NAME OF THE MEDICINAL PRODUCT
INTELENCE™ 100 mg tablets
INTELENCE™ 200 mg tablets

DOSAGE FORMS AND STRENGTHS
100 mg tablet: Contains 100mg of etravirine. White to off-white, oval tablet, debossed with "T125" on one side and "100" on the other side. Contains 160mg lactose.
200 mg tablet: Contains 200mg of etravirine. White to off-white, biconvex, oblong tablet debossed with "T200" on one side

For excipients, see '*List of Excipients'.*

CLINICAL INFORMATION
Indications
INTELENCE™, in combination with other antiretroviral medicinal products, 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 randomised, 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 Pharmacodynamic Properties).
- The risks and benefits of INTELENCE™ have not been established in pediatric patients or in treatment naïve adult patients.

Dosage and Administration
INTELENCE™ must always be given in combination with other antiretroviral medicinal products.

Adults
The recommended dose of INTELENCE™ is 200 mg (one 200mg tablet or two 100 mg tablets) taken orally twice daily (b.i.d.), following a meal (see *Pharmacokinetic Properties*). 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 the tablets are dispersed, patients should stir the dispersion well, and drink it immediately. The glass should be rinsed with water several times, and each rinse completely swallowed to ensure the entire dose is consumed.

Children (less than 12 years of age) and adolescents (12 to 17 years of age)
Treatment with INTELENCE™ is not recommended in children and adolescents. The safety and efficacy of INTELENCE™ in these populations are under investigation (see *Pharmacokinetic Properties*).

Elderly
Limited information is available in this population (see *Warnings and Precautions* and *Pharmacokinetic Properties*).

Pregnancy
No dose adjustment is required during pregnancy and postpartum. Given the increased etravirine exposure during pregnancy, caution should be applied for those pregnant patients that require concomitant medications or have comorbidities that may further increase etravirine exposure.

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). The pharmacokinetics of INTELENCE™ have not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see *Warnings and Precautions* and *Pharmacokinetic Properties*).

Renal impairment
No dose adjustment is required in patients with renal impairment (see *Warnings and Precautions* and *Pharmacokinetic Properties*).

Missed doses
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.

Contraindications
Hypersensitivity to etravirine or to any of the excipients.

Warnings and Precautions
Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.

Clinical studies are ongoing in HIV-1 infected children and adolescents (between the ages of 6 and 17 years, inclusive).

Severe skin and hypersensitivity reactions
Severe, potentially life-threatening, and fatal skin reactions have been reported with INTELENCE™; Stevens-Johnson Syndrome and toxic epidermal necrolysis have been rarely (< 0.1%) reported. Hypersensitivity reactions including DRESS (Drug Rash with

Eosinophilia and Systemic Symptoms) have also been reported and were characterized by rash, constitutional findings, and infrequently organ dysfunction, including hepatic failure (see *Adverse Reactions*).

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, hepatitis, eosinophilia). 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.

Rash

Rash has been reported with INTELENCE™. Most frequently, rash was mild to moderate, occurred in the second week of therapy and was infrequent after week 4. Rash was mostly self-limiting and generally resolved within 1-2 weeks on continued therapy. The incidence of rash was higher in females (see Undesirable Effects).

Elderly

Experience in geriatric patients is limited: In the Phase III trials, 6 patients aged 65 years or older and 53 patients aged 56-64 years received INTELENCE™. The type and incidence of adverse events in patients > 55 years of age were similar to the ones in younger patients (see *Adverse Reactions* and *Pharmacokinetic Properties*).

Patients with coexisting conditions

Liver disease

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). The pharmacokinetics of INTELENCE™ have not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see *Dosage and Administration* and *Pharmacokinetic Properties*).

Renal disease

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 special precautions or dose adjustments are required in patients with renal impairment. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see *Dosage and Administration* and *Pharmacokinetic Properties*).

Fat redistribution

Combination antiretroviral therapy (CART) has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesized. A higher risk of lipodystrophy has been associated with individual factors such as older age and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution (see *Adverse Reactions*).

Immune Reconstitution Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary (see *Adverse Reactions*). Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment (see *Adverse Reactions*).

Interactions with medicinal products

For information on interactions with medicinal products. (see *Interactions*).

Interactions

Medicinal products that affect etravirine exposure

Etravirine is metabolised by cytochrome P450 (CYP) 3A, CYP2C9 and CYP2C19 followed by glucuronidation of the metabolites by uridine diphosphate glucuronosyl transferase (UDPGT). Medicinal products that induce CYP3A, CYP2C9, or CYP2C19 may increase the clearance of etravirine resulting in lowered plasma concentrations of etravirine. Co-administration of INTELENCE™ and medicinal products that inhibit CYP3A, CYP2C9, or CYP2C19 may decrease the clearance of etravirine and may result in increased plasma concentrations of etravirine.

Medicinal products that are affected by the use of etravirine

Etravirine is a weak inducer of CYP3A. Co-administration of INTELENCE™ with medicinal products primarily metabolised by CYP3A may result in decreased plasma concentrations of such medicinal products, which could decrease or shorten their therapeutic effects. Etravirine is a weak inhibitor of CYP2C9 and CYP2C19. Etravirine is also a weak inhibitor of P-glycoprotein but not a substrate. Co-administration with medicinal products primarily metabolised by CYP2C9 or CYP2C19 or transported by P-glycoprotein may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect or adverse events profile.
Known and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in the tables below. The tables are not all-inclusive.

Interaction table

Interactions between etravirine and co-administered medicinal products are listed in the tables below (increase is indicated as "↑", decrease as "↓", no change as "↔", not done as "ND", once daily as "q.d.", once daily in the morning as "q.a.m." and twice daily as "b.i.d."). The tables are not all-inclusive.

