AUSTRALIAN PRODUCT INFORMATION

INTELENCE®

ETRAVIRINE

TABLET

1. NAME OF THE MEDICINE

Etravirine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INTELENCE etravirine is available as 100 mg and 200 mg tablets.

Each tablet contains 100 mg or 200 mg of etravirine.

Excipient(s) with known effect:

The 100 mg tablets contain 160 mg of lactose monohydrate.

For a full list of excipients, see **section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Tablet

INTELENCE 100 mg tablet: white to off-white, oval tablet, debossed with “T125” on one side and “100” on the other side*.

INTELENCE 200 mg tablet: white to off-white, biconvex, oblong tablet, debossed with “T200” on one side.

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

INTELENCE (etravirine) is a substituted diarylpyrimidine (DAPY) derivative, with potent *in vitro* activity against wild-type HIV-1 as well as NNRTI-resistant HIV-1.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Etravirine, in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults who have evidence of viral replication and resistance to non-nucleoside transcriptase inhibitors and other antiretroviral agents.

This indication is based on 24-week analyses from 2 randomised, double-blind, placebo controlled trials of etravirine. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N(t)RTI, PI) treatment-experienced adults (see **section 5.1 Pharmacodynamic properties – Clinical trials**).

Treatment history of patients and genotypic testing should be performed to guide the use of etravirine.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

INTELENCE must always be given in combination with other antiretroviral medicinal products.

Adults:

The recommended oral dose of INTELENCE is 200 mg (one 200 mg tablet or two 100 mg tablets) taken orally twice daily (b.i.d.), following a meal (see **section 5.2 Pharmacokinetic properties**). Patients should be instructed to swallow the tablet(s) as a whole with a liquid such as water. Patients who are unable to swallow the INTELENCE tablet(s) whole may disperse the tablet(s) in a glass of water. The patient should be instructed to do the following:

- place the tablet(s) in 5 mL (1 teaspoon) of water, or at least enough water to cover the medication,
- stir well for about 1 minute until the water looks milky,
- if desired, add up to 30 mL (2 tablespoons) more water or alternatively orange juice or milk (patients should not place the tablets in orange juice or milk without first adding water),
- drink it immediately,
- rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the patient takes the entire dose.

The use of warm (>40°C) or carbonated beverages should be avoided.

It is recommended that INTELENCE tablet(s) dispersed in water be taken before other antiretroviral liquids that may need to be taken concomitantly.

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 **section 4.4 Special warnings and precautions for use** and **section 5.2 Pharmacokinetic properties**).

Renal impairment:

No dose adjustment is required in patients with renal impairment (see **4.4 Special warnings and precautions for use** and **section 5.2 Pharmacokinetic properties**).

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 **section 5.2 Pharmacokinetic properties**).

Elderly:

Limited information is available in this population (see **section 4.4 Special warnings and precautions for use** and **section 5.2 Pharmacokinetic properties**).

Pregnancy:

INTELENCE should be used during pregnancy only if the potential benefit justifies the potential risk. Based on limited data available, no dose adjustment is required during pregnancy and postpartum. (See **section 5.2 Pharmacokinetic properties – Pregnancy and Postpartum**, **section 4.6 Fertility, pregnancy & lactation**, and **section 4.2 Dose and method of administration - pregnancy**).

Missed Dose

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.

4.3 CONTRAINDICATIONS

Hypersensitivity to etravirine or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The use of other active antiretroviral agents with etravirine is associated with an increased likelihood of treatment response.

In patients who have experienced virological failure on an NNRTI and nucleoside or nucleotide reverse transcriptase inhibitor (N[t]RTI)-containing regimen, etravirine should not be used in combination with N(t)RTIs only.

The risks and benefits of etravirine have not been established in treatment of naïve patients.

Transmission of HIV

Patients should be advised that current antiretroviral therapy does not cure HIV. Reduction in the risk of sexual transmission is dependent on effective viral suppression. Appropriate precautions to prevent the sexual and bloodborne transmission of HIV should continue to be employed.

Severe skin rash 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 **section 4.8 Adverse effects (Undesirable effects)**).

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.

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 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 to 2 weeks on continued therapy. The incidence of rash was higher in females (see **section 4.8 Adverse effects (Undesirable effects)**).

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 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 **section 4.8 Adverse effects (Undesirable effects)**).

