12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Raltegravir is an HIV-1 antiviral drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

In a monotherapy study raltegravir (400 mg twice daily) demonstrated rapid antiviral activity with mean viral load reduction of 1.66 $\log_{10}$ copies/mL by Day 10.

In Protocol 005 and Protocols 018 and 019, antiviral responses were similar among subjects regardless of dose.

Effects on Electrocardiogram

In a randomized, placebo-controlled, crossover study, 31 healthy subjects were administered a single oral supratherapeutic dose of raltegravir 1600 mg and placebo. Peak raltegravir plasma concentrations were approximately 4-fold higher than the peak concentrations following a 400 mg dose. ISENTRESS did not appear to prolong the QTc interval for 12 hours postdose. After baseline and placebo adjustment, the maximum mean QTc change was -0.4 msec (1-sided 95% upper CI: 3.1 msec).

12.3 Pharmacokinetics

Absorption

Raltegravir is absorbed with a T_{max} of approximately 3 hours postdose in the fasted state. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1600 mg. Raltegravir C_{12hr} increases dose proportionally over the dose range of 100 to 800 mg and increases slightly less than dose proportionally over the dose range 100 mg to 1600 mg. With twice-daily dosing, pharmacokinetic steady state is achieved within approximately the first 2 days of dosing. There is little to no accumulation in AUC and C_{max}. The average accumulation ratio for C_{12hr} ranged from approximately 1.2 to 1.6.

The absolute bioavailability of raltegravir has not been established.

In subjects who received 400 mg twice daily alone, raltegravir drug exposures were characterized by a geometric mean $AUC_{0\text{-}12hr}$ of 14.3 μM•hr and C_{12hr} of 142 nM.

Considerable variability was observed in the pharmacokinetics of raltegravir: For observed C_{12hr} in Protocols 018 and 019, the coefficient of variation (CV) for inter-subject variability = 212% and the CV for intra-subject variability = 122%.

Effect of Food on Oral Absorption

ISENTRESS may be administered without regard to food. Administration of raltegravir following a high-fat meal increased raltegravir AUC by approximately 19%. A high-fat meal slowed the rate of absorption resulting in an approximately 34% decrease in C_{max}, an 8.5-fold increase in C_{12hr}, and a delay in T_{max} following a single 400 mg dose. The effect of consumption of a range of food types on steady-state pharmacokinetics is not known. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-1 positive subjects.

Distribution

Raltegravir is approximately 83% bound to human plasma protein over the concentration range of 2 to 10 μM.

Metabolism and Excretion

The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. Following administration of an oral dose of radiolabeled raltegravir, approximately 51 and 32% of the dose was excreted in feces and urine, respectively. In feces, only raltegravir was present, most of which is likely derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23% of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70% of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus, the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

Special Populations

Pediatric

The pharmacokinetics of raltegravir in pediatric patients has not been established.

Age

The effect of age on the pharmacokinetics of raltegravir was evaluated in the composite analysis. No dosage adjustment is necessary.

Race

The effect of race on the pharmacokinetics of raltegravir was evaluated in the composite analysis. No dosage adjustment is necessary.

Gender

A study of the pharmacokinetics of raltegravir was performed in young healthy males and females. Additionally, the effect of gender was evaluated in a composite analysis of pharmacokinetic data from 103 healthy subjects and 28 HIV-1 infected subjects receiving raltegravir monotherapy with fasted administration. No dosage adjustment is necessary.

Hepatic Impairment

Raltegravir is eliminated primarily by glucuronidation in the liver. A study of the pharmacokinetics of raltegravir was performed in subjects with moderate hepatic impairment. Additionally, hepatic impairment was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied.

Renal Impairment

Renal clearance of unchanged drug is a minor pathway of elimination. A study of the pharmacokinetics of raltegravir was performed in subjects with severe renal impairment. Additionally, renal impairment was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects. No dosage adjustment is necessary. Because the extent to which ISENTRESS may be dialyzable is unknown, dosing before a dialysis session should be avoided.

UGT1A1 Polymorphism

Data currently available are not sufficient to determine the impact of UGT1A1 polymorphism on raltegravir pharmacokinetics.