Drug interactions –etravirine co-administered with antiretroviral medicinal products

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Medicinal Product Assessed	AUC	C_{min}
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				

NNRTIs (e.g., efavirenz, nevirapine, delavirdine, rilpivirine)	It is not recommended to co-administer INTELENCE™ with other NNRTIs.			
Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)				
didanosine	400 mg q.d.	didanosine	↔	ND
		etravirine	↔	↔
	The combination of INTELENCE™ and didanosine can be used without dose adjustments. As didanosine is administered on an empty stomach, didanosine should be administered one hour before or two hours after INTELENCE™ (which should be administered following a meal).			
tenofovir disoproxil fumarate	300 mg q.d.	tenofovir	↔	↑ 19%
		etravirine	↓ 19%	↓ 18%
	The combination of INTELENCE™ and tenofovir disoproxil fumarate can be used without dose adjustments.			
other NRTIs	Based on the primarily renal elimination route for other NRTIs (e.g., abacavir, emtricitabine, lamivudine, stavudine and zidovudine), no drug interactions are expected between these medicinal products and INTELENCE™.			
HIV Protease Inhibitors (PIs)—Unboosted (i.e., without co-administration of low dose ritonavir)				
atazanavir, unboosted	400 mg q.d.	atazanavir	↓ 17%	↓ 47%
		etravirine	↑ 50%	↑ 58%
	It is not recommended to co-administer unboosted atazanavir and INTELENCE™.			
ritonavir	Concomitant use of INTELENCE™ with full-dose ritonavir (600 mg b.i.d.) may cause a significant decrease in the plasma concentrations of etravirine. This may result in loss of therapeutic effect of INTELENCE™. It is not recommended to co-administer full-dose ritonavir (600 mg b.i.d.) with INTELENCE™.			
nelfinavir	Concomitant use of INTELENCE™ with nelfinavir may cause an increase in the plasma concentrations of nelfinavir.			
fosamprenavir, unboosted	Concomitant use of INTELENCE™ with unboosted fosamprenavir may cause an increase in the plasma concentrations of amprenavir.			
other unboosted PIs	It is not recommended to co-administer INTELENCE™ with other unboosted PIs (including indinavir and saquinavir).			
HIV PIs—Boosted (with low dose ritonavir)				
tipranavir/ritonavir	500/200 mg b.i.d.	tipranavir	↑ 18%	↑ 24%
		etravirine	↓ 76%	↓ 82%
	It is not recommended to co-administer tipranavir/ritonavir and INTELENCE™.			
fosamprenavir/ ritonavir	700/100 mg b.i.d.	amprenavir	↑ 69%	↑ 77%
		etravirine	↔	↔

	Amprenavir and fosamprenavir/ritonavir may require dose adjustment when co-administered with INTELENCE™.			
atazanavir/ritonavir	300/100 mg q.d.	atazanavir	↓ 14%	↓ 38%
		etravirine	↑ 30%	↑ 26%
	The combination of INTELENCE™ and atazanavir/ritonavir can be used without dose adjustments.			
darunavir/ritonavir	600/100 mg b.i.d.	darunavir	↔	↔
		etravirine	↓ 37%	↓ 49%
	The combination of INTELENCE™ and darunavir/ritonavir can be used without dose adjustments.			
lopinavir/ritonavir (soft-gel capsule)	400/100 mg b.i.d.	lopinavir	↓ 20%	↓ 8%
		etravirine	↑ 17%	↑ 23%
	The combination of INTELENCE™ and lopinavir/ritonavir (soft-gel capsule) can be used without dose adjustments.			
lopinavir/ritonavir (melt extrusion tablet)	400/100 mg b.i.d.	lopinavir	↔	↓ 20%
		etravirine	↓ 35%	↓ 45%
	The combination of INTELENCE™ and lopinavir/ritonavir (melt extrusion tablet) can be used without dose adjustments.			
saquinavir/ritonavir (soft-gel capsule)	1000/100 mg b.i.d.	saquinavir	↔	↓ 20%
		etravirine	↓ 33%	↓ 29%
	The combination of INTELENCE™ and saquinavir/ritonavir can be used without dose adjustments.			
Dual Boosted HIV PI				
lopinavir/saquinavir/ ritonavir	400/800 mg -1000/100 mg b.i.d.	lopinavir	↓ 18%	↓ 24%
		saquinavir	↓ 13%	↓ 13%
		etravirine	↔	↔
	The combination of INTELENCE™ and lopinavir/saquinavir/ritonavir can be used without dose adjustments.			
CCR5 Antagonists				
maraviroc	300 mg b.i.d.	maraviroc	↓ 53%	↓ 39%
		etravirine	↔	↔
	Concomitant use of INTELENCE™ with maraviroc may cause a significant decrease in the plasma concentration of maraviroc. When INTELENCE™ is co-administered with maraviroc in the absence of a potent CYP3A inhibitor (e.g., a boosted PI), the recommended dose of maraviroc is 600 mg b.i.d. No dose adjustment for INTELENCE™ is needed.			
maraviroc/darunavir/ ritonavir	150/600/100 mg b.i.d.	maraviroc	↑ 3.1-fold*	↑ 5.3-fold*
		etravirine	↔	↔
	When INTELENCE™ is co-administered with maraviroc in the presence of a potent CYP3A inhibitor (e.g., a boosted PI), the recommended dose of maraviroc is 150mg b.i.d. No dose adjustment for INTELENCE™ is needed. *compared to maraviroc 150 mg b.i.d.			
Fusion Inhibitor				
enfuvirtide	90 mg b.i.d.	enfuvirtide	ND	ND
		etravirine*	↔	↔
	No interaction is expected for either INTELENCE™ or enfuvirtide when co-administered. * based on population pharmacokinetic analysis			
Integrase Strand Transfer Inhibitors				

dolutegravir	50 mg q.d.	dolutegravir	↓ 71%	↓ 88%
		etravirine	↔	↔
dolutegravir/darunavir /ritonavir	50 mg q.d. + 600/100 mg b.i.d.	dolutegravir	↓ 25%	↓ 37%
		etravirine	↔	↔
dolutegravir/lopinavir /ritonavir	50 mg q.d. + 400/100 mg b.i.d.	dolutegravir	↔	↑ 28%
		etravirine	↔	↔
	Etravirine significantly reduced plasma concentrations of dolutegravir. Using cross-study comparisons to historical pharmacokinetic data for etravirine, dolutegravir did not appear to affect the pharmacokinetics of etravirine. The effect of etravirine on dolutegravir plasma concentrations was mitigated by co-administration of darunavir/ritonavir or lopinavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir. Dolutegravir should only be used with INTELENCE™ when co-administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.			
raltegravir	400 mg b.i.d.	raltegravir	↓ 10%	↓ 34%
		etravirine	↔	↔
	The combination of INTELENCE™ and raltegravir can be used without dose adjustments.			