Immune reconstitution inflammatory 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. 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 **section 4.8 Adverse effects (Undesirable effects)**).

Use in 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 **section 4.2 Dose and method of administration** and **section 5.2 Pharmacokinetic properties**).

Use in 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 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 **section 4.2 Dose and method of administration** and **section 5.2 Pharmacokinetic properties**).

Use in the 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 **section 4.2 Dose and method of administration** and **section 5.2 Pharmacokinetic properties**).

Paediatric use

The safety and efficacy of etravirine have not been established in children or adolescents. Etravirine studies are ongoing in HIV-1-infected children and adolescents (between the ages of 6 and 17 years, inclusive).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicinal products that affect etravirine exposure

Etravirine is metabolised by cytochrome P450 (CYP) 3A4, CYP2C9 and CYP2C19 followed by glucuronidation of the metabolites by uridine diphosphate glucuronosyl transferase (UDPGT). Medicinal products that induce CYP3A4, 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 CYP3A4, 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 an inducer of CYP3A4. Co-administration of INTELENCE with medicinal products primarily metabolised by CYP3A4 may result in decreased plasma concentrations of such medicinal products, which could decrease or shorten their therapeutic effects. Etravirine is an 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.

Drugs that are not recommended for co-administration with INTELENCE are included in **Table 1**. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 1: Drugs That Should Not Be Co-administered With INTELENCE

Concomitant Drug Class: Drug Name	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
NNRTIs (e.g., efavirenz, nevirapine, delavirdine, rilpivirine)	It is not recommended to co-administer INTELENCE with other NNRTIs.
HIV-Antiviral Agents: Protease Inhibitors (PIs) – Unboosted (i.e., without co-administration of low-dose ritonavir or cobicistat)	
atazanavir, unboosted	Concomitant use of INTELENCE with unboosted atazanavir may cause a significant decrease in the plasma concentration of atazanavir. It is not recommended to co-administer unboosted atazanavir and INTELENCE.

Concomitant Drug Class: Drug Name	Clinical Comment
ritonavir, full dose	Concomitant use of INTELENCE with full-dose ritonavir (600 mg b.i.d.) may cause a significant decrease in the plasma concentration of etravirine. This may result in loss of therapeutic effect of INTELENCE. It is not recommended to co-administer full-dose ritonavir (600 mg b.i.d.) with INTELENCE.
Other Unboosted PIs	Other Unboosted PIs: It is not recommended to co-administer INTELENCE with other unboosted PIs (including indinavir and saquinavir).
HIV-Antiviral Agents: PIs – Boosted (with co-administration of low-dose ritonavir)	
tipranavir/ritonavir	Concomitant use of INTELENCE with tipranavir/low-dose ritonavir may cause a significant decrease in the plasma concentration of etravirine. This may result in loss of therapeutic effect of INTELENCE. It is not recommended to co-administer tipranavir/low-dose ritonavir and INTELENCE.
HIV-Antiviral Agents: PIs – Boosted (with co-administration of cobicistat)	
atazanavir/cobicistat, darunavir/cobicistat	Co-administration of INTELENCE with atazanavir/cobicistat or darunavir/cobicistat may decrease plasma concentrations of the PI and/or cobicistat, which may result in loss of therapeutic effect and development of resistance. Co-administration of INTELENCE with atazanavir/cobicistat or darunavir/cobicistat is not recommended.
Other Agents	
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.
Antimycobacterials: rifampin, rifapentine	Rifampin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE should not be used in combination with rifampin or rifapentine as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE.
Herbal Products: 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.
Hepatitis C Virus (HCV) Direct-Acting Antivirals: elbasvir/grazoprevir	Co-administration of INTELENCE with elbasvir/grazoprevir may decrease elbasvir and grazoprevir concentrations, leading to reduced therapeutic effect of elbasvir/grazoprevir. It is not recommended to co-administer INTELENCE with elbasvir/grazoprevir.