Drug Interactions *[see Drug Interactions (7)].*

Table 4: Effect of Other Agents on the Pharmacokinetics of Raltegravir

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
			n	C_{max}	AUC	C_{min}
atazanavir	400 mg daily	100 mg single dose	10	1.53 (1.11, 2.12)	1.72 (1.47, 2.02)	1.95 (1.30, 2.92)
atazanavir/ritonavir	300 mg/100 mg daily	400 mg twice daily	10	1.24 (0.87, 1.77)	1.41 (1.12, 1.78)	1.77 (1.39, 2.25)
efavirenz	600 mg daily	400 mg single dose	9	0.64 (0.41, 0.98)	0.64 (0.52, 0.80)	0.79 (0.49, 1.28)
rifampin	600 mg daily	400 mg single dose	9	0.62 (0.37, 1.04)	0.60 (0.39, 0.91)	0.39 (0.30, 0.51)
ritonavir	100 mg twice daily	400 mg single dose	10	0.76 (0.55, 1.04)	0.84 (0.70, 1.01)	0.99 (0.70, 1.40)
tenofovir	300 mg daily	400 mg twice daily	9	1.64 (1.16, 2.32)	1.49 (1.15, 1.94)	1.03 (0.73, 1.45)
tipranavir/ritonavir	500 mg/200 mg twice daily	400 mg twice daily	15 (14 for C_{min})	0.82 (0.46, 1.46)	0.76 (0.49, 1.19)	0.45 (0.31, 0.66)

12.4 Microbiology

Mechanism of Action

Raltegravir inhibits the catalytic activity of HIV-1 integrase, an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus. The provirus is required to direct the production of progeny virus, so inhibiting integration prevents propagation of the viral infection. Raltegravir did not significantly inhibit human phosphoryltransferases including DNA polymerases α, β, and γ.

Antiviral Activity in Cell Culture

Raltegravir at concentrations of 31 ± 20 nM resulted in 95% inhibition (EC_{95}) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir at concentrations of 6 to 50 nM resulted in 95% inhibition of viral spread in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates resistant to reverse transcriptase inhibitors and protease inhibitors. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (EC_{95} value = 6 nM). Additive to synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine); protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir); or the entry inhibitor enfuvirtide.

Resistance

The mutations observed in the HIV-1 integrase coding sequence that contributed to raltegravir resistance (evolved either in cell culture or in subjects treated with raltegravir) generally included an amino acid substitution at either Q148 (changed to H, K, or R) or N155 (changed to H) plus one or more additional substitutions (i.e., L74M/R, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226D/F/H, S230R and D232N). Amino acid substitution at Y143C/H/R is another pathway to raltegravir resistance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term (2-year) carcinogenicity studies of raltegravir in rodents are ongoing.

No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage and *in vitro* and *in vivo* chromosomal aberration studies.

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in a 3-fold exposure above the exposure at the recommended human dose.

14 CLINICAL STUDIES

Description of Clinical Studies

The evidence of efficacy of ISENTRESS is based on the analyses of 24-week data from 2 ongoing, randomized, double-blind, placebo-controlled trials, BENCHMRK 1 and BENCHMRK 2 (Protocols 018 and 019), in antiretroviral treatment-experienced HIV-1 infected adult subjects. These efficacy results were supported by the 48-week analysis of a randomized, double-blind, controlled, dose-ranging trial, Protocol 005, in antiretroviral treatment-experienced HIV-1 infected adult subjects.

Treatment-Experienced Subjects

BENCHMRK 1 and BENCHMRK 2 are Phase III studies to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg twice daily in combination with an optimized background therapy (OBT), versus OBT alone, in HIV-infected subjects, 16 years or older, with documented resistance to at least 1 drug in each of 3 Classes (NNRTIs, NRTIs, PIs) of antiretroviral therapies. Randomization was stratified by degree of resistance to PI (1PI vs. >1PI) and the use of enfuvirtide in the OBT. Prior to randomization, OBT was selected by the investigator based on genotypic/phenotypic resistance testing and prior ART history.

Table 5 shows the demographic characteristics of subjects in the ISENTRESS 400 mg twice daily arm and subjects in the placebo arm.