Drug interactions – etravirine co-administered with non-antiretroviral medicinal products

Co-administered medicinal product	Dose of co-administered medicinal product (mg)	Medicinal product assessed	AUC	C_{min}
Antiarrhythmics				
digoxin	0.5 mg single dose	digoxin	↑ 18%	ND
		etravirine	↔	↔
	The combination of INTELENCE™ and digoxin can be used without dose adjustments. It is recommended that digoxin levels be monitored when digoxin is combined with INTELENCE™.			
amiodarone bepridil disopyramide flecainide lidocaine (systemic) mexiletine propafenone quinidine	Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE™. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with INTELENCE™.			
Anticoagulant				
warfarin	Warfarin concentrations may be affected when co-administered with INTELENCE™. It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with INTELENCE™.			
Anticonvulsants				
carbamazepine phenobarbital phenytoin	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. This may result in loss of therapeutic effect of INTELENCE™.			
Antifungals				

fluconazole	200 mg q.a.m.	fluconazole	↔	↔
		etravirine	↑ 86%	↑ 109%
	The incidence of adverse events was similar in patients coadministering fluconazole and INTELENCE™ or placebo in the Phase III trials. The combination of INTELENCE™ and fluconazole can be used without dose adjustments.			
voriconazole	200 mg b.i.d.	voriconazole	↑ 14%	↑ 23%
		etravirine	↑ 36%	↑ 52%
	The combination of INTELENCE™ and voriconazole can be used without dose adjustments. Voriconazole is a CYP2C19 substrate and CYP3A4 and CYP2C inhibitor. Concomitant use of voriconazole and INTELENCE™ may increase plasma concentrations of both drugs.			
itraconazole ketoconazole posaconazole	Posaconazole is a potent inhibitor of CYP3A and may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE™ may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE™. The combination of INTELENCE™ and these antifungals can be used without dose adjustments.			
Antiinfectives				
azithromycin	Based on the renal elimination pathway of azithromycin, no drug interactions are expected between azithromycin and INTELENCE™.			
clarithromycin	500 mg b.i.d.	clarithromycin	↓ 39%	↓ 53%
		14-hydroxy-clarithromycin	↑ 21%	↔
		etravirine	↑ 42%	↑ 46%
	Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.			
Antimalarial				
artemether/lumefantrine	80/480mg, 6 doses at 0, 8, 24, 36, 48 and 60 hours	Artemether	↓ 38%	↓ 18%
		Dihydroartemisinin	↓ 15%	↓ 17%
		Lumefantrine	↓ 13%	↔
		Etravirine	↔	↔
	No dose adjustment is needed for INTELENCE™. Caution is warranted when co-administering INTELENCE™ and artemether/lumefantrine as it is unknown whether the decrease in exposure of artemether or its active metabolite, dihydroartemisinin, could result in decreased antimalarial efficacy.			
Antimycobacterials				
rifampicin/rifampin rifapentine	Rifampicin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE™ should not be used in combination with rifampicin or rifapentine as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE™.			
rifabutin	300 mg q.d.	rifabutin	↓ 17%	↓ 24%

		25-*O*-desacetylrifabutin	↓ 17%	↓ 22%
		etravirine	↓ 37%	↓ 35%
	If INTELENCE™ is not co-administered with a boosted PI, then INTELENCE™ and rifabutin can be used without dose adjustments. If INTELENCE™ is co-administered with boosted darunavir, lopinavir or saquinavir, then rifabutin should not be co-administered due to the potential for significant reductions in etravirine exposure.			
Benzodiazepine				
diazepam	Concomitant use of INTELENCE™ with diazepam may increase plasma concentrations of diazepam.			
Corticosteroid				
dexamethasone (systemic)	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.			
Estrogen-Based Contraceptive				
ethinylestradiol norethindrone	0.035 mg q.d. 1 mg q.d.	ethinylestradiol	↑ 22%	↔
		norethindrone	↔	↓ 22%
		etravirine	↔	↔
	The combination of estrogen- and/or progesterone-based contraceptives and INTELENCE™ can be used without dose adjustment.			
Hepatitis C Virus (HCV) Direct-Acting Antivirals (DAAs)				
daclatasvir	Co administration of INTELENCE™ with daclatasvir may decrease daclatasvir concentrations. Due to the lack of data, co-administration of INTELENCE™ and daclatasvir is not recommended			
simeprevir	Concomitant use of INTELENCE™ with simeprevir may decrease plasma concentrations of simeprevir. It is not recommended to co-administer INTELENCE™ with simeprevir.			
boceprevir	800 mg t.i.d.	boceprevir	↑ 10%	↓ 12%
		etravirine	↓ 23%	↓ 29%
	Caution should be applied if INTELENCE™ is co-administered with boceprevir and another drug that potentially decreases etravirine plasma concentrations. Close monitoring for HIV and HCV virologic response is recommended. Please refer to the product information of the associated medications.			
ribavirin	Based on the renal elimination pathway of ribavirin, no drug interactions are expected between ribavirin and INTELENCE™.			
Herbal Product				
St John's wort (*Hypericum perforatum*)	INTELENCE™ should not be used concomitantly with products containing St John's wort because co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE™.			
HMG Co-A Reductase Inhibitors				
atorvastatin	40 mg q.d.	atorvastatin	↓ 37%	ND
		2-hydroxy-atorvastatin	↑ 27%	ND
		etravirine	↔	↔
	Dose adjustment of atorvastatin may be necessary to tailor the clinical response when combined with INTELENCE™.			

