All ranges	61% (253/416)	76% (109/143)	Overall Response
0 - 3	69% (188/274)	83% (75/90)	Higher than Overall Response
> 3 - 13	50% (39/78)	66% (25/38)	Lower than Overall Response
> 13	41% (26/64)	60% (9/15)	Lower than Overall Response
	Placebo Arms N = 583		
All ranges	34% (145/429)	60% (92/154)	

* Non-VF excluded analysis

The proportion of virologic responders (viral load < 50 HIV-1 RNA copies/mL) by the phenotypic susceptibility score (PSS) of the background therapy, including enfuvirtide, is shown in Table 9.

Table 9: Virologic Response (Viral Load < 50 HIV-1 RNA copies/mL) at Week 48 by Phenotypic Susceptibility Score in the Non-VF Excluded Population of TMC125-C206 and TMC125-C216 Trials (Pooled Analysis)

	INTELENCE® + BR N=559	Placebo + BR N=586
PSS*		
0	43% (40/93)	5% (5/95)
1	61% (125/206)	28% (64/226)
2	77% (114/149)	59% (97/165)
≥ 3	75% (83/111)	72% (72/100)

* The phenotypic susceptibility score (PSS) was defined as the total number of active antiretroviral drugs in the background therapy to which a subject's baseline viral isolate showed sensitivity in phenotypic resistance tests. Each drug in the background therapy was scored as a '1' or '0' based on whether the viral isolate was considered susceptible or resistant to that drug, respectively. 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® was not included in this calculation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to approximately 104 weeks. Daily doses of 50, 200 and 400 mg/kg were administered to mice and doses of 70, 200 and 600 mg/kg were administered to rats in the initial period of approximately 41-52 weeks. The high and middle doses were subsequently adjusted due to tolerability and reduced by 50% in mice and by 50-66% in rats to allow for completion of the studies. In the mouse study, statistically significant increases in the incidences of hepatocellular carcinoma and incidences of hepatocellular adenomas or carcinomas combined were observed in treated females. In the rat study, no statistically significant increases in tumor findings were observed in either sex. The relevance of these liver tumor findings in mice to humans is not known. Because of tolerability of the formulation in these rodent studies, maximum systemic drug exposures achieved at the doses tested were lower than those in humans at the clinical dose (400 mg/day), with animal vs. human AUC ratios being 0.6-fold (mice) and 0.2-0.7-fold (rats).

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 48-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 48 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 (0-8)

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%	12.6%
Median (range) Number of NNRTI RAMs*	2 (0-8)	2 (0-7)
Median Fold Change of the Virus for the Following NNRTIs:		
Delavirdine	27.3	26.1
Efavirenz	63.9	45.4
Etravirine	1.6	1.5
Nevirapine	74.3	74.0
Percentage of Subjects with Previous Use of a Fusion Inhibitor	39.6%	42.2%
Percentage of Subjects with a Phenotypic Sensitivity Score (PSS) for the background therapy ‡ of:		
0	17.0%	16.2%
1	36.5%	38.7%
2	26.9%	27.8%
≥ 3	19.7%	17.3%

RAMs = Resistance-Associated Mutations, BR=background regimen

FC = fold change in EC_{50}

*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

†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

‡ 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.

Efficacy at Week 48 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 48 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 48 Viral Load < 50 HIV-1 RNA copies/mL	359 (60%)	232 (38%)
Virologic Failures (VF) at Week 48 Viral Load ≥ 50 HIV-1 RNA copies/mL	123 (21%)	201 (33%)
Death	11 (2%)	19 (3%)
Discontinuations before Week 48:		
due to VF	58 (10%)	110 (18%)
due to Adverse Events	31 (5%)	14 (2%)
due to other reasons	17 (3%)	28 (5%)

BR=background regimen

At Week 48, 70.8% of INTELENCE®-treated subjects achieved HIV-1 RNA < 400 copies/mL as compared to 46.4% of placebo-treated subjects. The mean decrease in plasma HIV-1 RNA from baseline to Week 48 was –2.23 $\log_{10}$ copies/mL for INTELENCE®-treated subjects and –1.46 $\log_{10}$ copies/mL for placebo-treated subjects. The mean CD4+ cell count increase from baseline for INTELENCE®-treated subjects was 96 cells/mm^3 and 68 cells/mm^3 for placebo-treated subjects.

Of the study population who either re-used or did not use ENF, 57.4% of INTELENCE®-treated subjects and 31.7% of placebo-treated subjects achieved HIV-1 RNA < 50 copies/mL. Of the study population using ENF *de novo*, 67.3% of INTELENCE®-treated subjects and 57.2% of placebo-treated subjects achieved HIV-1 RNA < 50 copies/mL.

Treatment-emergent CDC category C events occurred in 4% of INTELENCE®-treated subjects and 8.4% of placebo-treated subjects.

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. 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.