Table 5: Baseline Characteristics

BENCHMRK 1 and 2 Pooled	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Gender n (%)		
Male	405 (87.7)	210 (88.6)
Female	57 (12.3)	27 (11.4)
Race n (%)		
White	301 (65.2)	173 (73.0)
Black	66 (14.3)	26 (11.0)
Asian	16 (3.5)	6 (2.5)
Hispanic	53 (11.5)	19 (8.0)
Others	26 (5.6)	13 (5.5)
Age (years)		
Median (min, max)	45.0 (16 to 74)	45.0 (17 to 70)
CD4+ Cell Count		
Median (min, max), cells/mm^3	119 (1 to 792)	123 (0 to 759)
≤50 cells/mm^3, n (%)	146 (31.6)	78 (32.9)
>50 and ≤200 cells/mm^3, n (%)	173 (37.4)	85 (35.9)
Plasma HIV-1 RNA		
Median (min, max), log_{10} copies/mL	4.8 (2 to 6)	4.7 (2 to 6)
>100,000 copies/mL, n (%)	164 (35.5)	78 (32.9)
History of AIDS n (%)		
Yes	426 (92.2)	216 (91.1)
Prior Use of ART, Median (1st Quartile, 3rd Quartile)		
Years of ART Use	10.1 (7.4 to 12.1)	10.2 (7.9 to 12.4)
Number of ART	12.0 (9 to 15)	12.0 (9 to 14)
Hepatitis Co-infection* n (%)		
No Hepatitis B or C virus	385 (83.3)	201 (84.8)
Hepatitis B virus only	36 (7.8)	7 (3.0)
Hepatitis C virus only	37 (8.0)	27 (11.4)
Co-infection of Hepatitis B and C virus	4 (0.9)	2 (0.8)
Stratum n (%)		
Enfuvirtide in OBT	175 (37.9)	89 (37.6)
Resistant to ≥2 PI	447 (96.8)	226 (95.4)

*Hepatitis B virus surface antigen positive or hepatitis C virus antibody positive.

Table 6 compares the characteristics of optimized background therapy at baseline in the ISENTRESS 400 mg twice daily arm and subjects in the control arm.

Table 6: Characteristics of Optimized Background Therapy at Baseline

BENCHMRK 1 and 2 Pooled	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Number of ARTs in OBT		
Median (min, max)	4.0 (1 to 7)	4.0 (2 to 7)
Number of Active PI in OBT by Phenotypic Resistance Test*		
0	166 (35.9)	97 (40.9)
1 or more	278 (60.2)	137 (57.8)

Phenotypic Sensitivity Score (PSS)†		
0	67 (14.5)	44 (18.6)
1	145 (31.4)	71 (30.0)
2	142 (30.7)	66 (27.8)
3 or more	85 (18.4)	48 (20.3)
Genotypic Sensitivity Score (GSS)†		
0	115 (24.9)	65 (27.4)
1	178 (38.5)	96 (40.5)
2	111 (24.0)	49 (20.7)
3 or more	51 (11.0)	23 (9.7)

*Darunavir use in OBT in darunavir naïve subjects was counted as one active PI.

†The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve subjects was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve subjects was counted as one active drug in OBT.

Week 24 outcomes for subjects on the recommended dose of ISENTRESS 400 mg twice daily from the pooled studies BENCHMRK 1 and 2 are shown in Table 7. The efficacy responses were evaluated based upon the 436 subjects from the pooled studies BENCHMRK 1 and 2 who had completed 24 weeks of treatment or discontinued earlier. All other outcomes were based upon the total 699 subjects who were randomized and treated.

Table 7: Outcomes by Treatment Group through Week 24

BENCHMRK 1 and 2 Pooled n (%)	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Outcome at Week 24	n (%)	n (%)
Subjects with Week 24 data	286	150
Subjects with HIV-1 RNA less than 400 copies/mL*	216 (75.5)	59 (39.3)
Subjects with HIV-1 RNA less than 50 copies/mL*	179 (62.6)	50 (33.3)
Virologic Failure (confirmed)†,‡	74 (16.0)	121 (51.1)
Non-responder†,‡	13 (2.8)	78 (32.9)
Rebound†,‡	61 (13.2)	43 (18.1)
Death‡,§	6 (1.3)	3 (1.3)
Discontinuation due to adverse experiences‡,§	9 (1.9)	5 (2.1)
Discontinuation due to other reasons‡,§,¶	6 (1.3)	1 (0.4)