fluvastatin lovastatin pitavastatin rosuvastatin simvastatin	Lovastatin, rosuvastatin and simvastatin are CYP3A substrates and co-administration with INTELENCE™ may result in lower plasma concentrations of the HMG Co-A reductase inhibitor. Fluvastatin, rosuvastatin and, to a lesser extent, pitavastatin are metabolised by CYP2C9 and co-administration with INTELENCE™ may result in higher plasma concentrations of the HMG Co-A reductase inhibitor. Dose adjustments for these HMG Co-A reductase inhibitors may be necessary.			
pravastatin	No interaction between pravastatin and INTELENCE™ is expected.			
H_2-Receptor Antagonists				
ranitidine	150 mg b.i.d.	etravirine	↓ 14%	ND
	INTELENCE™ can be co-administered with H_2-receptor antagonists without dose adjustments.			
Immunosuppressants				
cyclosporine sirolimus tacrolimus	Co-administration with systemic immunosuppressants should be done with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected when co-administered with INTELENCE™.			
Narcotic Analgesic				
methadone	individual dose ranging from 60 to 130 mg/day	R(-) methadone	↔	↔
		S(+) methadone	↔	↔
		etravirine	↔	↔
	No changes in methadone dosage were required based on clinical status during or after the period of INTELENCE™ co-administration.			
Phosphodiesterase, Type 5 (PDE-5) Inhibitors				
sildenafil vardenafil tadalafil	50 mg single dose	sildenafil	↓ 57%	ND
		N-desmethyl-sildenafil	↓ 41%	ND
	Concomitant use of PDE-5 inhibitors with INTELENCE™ may require dose adjustment of the PDE-5 inhibitor to attain the desired clinical effect.			
Platelet Aggregation Inhibitor				
clopidogrel	Activation of clopidogrel to its active metabolite may be decreased when clopidogrel is co-administered with INTELENCE™. Alternatives to clopidogrel should be considered.			
Proton Pump Inhibitors				
omeprazole	40 q.d.	etravirine	↑ 41%	ND
	INTELENCE™ can be co-administered with proton pump inhibitors without dose adjustments.			
Selective Serotonin Reuptake Inhibitor (SSRI)				
paroxetine	20 q.d.	paroxetine	↔	↓ 13%
		etravirine	↔	↔
	INTELENCE™ can be co-administered with paroxetine without dose adjustments.			

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

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no adequate and well-controlled studies with etravirine in pregnant women. Studies in animals have not shown evidence of developmental toxicity or effect on reproductive function and fertility (see *Non-Clinical Information*).

INTELENCE™ (200 mg b.i.d.), evaluated in combination with other antiretroviral agents in a study of 15 pregnant women during the second and third trimesters of pregnancy and postpartum, demonstrated that exposure to total etravirine was generally higher during pregnancy compared with postpartum, and less so for unbound etravirine exposure (see *Pharmacokinetic Properties*). There were no relevant clinical findings in the mothers or in the newborns in this trial.

INTELENCE™ should be used during pregnancy only if the potential benefit justifies the potential risk.

Breast-feeding
Etravirine is excreted in human breast milk. Because of both the potential for HIV transmission and the potential for adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving INTELENCE™.

Fertility
No human data on the effect of etravirine on fertility are available. In rats, there was no effect on mating or fertility with INTELENCE™ treatment (see *Non-Clinical Information*).

Effects on Ability to Drive and Use Machines
No studies on the effects of INTELENCE™ on the ability to drive or operate machines have been performed. There is no evidence that INTELENCE™ may alter the patient's ability to drive and operate machines, however, the adverse drug reaction profile of INTELENCE™ should be taken into account (see *Adverse Reactions*).

Adverse Reactions
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of etravirine based on the comprehensive assessment of the available adverse event information. A causal relationship with etravirine usually cannot be reliably established in individual cases. Further, 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 clinical practice.

Adverse reactions from clinical trials with adult patients
The safety assessment is based on all data from 1203 patients in the Phase III placebo-controlled trials DUET-1 and DUET-2 in antiretroviral treatment-experienced HIV-1 infected adult patients, 599 of whom received INTELENCE™ (200 mg b.i.d.) (see *Pharmacodynamic Properties*). In these pooled trials, the median exposure for patients in the INTELENCE™ arm and placebo arm was 52.3 and 51.0 weeks, respectively.

The most frequently reported adverse reactions (≥ 5%) that were at least grade 2 in severity were rash (10.0% in the INTELENCE™ arm and 3.5% in the placebo arm), diarrhea (7.0% in the INTELENCE™ arm and 11.3% in the placebo arm), hypertriglyceridemia (6.3% in the INTELENCE™ arm and 4.3% in the placebo arm) and nausea (5.2% in the INTELENCE™ arm and 4.8% in the placebo arm) (see table below).

The majority of the adverse reactions reported during treatment with INTELENCE™ were grade 1 to 2 in severity. Grade 3 or 4 adverse reactions were reported in 22.2% and 17.2% of the INTELENCE™ and placebo treated patients, respectively. The most commonly reported grade 3 or 4 adverse reactions were hypertriglyceridemia (4.2% in the INTELENCE™ arm and 2.3% in the placebo arm), hypercholesterolemia (2.2% in the INTELENCE™ arm and 2.3% in the placebo arm), renal failure (2.0% in the INTELENCE™ arm and 1.2% in the placebo arm) and anemia (1.7% in the INTELENCE™ arm and 1.3% in the placebo arm). For treatment emergent clinical laboratory abnormalities (grade 3 or 4) reported in greater than or equal to 2% of INTELENCE™ treated patients, see table "Treatment Emergent Laboratory Abnormalities". All other grade 3 and/or 4 adverse reactions were reported in less than 1.5% of the INTELENCE™ treated patients. 5.2% of patients in the INTELENCE™ arm discontinued treatment due to adverse reactions compared to 2.6% of patients in the placebo arm. The most common adverse reactions leading to discontinuation was rash (2.2% in the INTELENCE™ arm versus 0% in the placebo arm).

Rash was most frequently mild to moderate, generally macular to maculopapular or erythematous, mostly occurred in the second week of therapy and was infrequent after week 4. Rash was mostly self-limiting and generally resolved within 1-2 weeks on continued therapy (see *Warnings and Precautions*). The incidence of rash was higher in women compared to men in the INTELENCE™ arm in the DUET trials (rash ≥ Grade 2 was reported in 9/60 [15.0%] women versus 51/539 [9.5%] men; discontinuations due to rash were reported in 3/60 [5.0%] women versus 10/539 [1.9%] men) (see *Warnings and Precautions)*. In patients with a history of NNRTI-related rash, there was no apparent increased risk for the development of INTELENCE™-related rash compared to patients without a history of NNRTI-related rash.

Adverse reactions of moderate intensity or greater (≥ grade 2) and reported in ≥1% of patients treated with INTELENCE™ are summarised in the table below. The adverse reactions are listed by system organ class (SOC) and frequency. Laboratory abnormalities considered adverse reactions are included in a table below (see *Treatment emergent Grade 3 to 4 laboratory abnormalities reported in ≥ 2% of patients*).