Patients should be informed that severe and potentially life-threatening rash has been reported with INTELENCE®. Rash has been reported most commonly in the first 6 weeks of therapy. Patients should be advised to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking INTELENCE® and seek medical attention if they develop a rash associated with any of the following symptoms as it may be a sign of a more serious reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis or severe hypersensitivity: fever, generally ill feeling, extreme tiredness, muscle or joint aches, blisters, oral lesions, eye inflammation, facial swelling, swelling of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver problems (e.g., yellowing of your skin or whites of your eyes, dark or tea colored urine, pale colored stools/bowel movements, nausea, vomiting, loss of appetite, or pain, aching or sensitivity on your right side below your ribs). Patients should understand that if severe rash occurs, they will be closely monitored, laboratory tests will be ordered and appropriate therapy will be initiated.

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.

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tibotec

Manufactured for Tibotec, Inc. by:
Janssen Cilag S.p.A., Latina, Italy
Distributed by:
Tibotec Therapeutics, Division of Centocor 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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Issued November 2009

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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 NNRTI and other anti-HIV medicines and these medicines are not controlling their HIV infection.
- 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® can help:
  - 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).

* Registered trademark of Tibotec Pharmaceuticals

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

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®) digoxin (Lanoxin®) 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 (to treat inflammation or asthma)	dexamethasone (Decadron®)

Type of Drug	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. Call your doctor right away if you get a rash. Your doctor will decide if INTELENCE® must be stopped.

Other common side effects of INTELENCE® include tingling or pain in hands or feet and numbness.

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

tibotec
THERAPEUTICS

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

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Issued November 2009

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ISENTRESS (raltegravir) Tablets
Initial U.S. Approval: 2007

----------RECENT MAJOR CHANGES ----------

Indications And Usage (1)	07/2009
Dosage And Administration (2)	01/2009
Warnings And Precautions (5.2) - removal	07/2009

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

ISENTRESS® is a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI) indicated:

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients (1).

The safety and efficacy of ISENTRESS have not been established in pediatric patients (1).

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

- 400 mg administered orally, twice daily with or without food (2).
- During coadministration with rifampin, 800 mg twice daily (2).

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

Tablets: 400 mg (3).

----------CONTRAINDICATIONS ----------

None (4)

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

Monitor for Immune Reconstitution Syndrome (5.1).

---------- ADVERSE REACTIONS----------

- The most common adverse reactions of moderate to severe intensity (≥2%) which occurred at a higher rate than the comparator are insomnia, headache, nausea, asthenia and fatigue (6.1).
- Creatine kinase elevations were observed in subjects who received ISENTRESS. Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Coadministration of ISENTRESS with drugs that are strong inducers of UGT1A1 may result in reduced plasma concentrations of raltegravir (7.2).

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

Pregnancy:

- ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Physicians are encouraged to register pregnant women exposed to ISENTRESS by calling 1-800-258-4263 so that Merck can monitor maternal and fetal outcomes (8.1).

Nursing Mothers:

- Breast-feeding is not recommended while taking ISENTRESS (8.3).

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

Revised: 12/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the Full Prescribing Information are not listed.

1 INDICATIONS AND USAGE

ISENTRESS[1] is indicated in combination with other anti-retroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.

This indication is based on analyses of plasma HIV-1 RNA levels up through 48 weeks in three double-blind controlled studies of ISENTRESS. Two of these studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults and one was conducted in treatment-naïve adults.

The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response *[see Clinical Studies (14)]*.

The safety and efficacy of ISENTRESS have not been established in pediatric patients.

2 DOSAGE AND ADMINISTRATION

For the treatment of patients with HIV-1 infection, the dosage of ISENTRESS is 400 mg administered orally, twice daily with or without food. During coadministration with rifampin, the recommended dosage of ISENTRESS is 800 mg twice daily with or without food.

3 DOSAGE FORMS AND STRENGTHS

400 mg pink, oval-shaped, film-coated tablets with "227" on one side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Immune Reconstitution Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, *Mycobacterium* tuberculosis, or reactivation of varicella zoster virus), 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.

Treatment-Naïve Studies

The following safety assessment of ISENTRESS in treatment-naïve subjects is based on the randomized double-blind active controlled study of treatment-naïve subjects, STARTMRK (Protocol 021) with ISENTRESS 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 300 mg, (N=281) versus efavirenz (EFV) 600 mg at bedtime in combination with emtricitabine (+) tenofovir, (N=282). During double-blind treatment, the total follow-up for subjects receiving ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir was 247 patient-years and 241 patient-years for subjects receiving efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir.

In Protocol 021, the rate of discontinuation of therapy due to adverse reactions was 3% in subjects receiving ISENTRESS + emtricitabine (+) tenofovir and 6% in subjects receiving efavirenz + emtricitabine (+) tenofovir.

The clinical adverse drug reactions (ADRs) listed below were considered by investigators to be causally related to ISENTRESS + emtricitabine (+) tenofovir or efavirenz + emtricitabine (+) tenofovir. Clinical ADRs of moderate to severe intensity occurring in ≥2% of treatment-naïve subjects treated with ISENTRESS and occurring at a higher rate than efavirenz are presented in Table 1.

[1] Registered trademark of MERCK & CO., Inc.

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