*Based upon the 436 subjects with Week 24 data

†Virologic failure: defined as non-responders who did not achieve >1.0 $\log_{10}$ HIV-1 RNA reduction and <400 HIV-1 RNA copies/mL by Week 16, or viral rebound, which was defined as: (a) HIV-1 RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV-1 RNA <400 copies/mL, or (b) >1.0 $\log_{10}$ increase in HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

‡Based upon the total 699 subjects randomized and treated, not all subjects complete to Week 24

§Includes available data beyond Week 24

¶Includes loss to follow-up, subjects withdrew consent, noncompliance, protocol violation and other reasons.

The mean changes in plasma HIV-1 RNA from baseline were -1.85 $\log_{10}$ copies/mL in the ISENTRESS 400 mg twice daily arm and -0.84 $\log_{10}$ copies/mL for the control arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving ISENTRESS 400 mg twice daily (89 cells/mm^3) than in the control arm (35 cells/mm^3).

Virologic responses at Week 24 by baseline genotypic and phenotypic sensitivity score are shown in Table 8.

Table 8: Virologic Response at Week 24 by Baseline Genotypic/Phenotypic Sensitivity Score

BENCHMRK 1 and 2 Pooled (Noncompleters as failures approach)	Percent with HIV RNA <400 copies/mL at Week 24				Percent with HIV RNA <50 copies/mL at Week 24			
	n	ISENTRESS 400 mg Twice Daily + OBT (N = 286)	n	Placebo + OBT (N = 150)	n	ISENTRESS 400 mg Twice Daily + OBT (N = 286)	n	Placebo + OBT (N = 150)
Phenotypic Sensitivity Score (PSS)*								
0	44	50	26	4	44	41	26	4
1	89	75	50	34	89	66	50	30
2	95	86	36	42	95	70	36	36
3 or more	48	73	33	67	48	56	33	55
Genotypic Sensitivity Score (GSS)*								
0	69	54	40	8	69	41	40	5
1	115	82	64	36	115	70	64	33
2	67	88	27	78	67	75	27	63
3 or more	30	70	18	61	30	53	18	50

*The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve subjects was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve subjects was counted as one active drug in OBT.

16 HOW SUPPLIED/STORAGE AND HANDLING

ISENTRESS tablets 400 mg are pink, oval-shaped, film-coated tablets with "227" on one side. They are supplied as follows:

NDC 0006-0227-61 unit-of-use bottles of 60.

No. 3894

Storage and Handling

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling].

Patients should be informed that ISENTRESS is not a cure for HIV infection or AIDS. They should also be told that people taking ISENTRESS may still get infections or other conditions common in people with HIV (opportunistic infections). In addition, patients should be told that the long-term effects of ISENTRESS are not known at this time. Patients should also be told that it is very important that they stay under a physician's care during treatment with ISENTRESS.

Patients should be informed that ISENTRESS does not reduce the chance 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 or other barrier methods 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.

Physicians should instruct their patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not take two tablets of ISENTRESS at the same time.

Physicians should instruct their patients to read the Patient Package Insert before starting ISENTRESS therapy and to reread each time the prescription is renewed. Patients should be instructed

to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Manufactured and Distributed by:
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Printed in USA

9795100

U.S. Patent Nos. US 7,169,780

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

----------RECENT MAJOR CHANGES----------
- Warnings and Precautions
  - Severe Skin and Hypersensitivity Reactions (5.1) 08/2009

----------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, potentially life threatening and fatal skin reactions have been reported. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction, toxic epidermal necrolysis and erythema multiforme. Immediately discontinue treatment if severe hypersensitivity, severe rash or rash with systemic symptoms or liver transaminase elevations develops and monitor clinical status, including liver transaminases closely. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse drug reactions of moderate to severe intensity (≥ 2%) which occurred at a higher rate than placebo are rash and peripheral neuropathy. (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 CYP3A, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of etravirine. (7)

Co-administration of INTELENCE® with drugs that are substrates of CYP3A, CYP2C9, and/or CYP2C19 or are transported by P-glycoprotein may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s). (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.