Adverse reactions of moderate intensity or greater (≥ grade 2) and reported in ≥ 1% of adult patients treated with INTELENCE™		
DUET-1 and DUET-2 Trials		
System Organ Class (SOC) **Adverse Reaction**	INTELENCE™ **+ BR** **N=599**	**Placebo + BR** **N=604**
Cardiac disorders		
Myocardial infarction	1.3%	0.3%
Blood and lymphatic system disorders		
Anemia	4.0%	3.8%
Thrombocytopenia	1.3%	1.5%
Nervous system disorders		
Peripheral neuropathy	3.8%	2.0%
Headache	3.0%	4.5%
Gastrointestinal disorders		
Diarrhea	7.0%	11.3%
Nausea	5.2%	4.8%
Abdominal pain	3.5%	3.1%
Vomiting	2.8%	2.8%
Gastroesophageal reflux disease	1.8%	1.0%

Flatulence	1.5%	1.0%
Gastritis	1.5%	1.0%
Renal and urinary disorders		
Renal failure	2.7%	2.0%
Skin and subcutaneous tissue disorders		
Rash	10.0%	3.5%
Lipohypertrophy	1.0%	0.3%
Night sweats	1.0%	1.0%
Metabolism and nutrition disorders		
Hypertriglyceridemia	6.3%	4.3%
Hypercholesterolemia	4.3%	3.6%
Hyperlipidemia	2.5%	1.3%
Hyperglycemia	1.5%	0.7%
Diabetes mellitus	1.3%	0.2%
Vascular disorders		
Hypertension	3.2%	2.5%
General disorders and administration site conditions		
Fatigue	3.5%	4.6%
Psychiatric disorders		
Insomnia	2.7%	2.8%
Anxiety	1.7%	2.6%

Treatment emergent adverse reactions of moderate intensity or greater (≥ grade 2) and occurring in less than 1% of patients receiving INTELENCE™ were:

- cardiac disorders: angina pectoris, atrial fibrillation
- nervous system disorders: paresthesia, somnolence, convulsion, hypoesthesia, amnesia, syncope, disturbance in attention, hypersomnia, tremor
- eye disorders: blurred vision
- ear and labyrinth disorders: vertigo
- respiratory, thoracic and mediastinal disorders: exertional dyspnea, bronchospasm
- gastrointestinal disorders: abdominal distension, pancreatitis, constipation, dry mouth, hematemesis, retching, stomatitis
- skin and subcutaneous tissue disorders: prurigo, hyperhidrosis, dry skin, swelling face
- metabolism and nutrition disorders: anorexia, dyslipidemia
- general disorders and administration site conditions: sluggishness
- immune system disorders: drug hypersensitivity, immune reconstitution syndrome
- hepatobiliary disorders: hepatomegaly, cytolytic hepatitis, hepatic steatosis, hepatitis
- reproductive system and breast disorders: gynecomastia
- psychiatric disorders: sleep disorders, abnormal dreams, confusional state, disorientation, nervousness, nightmares

Additional adverse reactions 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 patients. Stevens-Johnson Syndrome (rare; < 0.1%) and toxic epidermal necrolysis (very rare; < 0.01%) have been reported during clinical development with INTELENCE™.

Laboratory abnormalities

Treatment emergent clinical laboratory abnormalities (grade 3 or 4), considered adverse reactions, reported in ≥ 2% of INTELENCE™ treated patients are shown in the table below.

Treatment Emergent Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% of Patients

Pooled DUET-1 and DUET-2 Trials			
Laboratory Parameter Preferred Term, n (%)	**DAIDS Toxicity Range**	**INTELENCE™ + BR N=599**	**Placebo + BR N=604**
GENERAL BIOCHEMISTRY			
Pancreatic Amylase		**53 (8.9)**	**57 (9.4)**
grade 3	> 2-5 x ULN	44 (7.4)	51 (8.4)
grade 4	> 5 x ULN	9 (1.5)	6 (1.0)
Creatinine		**12 (2.0)**	**10 (1.7)**
grade 3	> 1.9-3.4 x ULN	12 (2.0)	9 (1.5)
grade 4	> 3.4 x ULN	0 (0)	1 (0.2)
Lipase		**20 (3.4)**	**16 (2.6)**
grade 3	> 3-5 x ULN	12 (2.0)	13 (2.2)
grade 4	> 5 x ULN	8 (1.3)	3 (0.5)
GENERAL HEMATOLOGY			
White blood cell count		**12 (2.0)**	**26 (4.3)**
grade 3	1.0-1.499 giga/l 1,000-1,499/mm^3	6 (1.0)	22 (3.6)
grade 4	< 1.0 giga/l < 1,000/mm^3	6 (1.0)	4 (0.7)
HEMATOLOGY DIFFERENTIAL COUNTS			
Neutrophils		**30 (5.1)**	**45 (7.5)**
grade 3	0.5-0.749 giga/l 500-749/mm^3	21 (3.5)	26 (4.3)
grade 4	< 0.5 giga/l < 500/mm^3	9 (1.5)	19 (3.1)
LIPIDS AND GLUCOSE			
Total cholesterol		**48 (8.1)**	**32 (5.3)**
grade 3	> 7.77 mmol/l > 300 mg/dl	48 (8.1)	32 (5.3)
Low density lipoprotein		**42 (7.2)**	**39 (6.6)**
grade 3	> 4.9 mmol/l > 190 mg/dl	42 (7.2)	39 (6.6)
Triglycerides		**55 (9.2)**	**35 (5.8)**
grade 3	8.49-13.56 mmol/l 751 - 1200 mg/dl	34 (5.7)	24 (4.0)
grade 4	> 13.56 mmol/l > 1200 mg/dl	21 (3.5)	11 (1.8)
Elevated Glucose Levels		**21 (3.5)**	**14 (2.3)**
grade 3	13.89-27.75 mmol/l 251–500 mg/dl	21 (3.5)	13 (2.2)
grade 4	> 27.75 mmol/l > 500 mg/dl	0 (0)	1 (0.2)
HEPATIC PARAMETERS			
Alanine amino transferase		**22 (3.7)**	**12 (2.0)**
grade 3	5.1-10 x ULN	16 (2.7)	10 (1.7)
grade 4	> 10 x ULN	6 (1.0)	2 (0.3)
Aspartate amino transferase		**19 (3.2)**	**12 (2.0)**
grade 3	5.1-10 x ULN	16 (2.7)	10 (1.7)
grade 4	> 10 x ULN	3 (0.5)	2 (0.3)
ULN=Upper Limit of Normal			

Lipodystrophy

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see *Warnings and Precautions*).