Established and other potentially significant drug interactions with INTELENCE are included in **Table 2**. These recommendations are based on either drug interaction studies

or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 2: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)		
didanosine	↔ etravirine ↔ didanosine	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	↓ etravirine ↔ tenofovir	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 drugs and INTELENCE.		
HIV-Antiviral Agents: Protease Inhibitors (PIs) – Unboosted (i.e., without co-administration of low-dose ritonavir or cobicistat)		
nelfinavir	↑ nelfinavir	Concomitant use of INTELENCE with nelfinavir may cause an increase in the plasma concentrations of nelfinavir.
fosamprenavir, unboosted	↑ amprenavir	Concomitant use of INTELENCE with unboosted fosamprenavir may cause an increase in the plasma concentrations of amprenavir.
HIV-Antiviral Agents: PIs – Boosted (with co-administration of low-dose ritonavir)		
atazanavir/ritonavir	↑ etravirine ↓ atazanavir	The combination of INTELENCE and atazanavir/ritonavir can be used without dose adjustments.
darunavir/ritonavir	↓ etravirine ↔ darunavir	The combination of INTELENCE and darunavir/ritonavir can be used without dose adjustments.
fosamprenavir/ritonavir	↔ etravirine ↑ amprenavir	In the presence of etravirine, an increase of 69% for amprenavir exposure was observed when fosamprenavir/ritonavir was co-administered. Amprenavir and fosamprenavir/ritonavir may require dose adjustment when co-administered with INTELENCE.
lopinavir/ritonavir (soft gel capsule)	↑ etravirine ↓ lopinavir	The combination of INTELENCE and lopinavir/ritonavir (soft-gel capsule) can be used without dose adjustments.

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
lopinavir/ritonavir (melt extrusion tablet)	↓ etravirine ↔ lopinavir	The combination of INTELENCE and lopinavir/ritonavir (melt extrusion tablet) can be used without dose adjustments. The mean systemic exposure (AUC) of etravirine was reduced by 35% after co-administration of INTELENCE with lopinavir/ritonavir (melt extrusion tablet). Because the reduction in the mean systemic exposure of etravirine in the presence of lopinavir/ritonavir is similar to the reduction in mean systemic exposure of etravirine in the presence of darunavir/ritonavir, the combination of INTELENCE and lopinavir/ritonavir can be used without dose adjustments.
saquinavir/ritonavir (soft-gel capsule)	↓ etravirine ↔ saquinavir	The combination of INTELENCE and saquinavir/ritonavir can be used without dose adjustments.
HIV-Antiviral Agents: Dual Boosted PIs		
lopinavir/saquinavir/ ritonavir	↔ etravirine ↓ lopinavir ↓ saquinavir	The combination of INTELENCE and lopinavir/saquinavir/ritonavir can be used without dose adjustments.
HIV-Antiviral Agents: CCR5 Antagonists		
maraviroc	↓ maraviroc ↔ etravirine	INTELENCE acts as a CYP3A inducer and may cause significant decrease in the plasma concentration of maraviroc. A mean decrease of 46.8% (90% CI 38.1, 57.6) has been demonstrated in maraviroc AUC_{12} in a pharmacokinetic study in which maraviroc 300 mg and INTELENCE 200 mg were co-administered twice daily (Refer also to prescribing information for maraviroc). No dose adjustment for INTELENCE is needed.
maraviroc/darunavir/ritonavir	↑ maraviroc ↔ etravirine	INTELENCE acts as a CYP3A inducer and maraviroc plasma concentrations are decreased by 47% when combined with INTELENCE. Maraviroc dose should be increased to 600 mg twice daily when co-administered with INTELENCE in the absence of a boosted HIV protease inhibitor or other potent CYP3A inhibitor. No dose adjustment for INTELENCE is necessary. The potent CYP3A inhibitor effect of the boosted protease inhibitor darunavir/ritonavir overrides the inducer effect of INTELENCE. Maraviroc

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
		plasma concentrations increased 310% when maraviroc 150 mg, INTELENCE 200 mg and darunavir/ritonavir 600/100 mg were co-administered twice daily. Maraviroc dose should be decreased to 150 mg twice daily when co-administered with INTELENCE in the presence of a boosted HIV protease inhibitor or other potent CYP3A inhibitor. No dose adjustment for INTELENCE is necessary.
HIV-Antiviral Agents: Fusion Inhibitors		
enfuvirtide	↔ etravirine ↔ enfuvirtide	No interaction is expected for either INTELENCE or enfuvirtide when co-administered.
HIV-Antiviral Agents: Integrase Strand Transfer Inhibitors		
raltegravir	↔ etravirine ↓ raltegravir	The combination of INTELENCE and raltegravir can be used without dose adjustments.
dolutegravir	↓ dolutegravir ↔ etravirine	*Etravirine significantly reduced plasma concentrations of dolutegravir.
dolutegravir/darunavir /ritonavir	↓ dolutegravir ↔ etravirine	*Using cross-study comparisons to historical pharmacokinetic data for etravirine, dolutegravir did not appear to affect the pharmacokinetics of etravirine.
dolutegravir/lopinavir /ritonavir	AUC ↔, C_{min} 28% ↑ dolutegravir ↔ 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.
Other Agents		
Antiarrhythmics: digoxin	↑ digoxin ↔ 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,	↓ antiarrhythmics	