Revised: 02/2010

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 48 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 and Hypersensitivity Reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. In Phase 3 clinical trials, Grade 3 and 4 rashes were reported in 1.3% of subjects receiving INTELENCE® compared to 0.2% of placebo subjects. A total of 2.2% of HIV-1-infected subjects receiving INTELENCE® discontinued from Phase 3 trials due to rash [*see Adverse Reactions (6)*]. Rash occurred most commonly during the first 6 weeks of therapy.

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

* Registered trademark of Tibotec Pharmaceuticals

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

The following adverse reactions are described in greater detail in other sections:

- Severe skin and hypersensitivity reactions [*see Warnings and Precautions (5.1)*].

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 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 52.3 and 51.0 weeks, respectively. Discontinuations due to adverse drug reactions (ADRs) were 5.2% in the INTELENCE® arm and 2.6% in the placebo arm.

The most frequently reported ADR at least Grade 2 in severity was rash (10.0%). Stevens-Johnson syndrome, drug hypersensitivity reaction and erythema multiforme were reported in $< 0.1\%$ of subjects during clinical development with INTELENCE® [*see Warnings and Precautions (5.1)*]. A total of 2.2% 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. The incidence of rash was higher in women compared to men in the INTELENCE® arm in the Phase 3 trials. 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

Clinical ADRs of moderate intensity or greater (≥ Grade 2) and reported in ≥ 2% of subjects treated with INTELENCE® and occurring at a higher rate compared to placebo (excess of 1%) are presented in Table 1. Laboratory abnormalities considered ADRs are included in Table 2.

Table 1: Treatment-Emergent Adverse Reactions* of at least Moderate Intensity† (Grades 2-4) in ≥ 2% of Adult Subjects in the INTELENCE® Treatment Groups and at a higher rate compared to placebo (excess of 1%)

System Organ Class, Preferred Term, %	Pooled TMC125-C206 and TMC125-C216 Trials	
	INTELENCE® + BR N=599	Placebo + BR N=604
Nervous System Disorders		
Peripheral neuropathy	4%	2%
Skin and Subcutaneous Tissue Disorders		
Rash	10%	3%

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: hemolytic anemia
Hepatobiliary Disorders: hepatic failure, hepatomegaly, cytolytic hepatitis, hepatic steatosis, hepatitis
Immune System Disorders: drug hypersensitivity, immune reconstitution syndrome
Metabolism and Nutrition Disorders: diabetes mellitus, anorexia, dyslipidemia
Nervous System Disorders: paraesthesia, somnolence, convulsion, hypoesthesia, amnesia, syncope, disturbance in attention, hypersomnia, tremor
Psychiatric Disorders: anxiety, sleep disorders, abnormal dreams, confusional state, disorientation, nervousness, nightmares
Renal and Urinary Disorders: acute renal failure
Reproductive System and Breast Disorders: gynecomastia
Respiratory, Thoracic and Mediastinal Disorders: exertional dyspnea, bronchospasm
Skin and Subcutaneous Tissue Disorders: night sweats, lipohypertrophy, prurigo, hyperhidrosis, dry skin, 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 2.

Table 2: 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	7%	8%
Grade 3	> 2-5 x ULN	7%	8%
Grade 4	> 5 x ULN	2%	1%
Lipase			
Grade 2	> 1.5-3 x ULN	4%	6%
Grade 3	> 3-5 x ULN	2%	2%
Grade 4	> 5xULN	1%	< 1%
Creatinine			
Grade 2	> 1.4-1.8 x ULN	6%	5%
Grade 3	> 1.9-3.4 x ULN	2%	1%
Grade 4	> 3.4 x ULN	0%	< 1%
HEMATOLOGY			
Decreased hemoglobin			
Grade 2	90-99 g/L	2%	4%
Grade 3	70-89 g/L	< 1%	< 1%
Grade 4	< 70 g/L	< 1%	< 1%
White blood cell count			
Grade 2	1,500-1,999/mm^3	2%	3%
Grade 3	1,000-1,499/mm^3	1%	4%
Grade 4	< 1,000/mm^3	1%	< 1%
Neutrophils			
Grade 2	750-999/mm^3	5%	6%
Grade 3	500-749/mm^3	4%	4%
Grade 4	< 500/mm^3	2%	3%
Platelet count			
Grade 2	50,000-99,999/mm^3	3%	5%
Grade 3	25,000-49,999/mm^3	1%	1%
Grade 4	< 25,000/mm^3	< 1%	< 1%
LIPIDS AND GLUCOSE			
Total cholesterol			
Grade 2	> 6.20-7.77 mmol/L 240-300 mg/dL	20%	17%
Grade 3	> 7.77 mmol/L > 300 mg/dL	8%	5%
Low density lipoprotein			
Grade 2	4.13-4.9 mmol/L 160-190 mg/dL	13%	12%
Grade 3	> 4.9 mmol/L > 190 mg/dL	7%	7%
Triglycerides			