Immune Reconstitution Syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reconstitution syndrome) (see *Warnings and Precautions*). Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported in the context of immune reconstitution syndrome (see *Warnings and Precautions*).

Additional information on special populations

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

Among co-infected patients (n=139) in the pooled analysis for DUET-1 and DUET-2, grade 3 or 4 elevations in AST developed in 9.7% of the 72 patients in the INTELENCE™ arm and in 6.0% of the 67 patients in the placebo arm and grade 3 or 4 elevations in ALT developed in 11.1% of patients in the INTELENCE™ arm and in 7.5% of patients in the placebo arm. Among co-infected patients, 1.4% of those treated with INTELENCE™ and 3.0% in the placebo arm discontinued because of liver or biliary system disorders. Standard clinical monitoring of patients with chronic hepatitis is considered adequate.

Postmarketing experience

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience. The frequencies are provided according to the following convention:

Very common	≥ 1/10 (≥ 10%)
Common	≥ 1/100 and <1/10 (≥ 1% and <10%)
Uncommon	≥ 1/1000 and <1/100 (≥ 0.1% and <1%)
Rare	≥ 1/10000 and <1/1000 (≥ 0.01 and <0.1%)
Very rare	<1/10000, including isolated reports (<0.01%)
Not known	Cannot be estimated from the available data

In the table below, adverse reactions are presented.

Post-marketing adverse reactions

System Organ Class	Adverse Reaction	Incidence
Immune system disorders	Hypersensitivity reactions, including DRESS [(Drug Rash with Eosinophilia and Systemic Symptoms) have been reported and were characterized by rash, constitutional findings, and infrequently organ dysfunction, including hepatic failure (see *Warnings and Precautions*).]	Not known
Musculoskeletal and connective tissue disorders	Myopathy, Rhabdomyolysis	Not known

Overdose

There is no specific antidote for overdose with INTELENCE™. Human experience of overdose with INTELENCE™ is limited. Treatment of overdose with INTELENCE™ consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. Since etravirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: NNRTI (non-nucleoside reverse transcriptase inhibitor)
ATC code: J05AG04

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 can bind in at least 2 conformationally distinct modes. Within a given binding mode, torsional flexibility of etravirine permits access to numerous conformational variants, while the compact design of etravirine permits significant repositioning and reorientation (translation and rotation) within the pocket. Etravirine does not inhibit the human DNA polymerases α, β and γ.

Antiviral activity in vitro

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

Etravirine demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (subtype A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from 0.7 to 21.7 nM. These EC_{50} values are well below the 50% cellular toxicity concentration range of 15 to > 100 µM.

The EC_{50} value of etravirine for HIV-1 increases by a median factor of 5.8 in the presence of human serum.

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

Resistance

In a panel of 65 HIV-1 strains with a single amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, etravirine shows potent antiviral activity against 56 of these strains. The amino acid

substitutions, which led to the highest resistance to etravirine in cell culture are Y181I (13-fold change in EC_{50} value) and Y181V (17-fold change in EC_{50} value). The antiviral activity of etravirine in cell culture against 24 HIV-1 strains with multiple amino acid substitutions associated with resistance to N(t)RTIs and/or PIs is comparable to that observed against wild type HIV-1.

In vitro selection of etravirine resistant strains originating from wild type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1 was performed at high and low virus inoculum. At high virus inoculum, emergence of resistant strains from wild type HIV-1 was delayed or prevented at concentrations of 40 nM or 200 nM. The same was observed with resistant strains harbouring the single NNRTI resistance-associated mutations K103N and Y181C. Regardless of the experimental design and the original HIV-1 strain, development of resistance against etravirine typically required multiple mutations in the RT of which the following were observed most frequently: L100I, E138K, E138G, V179I, Y181C and M230I.

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

Cross-resistance

Limited cross-resistance between etravirine and efavirenz was observed *in vitro* in 3 of the 65 site directed HIV-1 mutant strains containing an NNRTI resistance associated mutation. For the other strains, the amino acid positions associated with decreased susceptibility to etravirine and efavirenz were different. Etravirine retains an EC_{50} value < 10 nM against 83% of 6171 clinical isolates resistant to delavirdine, efavirenz and/or nevirapine. The treatment of patients with delavirdine, efavirenz or nevirapine following virologic failure of an etravirine-containing regimen is not recommended.

Clinical experience

Treatment-experienced patients

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

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

At 48 weeks, the virologic response rate was evaluated in patients receiving INTELENCE™ (200 mg b.i.d.) in addition to a BR versus patients receiving placebo in addition to a BR. The BR consisted of darunavir/ritonavir 600/100 mg b.i.d. and at least 2 other investigator-selected antiretroviral agents (N[t]RTIs with or without ENF). 45.6% of patients in the INTELENCE™ arm and 46.9% of patients in the placebo arm used ENF in the underlying antiretroviral therapy. 25.5% of patients in the INTELENCE™ arm used ENF for the first time (*de novo*), compared with 26.5% of patients in the placebo arm. 20.0% of patients in the INTELENCE™ arm re-used ENF, compared with 20.4% of patients in the placebo arm. Virologic response was defined as achieving a confirmed undetectable viral load (< 50 HIV-1 RNA copies/ml).

The table below shows the efficacy results at 48 weeks for patients in the INTELENCE™ arm and patients in the placebo arm from the pooled DUET-1 and DUET-2 trials.