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
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.
Anticoagulants: warfarin		Warfarin concentrations may be affected when co-administered with INTELENCE. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with INTELENCE.
Antifungals: fluconazole,	↑ etravirine ↔ fluconazole	The incidence of adverse events was similar in patients co-administering fluconazole and INTELENCE or placebo in the Phase III trials. The combination of INTELENCE and fluconazole can be used without dose adjustments.
voriconazole	↑ etravirine ↑ voriconazole	The amount of safety data at these increased etravirine/voriconazole exposures are limited, therefore, etravirine and voriconazole should be coadministered with caution. No dose adjustment of INTELENCE or voriconazole is needed.
itraconazole, ketoconazole, posaconazole,	↓ 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 etravirine may increase plasma concentrations of INTELENCE. 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	↔ etravirine ↔ azithromycin	Based on the renal elimination pathway of azithromycin, no drug interactions are expected between azithromycin and INTELENCE.
clarithromycin	↑ etravirine ↓ clarithromycin	

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
	↑ 14-OH-clarithromycin	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.
Antimalarials: artemether/lumefantrine	$AUC_{0\text{-last}}$ ↔ etravirine $AUC_{0\text{-last}}$ 38% ↓ artemether $AUC_{0\text{-last}}$ 15% ↓ dihydro-artemisinin $AUC_{0\text{-last}}$ 13% ↓ lumefantrine	*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: rifabutin	↓ etravirine ↓ rifabutin ↓ 25-*O*-desacetylrifabutin	If INTELENCE is not co-administered with a boosted protease inhibitor, then INTELENCE and rifabutin can be used without dose adjustments. If INTELENCE is co-administered with boosted darunavir, lopinavir or saquinavir, then the combination with rifabutin should be used with caution due to the potential for significant reductions in etravirine exposure. When INTELENCE is co-administered with rifabutin and a boosted protease inhibitor, the recommended dose of rifabutin is determined by the prescribing information for the protease inhibitor component of the regimen.
Benzodiazepines: diazepam	↑ diazepam	Concomitant use of INTELENCE with diazepam may increase plasma concentrations of diazepam.
Corticosteroids: dexamethasone (systemic)	↓ etravirine	Systemic dexamethasone induces CYP3A4 and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE. Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use.
Hepatitis C Virus (HCV) Direct-Acting Antivirals: boceprevir	boceprevir AUC 10% ↑ C_{max} 10% ↑ C_{min} 12% ↓	

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
daclatasvir	↓ etravirine AUC $_{0,t}$ 23% ↓ C_{max} 24% ↓ C_{min} 29% ↓ ↓ daclatasvir	*The clinical significance of the reductions in etravirine pharmacokinetic parameters and boceprevir C_{min} in the setting of the combination therapies with other HIV antiretroviral medicines has not been assessed in HIV/HCV infected patients. Increased clinical and laboratory monitoring for HIV and HCV suppression is recommended. Co-administration of INTELENCE with daclatasvir may decrease daclatasvir concentrations. The dose of daclatasvir should be increased to 90 mg once daily when co-administered with INTELENCE.
ribavirin	↔ etravirine ↔ ribavirin	Based on the renal elimination pathway of ribavirin, no drug interactions are expected between ribavirin and INTELENCE.
telaprevir	↔ etravirine AUC_{8h} 16% ↓ telaprevir	*The combination of INTELENCE and telaprevir can be used without dose adjustments.
Estrogen-based Contraceptives: ethinylestradiol norethindrone	↔ etravirine ↑ ethinylestradiol ↔ norethindrone	The combination of estrogen- and/or progesterone-based contraceptives and INTELENCE can be used without dose adjustment.
HMG-CoA Reductase Inhibitors: atorvastatin	↔ etravirine ↓ atorvastatin ↑ 2-OH-atorvastatin	Atorvastatin plasma concentrations are decreased 37% and plasma concentrations of the active metabolite, 2-hydroxy-atorvastatin, are increased by 27% when combined with INTELENCE. Dose adjustment of atorvastatin may be necessary to tailor the clinical response when combined with INTELENCE.
fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	↔ etravirine ↑ fluvastatin, ↓ lovastatin, ↔ pitavastatin, ↔ pravastatin, ↑ rosuvastatin, ↓ simvastatin	No interaction between pravastatin and INTELENCE is expected.