Grade 2	5.65-8.48 mmol/L 500 –750 mg/dL	9%	7%
Grade 3	8.49-13.56 mmol/L 751 - 1200 mg/dL	6%	4%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	4%	2%
Elevated glucose levels			
Grade 2	6.95-13.88 mmol/L 161-250 mg/dL	15%	13%
Grade 3	13.89-27.75 mmol/L 251 – 500 mg/dL	4%	2%
Grade 4	> 27.75 mmol/L > 500 mg/dL	0%	< 1%
HEPATIC PARAMETERS			
Alanine amino transferase			
Grade 2	2.6-5 x ULN	6%	5%
Grade 3	5.1-10 x ULN	3%	2%
Grade 4	> 10 x ULN	1%	< 1%
Aspartate amino transferase			
Grade 2	2.6-5 x ULN	6%	8%
Grade 3	5.1-10 x ULN	3%	2%
Grade 4	> 10 x ULN	< 1%	< 1%
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, 139 subjects (12.3%) with chronic hepatitis B and/or hepatitis C virus co-infection out of 1129 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 27.8%, 25.0% and 7.1% respectively, of INTELENCE®-treated co-infected subjects as compared to 6.7%, 7.5% and 1.8% 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.

6.2 Postmarketing Experience

The following events have been identified during postmarketing use of INTELENCE®. Because these events are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Fatal cases of toxic epidermal necrolysis have been reported. Severe hypersensitivity reactions including cases of hepatic failure have been reported [*see Warnings and Precautions (5.1)*].

7 DRUG INTERACTIONS

Etravirine is a substrate of CYP3A, CYP2C9, and CYP2C19. Therefore, co-administration of INTELENCE® with drugs that induce or inhibit CYP3A, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse reaction profile of INTELENCE® (see Table 3). [*See also Clinical Pharmacology (12.3)*.]

Etravirine is an inducer of CYP3A and inhibitor of CYP2C9, CYP2C19 and P-glycoprotein. Therefore, co-administration of drugs that are substrates of CYP3A, CYP2C9 and CYP2C19 or are transported by P-glycoprotein with INTELENCE® may alter the therapeutic effect or adverse reaction profile of the co-administered drug(s) (see Table 3). *[See also Clinical Pharmacology (12.3)*.]

Table 3 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 3.

Table 3: 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)		
atazanavir* (without ritonavir)	↓ atazanavir	Concomitant use of INTELENCE® with atazanavir without low-dose ritonavir may cause a significant alteration in the plasma concentration of atazanavir. INTELENCE® should not be co-administered with atazanavir without low-dose ritonavir.
atazanavir/ritonavir*	↓ atazanavir ↑ etravirine	Concomitant use of INTELENCE® with atazanavir/ritonavir may cause a significant decrease in atazanavir C_{min} 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 higher than the mean systemic exposure of etravirine observed in the Phase 3 trials after co-administration of INTELENCE® and darunavir/ritonavir (as part of the background regimen). INTELENCE® and atazanavir/ritonavir should not be co-administered.
darunavir/ritonavir*	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced 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 dose adjustments.
fosamprenavir (without ritonavir)	↑ amprenavir	Concomitant use of INTELENCE® with fosamprenavir without low-dose ritonavir may cause a significant alteration in the plasma concentration of amprenavir. INTELENCE® should not be co-administered with fosamprenavir without low-dose ritonavir.
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.