	DUET-1 and DUET-2 pooled data		
Baseline characteristics			
Median plasma HIV-1 RNA	4.8 $\log_{10}$ copies/ml		
Median CD4 cell count	99×10^6 cells/l		
Outcomes	**INTELENCE™ + BR N=599**	**Placebo + BR N=604**	**Treatment difference (95% CI)**
Confirmed Undetectable Viral Load (< 50 HIV-1 RNA copies/ml)[1] n (%)	363 (60.6%)	240 (39.7%)	20.9% (15.3%; 26.4%)[4]
< 400 HIV-1 RNA copies/ml[1] n (%)	428 (71.5%)	286 (47.4%)	24.1% (18.7%; 29.5%)[4]
HIV-1 RNA $\log_{10}$ mean decrease from baseline ($\log_{10}$ copies/ml)[2]	-2.25	-1.49	-0.64 (-0.82; -0.46)[3]
CD4 cell count mean increase from baseline (x 10^6/l)[2]	98.2	72.9	24.4 (10.4; 38.5)[3]
Any AIDS defining illness and/or death n (%)	35 (5.8%)	59 (9.8%)	-3.9% (-6.9; -0.9)[5]

1 Imputations according to the TLOVR algorithm.
2 Non-completer is failure (NC = F) imputation: patients who discontinued prematurely are imputed with a change equal to 0 at all timepoints after discontinuation.
3 Treatment differences are based on Least Square means from an ANCOVA model including the stratification factors. P-value < 0.0001 for mean decrease in HIV-1 RNA; p-value=0.0006 for mean change in CD4 cell count.
4 Confidence interval around observed difference of response rates; p-value < 0.0001 from logistic regression model, including stratification factors.
5 Confidence interval around observed difference of response rates; p-value=0.0408.

Since there was a significant interaction effect between treatment and ENF, the primary analysis was done for 2 ENF strata (patients re-using or not using ENF versus patients using ENF *de novo*). The week 48 results from the pooled analysis of DUET-1 and DUET-2 demonstrated that the INTELENCE™ arm was superior to the placebo arm irrespective of whether ENF was used *de novo* or not. In the population of patients who either re-used or did not use ENF, the proportion of patients with < 50 HIV-1 RNA copies/ml was 57.0% in the INTELENCE™ arm and 33.0% in the placebo arm (a difference of 24.0%, $p < 0.0001$). In the group of patients that used ENF *de novo*, 71.2% of patients in the INTELENCE™ arm

reached < 50 HIV-1 RNA copies/ml compared to 58.5% of patients in the placebo arm (a difference of 12.7%, p=0.0199).

At week 48, significantly fewer patients in the INTELENCE™ arm (35 patients, 5.8%) reached a clinical endpoint (AIDS-defining illness or death) as compared to the placebo arm (59 patients, 9.8%) (p=0.0408).

Patient-reported outcomes

In the pooled DUET trials, patients in the INTELENCE™ arm demonstrated at 48 weeks a statistically significant improvement from baseline on the Physical Well-being subscale of the patient-reported FAHI (Functional Assessment of Human Immunodeficiency Virus Infection) questionnaire. This improvement was statistically greater in patients in the INTELENCE™ arm compared to patients in the placebo arm. For the Functional and Global Well-being subscale, no statistical difference was found.

Baseline genotype or phenotype and virologic outcome analysis

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

Proportion of Patients with < 50 HIV-1 RNA copies/ml at Week 48 by Baseline Number of INTELENCE™ Resistance-Associated Mutations in the non-VF excluded Population of Pooled DUET studies

	Patients Re-Using or Not Using Enfuvirtide	
Number of INTELENCE™ RAMs	**INTELENCE™ + BR % (n/N)**	**Placebo + BR % (n/N)**
0	74.1% (117/158)	42.7% (61/143)
1	61.3% (73/119)	38.6% (59/153)
2	64.1% (41/64)	26.2% (16/61)
≥3	38.3% (23/60)	28.2% (11.39)

n = number of patients with observations; N = total number of patients
The population analysed was all patients excluding those that discontinued for reasons other than virologic failure (non-VF excluded)

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

Baseline etravirine phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline etravirine phenotype are shown in the table below. These baseline phenotype groups are based on the select patient populations in DUET-1 and DUET-2 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.

Response to INTELENCE™ by Baseline Etravirine Phenotype: Non-VF excluded population of the Pooled DUET studies - 'ENF re-using or ENF not using' patients				
Baseline etravirine Phenotype (fold change ranges)	**Mean (SE) change in viral load from baseline at week 48**		**Proportion of patients with < 50 copies/ml at week 48 % (n/N)**	
	INTELENCE™ + BR N=400	**Placebo + BR N=391**	**INTELENCE™ + BR N=400 % (n/N)**	**Placebo + BR N=391 % (n/N)**
All ranges	-2.37 (1.31)	-1.38 (1.49)	63% (253/400)	37% (145/391)
0–≤ 3	-2.58 (1.16)	-1.47 (1.46)	70% (188/267)	43% (112/262)
>3–≤13	-2.20 (1.39)	-1.33 (1.57)	53% (39/74)	29% (22/77)
> 13	-1.64 (1.51)	-1.04 (1.46)	44% (26/59)	21% (11/52)

n = number of patients with observations; N = total number of patients
The population analysed was all patients excluding those that discontinued for reasons other than virologic failure (non-VF excluded)

Pharmacokinetic Properties

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

Absorption

An intravenous formulation of etravirine is unavailable, thus, the absolute bioavailability of INTELENCE™ is unknown. After oral administration with food, the maximum plasma concentration of etravirine is generally achieved within 4 hours. In healthy subjects, the absorption of etravirine is not affected by co-administration of oral ranitidine or omeprazole, drugs that are known to increase gastric pH.

Effect of food on absorption

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

Distribution

Etravirine is approximately 99.9% bound to plasma proteins, primarily to albumin (99.6%) and α1-acid glycoprotein (97.66%-99.02%) *in vitro*. The distribution of etravirine into compartments other than plasma (e.g, cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Metabolism

In vitro experiments with human liver microsomes (HLMs) indicate that etravirine primarily undergoes oxidative metabolism by the hepatic cytochrome P450 (CYP) 3A system and, to a lesser extent, by the CYP2C family followed by glucuronidation.

Elimination

After administration of a radiolabeled ^{14}C-etravirine dose, 93.7% and 1.2% of the administered dose of ^{14}C-etravirine could be retrieved in faeces and urine, respectively. Unchanged etravirine accounted for 81.2% to 86.4% of the administered dose in feces. Unchanged etravirine was not detected in urine. The terminal elimination half-life of etravirine was approximately 30-40 hours.

Additional information on special populations

Children and adolescents

The pharmacokinetics of etravirine in pediatric patients are under investigation. There are insufficient data at this time to recommend a dose (see *Dosage and Administration*).