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
		Lovastatin, rosuvastatin, and simvastatin are CYP3A4 substrates and co-administration with INTELENCE may result in lower plasma concentrations of the HMG-CoA reductase inhibitor. Fluvastatin, rosuvastatin, and, to a lesser extent, pitavastatin are 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.
H_2-Receptor Antagonists: ranitidine	↓ etravirine	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 Analgesics: methadone	↔ etravirine ↔ R(-) methadone ↔ S(+) methadone	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	↓ sildenafil ↓ N-desmethyl-sildenafil	Sildenafil plasma concentrations are decreased by 57% and plasma concentrations of the active metabolite, N-desmethyl-sildenafil, are decreased by 41% when combined with INTELENCE. Concomitant use of PDE-5 inhibitors with INTELENCE may require dose adjustment of the PDE-5 inhibitor to attain the desired clinical effect.
Platelet Aggregation Inhibitors: 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	↑ etravirine	INTELENCE can be co-administered with proton pump inhibitors without dose adjustments.
Selective Serotonin Reuptake Inhibitors (SSRIs): paroxetine	↔ etravirine ↔ paroxetine	INTELENCE can be co-administered with paroxetine without dose adjustments.
↑ = increases, ↓ = decreases, ↔ = no change		

***Statement is based on a study conducted in healthy participants**

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data on the effect of etravirine on fertility are available. Etravirine treatment of male and female rats at oral doses up to 500 mg/kg/day had no effect on fertility, at exposures approximately equivalent to those obtained in humans, based on AUC values.

Use in pregnancy

Category B1

There are no adequate and well-controlled studies with etravirine in pregnant women. Studies in animals have not shown evidence of developmental toxicity or an effect on reproductive function.

Developmental studies have been performed at oral doses of INTELENCE up to 1000 mg/kg/day in rats and up to 375 mg/kg/day in rabbits with no evidence of major embryofetal abnormality. Minor vertebral and rib anomalies were found in rat foetuses at 1000 mg/kg/day. The maternal plasma exposures (AUC values) at the no observed effect levels (NOELS) were approximately equivalent in both species to those obtained in humans at the recommended clinical dose.

In the rat pre- and postnatal development study, development and reproductive performance of offspring was not affected by maternal treatment with etravirine at oral doses up to 500 mg/kg/day. The maximum plasma exposures achieved in rats were approximately half those obtained in humans at the recommended clinical dose.

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 **section 5.2 Pharmacokinetic properties**).

Etravirine was detectable in maternal cord blood.

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 (see **section 4.2 Dose and method of administration** and **section 5.2 Pharmacokinetic properties**).

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

Use in lactation

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

4.7 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 **section 4.8 Adverse effects (Undesirable effects)**).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions from clinical trials

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.). 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 drug reactions (ADRs) (≥ 5%) that were at least grade 2 in severity were rash (10.0% in the INTELENCE arm and 3.5% in the placebo arm), diarrhoea (7.0% in the INTELENCE arm and 11.3%), hypertriglyceridaemia (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 ADRs reported during treatment with INTELENCE were grade 1 to 2 in severity. Grade 3 or 4 ADRs were reported in 22.2% and 17.2% of the INTELENCE and placebo treated patients, respectively. The most commonly reported grade 3 or 4 ADRs were hypertriglyceridaemia (4.2% in the INTELENCE arm and 2.3% in the placebo arm) and hypercholesterolaemia (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 anaemia (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 4: Treatment Emergent Laboratory Abnormalities**). All other grade 3 and/or 4 ADRs were reported in less than 1.5% of the INTELENCE treated patients. 5.2% of patients in the INTELENCE arm discontinued treatment due to ADRs compared to 2.6% of patients in the placebo arm. The most common ADRs 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 **section 4.4 Special warnings and precautions for use**). 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). 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.