indinavir* (without ritonavir)	↓ indinavir	Concomitant use of INTELENCE® with indinavir without low-dose ritonavir may cause a significant alteration in the plasma concentration of indinavir. INTELENCE® should not be co-administered with indinavir without low-dose ritonavir.
lopinavir/ritonavir*	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced after co-administration of INTELENCE® with lopinavir/ritonavir (tablet). Because the reduction in the mean systemic exposures of etravirine in the presence of lopinavir/ritonavir is similar to the reduction in mean systemic exposures of etravirine in the presence of darunavir/ritonavir, INTELENCE® and lopinavir/ritonavir can be co-administered without dose adjustments.
nelfinavir (without ritonavir)	↑ nelfinavir	Concomitant use of INTELENCE® with nelfinavir without low-dose ritonavir may cause a significant alteration in the plasma concentration of nelfinavir. INTELENCE® should not be co-administered with nelfinavir 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.
saquinavir/ritonavir*	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced 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 dose adjustments.
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.
CCR5 Antagonists		
maraviroc*	↔ etravirine ↓ maraviroc	When INTELENCE® is co-administered with maraviroc in the absence of a potent CYP3A inhibitor (e.g., ritonavir boosted protease inhibitor), the recommended dose of maraviroc is 600 mg b.i.d. No dose adjustment of INTELENCE® is needed.
maraviroc/darunavir/ ritonavir*†	↔ etravirine ↑ maraviroc	When INTELENCE® is co-administered with maraviroc in the presence of a potent CYP3A inhibitor (e.g., ritonavir boosted protease inhibitor), the recommended dose of maraviroc is 150 mg b.i.d. No dose adjustment of INTELENCE® is needed.
Other Agents		
Antiarrhythmics: digoxin*	↔ etravirine ↑ digoxin	For patients who are initiating a combination of INTELENCE® and digoxin, the lowest dose of digoxin should initially be prescribed. For patients on a stable digoxin regimen and initiating INTELENCE®, no dose adjustment of either INTELENCE® or digoxin is needed. The serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.
amiodarone,	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-

bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine		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*, voriconazole*	↑ etravirine ↔ fluconazole ↑ voriconazole	Co-administration of etravirine and fluconazole significantly increased etravirine exposures. The amount of safety data at these increased etravirine exposures is limited, therefore, etravirine and fluconazole should be co-administered with caution. No dose adjustment of INTELENCE® or fluconazole is needed. Co-administration of etravirine and voriconazole significantly increased etravirine exposures. The amount of safety data at these increased etravirine exposures is limited, therefore, etravirine and voriconazole should be co-administered with caution. No dose adjustment of INTELENCE® or voriconazole is needed.
Antifungals: itraconazole, ketoconazole, posaconazole	↑ etravirine ↓ itraconazole ↓ ketoconazole ↔ posaconazole	Posaconazole, a potent inhibitor of CYP3A4, 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®. Dose adjustments for itraconazole, ketoconazole or posaconazole may be necessary depending on the 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*-	If INTELENCE® is NOT co-administered with a protease inhibitor/ritonavir, then rifabutin at a dose of 300 mg q.d. is recommended.

	desacetylrifabutin	If INTELENCE® is co-administered with darunavir/ritonavir, lopinavir/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 CYP3A 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 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 CYP3A 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: cyclosporine, sirolimus, tacrolimus	↓ immunosuppressant	INTELENCE® and systemic immunosuppressants should be co-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.
Platelet Aggregation Inhibitors: clopidogrel	↓ clopidogrel (active) metabolite	Activation of clopidogrel to its active metabolite may be decreased when clopidogrel is co-administered with INTELENCE®. Alternatives to clopidogrel should be considered.

↑ = increase, ↓ = decrease, ↔ = no change
* The interaction between INTELENCE® and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.
† The reference for etravirine exposure is the pharmacokinetic parameters of etravirine in the presence of

darunavir/ritonavir

In addition to the drugs included in Table 3, 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 (ENF), 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.

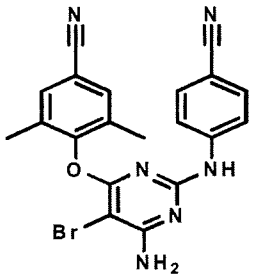
10 OVERDOSAGE

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.