Elderly

Population pharmacokinetic analysis in HIV infected patients showed that etravirine pharmacokinetics are not considerably different in the age range (18 to 77 years) evaluated (see *Dosage and Administration* and *Warnings and Precautions*).

Gender

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

Race

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

Hepatic impairment

Etravirine is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild (Child-Pugh score A) hepatic impairment to 8 matched controls and 8 patients with moderate (Child-Pugh score B) hepatic impairment to 8 matched controls, the multiple dose pharmacokinetic disposition of etravirine was not altered in patients with mild to moderate hepatic impairment. No dosing adjustment is required in patients with mild or moderate hepatic impairment. INTELENCE™ has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see *Dosage and Administration* and *Warnings and Precautions*).

Hepatitis B and/or hepatitis C virus co-infection

Population pharmacokinetic analysis of the DUET-1 and DUET-2 trials showed reduced clearance for INTELENCE™ in HIV-1 infected patients with hepatitis B and/or C virus co-infection. Based upon the safety profile (see *Adverse Reactions*), no dose adjustment is necessary in patients co-infected with hepatitis B and/or C virus.

Renal impairment

The pharmacokinetics of etravirine have not been studied in patients with renal insufficiency. Results from a mass balance study with radioactive ^{14}C-etravirine showed that <1.2% of the administered dose of etravirine is excreted in the urine. No unchanged drug was detected in urine so the impact of renal impairment on etravirine elimination is expected to be minimal. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis (see *Dosage and Administration* and *Warnings and Precautions*).

Pregnancy and postpartum

The total etravirine exposure after intake of INTELENCE™ 200 mg b.i.d. as part of an antiretroviral regimen was generally higher during pregnancy compared with postpartum (see table below). The differences were less pronounced for unbound etravirine exposure.

In women receiving INTELENCE™ 200 mg b.i.d., higher mean values for C_{max}, AUC_{12h} and C_{min} were observed during pregnancy compared to postpartum. During the 2nd and 3rd trimester of pregnancy mean values of these parameters were comparable.

Pharmacokinetic results of total etravirine after administration of etravirine 200 mg b.i.d. as part of an antiretroviral regimen, during the 2nd trimester of pregnancy, the 3rd trimester of pregnancy, and postpartum.

Pharmacokinetics of etravirine Mean ± SD (median)	**Etravirine 200 mg b.i.d. postpartum**	**Etravirine 200 mg b.i.d. 2nd trimester**	**Etravirine 200 mg b.i.d. 3rd trimester**
	N=10	N=13	N=10[a]
C_{min}, ng/mL	269 ± 182 (284)	383 ± 210 (346)	349 ± 103 (371)
C_{max}, ng/mL	569 ± 261 (528)	774 ± 300 (828)	785 ± 238 (694)
AUC_{12h}, ng•h/mL	5004 ± 2521 (5246)	6617 ± 2766 (6836)	6846 ± 1482 (6028)

[a] n=9 for AUC_{12h}

Each subject served as her own control, and with an intra-individual comparison, the total etravirine C_{min}, C_{max} and AUC_{12h} values were 1.2-, 1.4- and 1.4-fold higher, respectively, during the 2nd trimester of pregnancy as compared to postpartum, and 1.1-, 1.4- and 1.2-fold higher, respectively, based during the 3rd trimester of pregnancy as compared to postpartum.

NON-CLINICAL INFORMATION

Animal toxicology studies have been conducted with etravirine in mice, rats, rabbits and dogs. In mice, the key target organs identified were the liver and the coagulation system. Hemorrhagic cardiomyopathy was only observed in male mice and was considered to be secondary to severe coagulopathy mediated via the vitamin K pathway. This is considered not relevant to humans. In the rat, the key target organs identified were the liver, the thyroid and the coagulation system. Exposure in mice was equivalent to human exposure while in rats it was below the clinical exposure at the recommended dose. In the dog, changes in the liver and gall bladder were seen at exposures approximately 8-fold higher than human exposure observed at the recommended dose (200 mg b.i.d.).

In a study conducted in rats, there were no effects on mating or fertility with INTELENCE™ treatment up to 500 mg/kg/day and exposure levels equivalent to those in humans at the clinically recommended dose. There was no teratogenicity with etravirine in rats (1000 mg/kg) and rabbits (375 mg/kg) at exposures equivalent to those observed in humans at the recommended clinical dose. In a pre- and postnatal development assessment in rats, etravirine had no effect on offspring development during lactation or post weaning when the mother was dosed up to 500 mg/kg and at exposures equivalent to those observed at the recommended clinical dose.

Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 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. Etravirine was not carcinogenic in rats and in male mice. An increase in the incidences of hepatocellular adenomas and carcinomas were observed in female mice. Administration of etravirine did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in female mice are generally considered to be rodent specific, associated with liver enzyme induction, and of limited relevance to humans. At the highest tested doses, the systemic exposures (based on AUC) to etravirine were 0.6-fold (mice) and between 0.2- and 0.7-fold (rats), relative to those observed in humans at the recommended therapeutic dose (200 mg b.i.d.).

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

PHARMACEUTICAL PARTICULARS

List of Excipients

Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Croscarmellose sodium
Magnesium stearate
Lactose monohydrate (in 100mg tablet only)
Silicified microcrystalline cellulose (in 200mg tablet only)

Incompatibilities

None known.

Shelf Life

Observe expiry date on the outer pack.

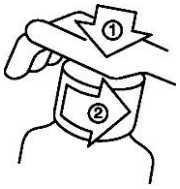
Storage Conditions

Do not store above 30°C. Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.
Keep out of the sight and reach of children.

Nature and Contents of Container

100 mg: High density polyethylene (HDPE) plastic bottles containing 120 tablets and 3 desiccant pouches, fitted with polypropylene (PP) child resistant closures.
200 mg: High density polyethylene (HDPE) plastic bottles containing 60 tablets and 3 desiccant pouches, fitted with polypropylene (PP) child resistant closures.

Instructions for Use and Handling



The plastic bottle comes with a child resistant cap and should be opened as follows:

- Push the plastic screw cap down while turning it counter clockwise.
- Remove the unscrewed cap.

BATCH RELEASER

Janssen Cilag S.p.A.
Via C. Janssen
Borgo S. Michele
04100 Latina, Italy

PRODUCT REGISTRANT

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DATE OF REVISION OF THE TEXT

19 October 2022 (CCDS 10 October 2018)