ADRs of moderate intensity or greater (≥ grade 2) and reported in ≥ 1% of patients treated with INTELENCE are summarised in the table below. The ADRs are listed by system organ class (SOC) and frequency. Laboratory abnormalities considered ADRs are included in a table below (see Treatment Emergent Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% of Patients).

Table 3: Treatment-Emergent Adverse Reactions of at least Moderate Intensity (Grades 2-4) in ≥ 1% of Adult Patients in the INTELENCE Treatment Groups		
System Organ Class, Preferred Term, %	**DUET-1 and DUET-2 Trials**	
	INTELENCE + BR N=599	**Placebo + BR N=604**
Cardiac Disorders		
Myocardial infarction	1.3%	0.3%
Blood and Lymphatic System Disorders		
Anaemia	4.0%	3.8%
Thrombocytopenia	1.3%	1.5%
Gastrointestinal Disorders		
Diarrhoea	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%
General Disorders and Administration Site Conditions		
Fatigue	3.5%	4.6%
Metabolism and Nutrition Disorders		
Hypertriglyceridemia	6.3%	4.3%
Hypercholesterolemia	4.3%	3.6%
Hyperlipidemia	2.5%	1.3%
Hyperglycaemia	1.5%	0.7%
Diabetes mellitus	1.3%	0.2%
Nervous System Disorders		
Peripheral neuropathy	3.8%	2.0%
Headache	3.0%	4.5%
Psychiatric Disorders		
Insomnia,	2.7%	2.8%
Anxiety	1.7%	2.6%
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%
Vascular Disorders		
Hypertension	3.2%	2.5%
N=total number of patients per treatment group BR = Background Regimen		

Treatment-emergent ADRs occurring in less than 1% of patients (n=599) receiving INTELENCE and of at least moderate intensity (≥ Grade 2) are listed below by body system:

Body as a Whole:	sluggishness
Cardiovascular System:	angina pectoris, atrial fibrillation
Digestive System:	abdominal distension, pancreatitis, constipation, dry mouth, hematemesis, retching, stomatitis
Immune System:	drug hypersensitivity, immune reconstitution syndrome
Liver and Biliary System:	hepatomegaly, cytolytic hepatitis, hepatic steatosis, hepatitis,
Metabolic and Nutritional:	anorexia, dyslipidaemia
Nervous System:	paraesthesia, somnolence, convulsion, hypoesthesia, amnesia, syncope, disturbance in attention, hypersomnia, tremor,
Respiratory System:	exertional dyspnea, bronchospasm
Skin and Appendages:	prurigo, hyperhidrosis, dry skin, swelling face
Special Senses:	blurred vision, vertigo
Urogenital System:	gynecomastia
Psychiatric:	sleep disorders, abnormal dreams, confusional state, disorientation, nervousness, nightmares

Additional ADRs of at least moderate intensity observed in other trials were acquired lipodystrophy, angioneurotic oedema, 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 in Treatment-Experienced Patients:

Treatment-emergent Grade 3 to Grade 4 laboratory abnormalities, considered ADRs, reported in ≥ 2% of adult patients treated with INTELENCE are presented in **Table 4**.

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

		Pooled DUET-1 and DUET-2 Trials	
Laboratory Parameter Preferred Term, %	**DAIDS Toxicity Range**	**INTELENCE + BR N=599**	**Placebo + BR N=604**
GENERAL BIOCHEMISTRY			
Pancreatic Amylase		8.9%	9.4%
Grade 3	> 2-5 x ULN	7.4%	8.4%
Grade 4	> 5 x ULN	1.5%	1.0%
Creatinine		2.0	1.7
Grade 3	> 1.9-3.4 x ULN	2.0	1.5

		Pooled DUET-1 and DUET-2 Trials	
Laboratory Parameter Preferred Term, %	**DAIDS Toxicity Range**	**INTELENCE + BR N=599**	**Placebo + BR N=604**
Grade 4	> 3.4 x ULN	0	0.2
Lipase		3.4%	2.6%
Grade 3	> 3-5 x ULN	2.0%	2.2%
Grade 4	> 5xULN	1.3%	0.5%
GENERAL HAEMATOLOGY			
White blood cell count		2.0	4.3
Grade 3	1,000-1,499/mm^3	1.0	3.6
Grade 4	<1,000/mm^3	1.0	0.7
HAEMATOLOGY DIFFERENTIAL COUNTS			
Neutrophils		5.1%	7.5%
Grade 3	500-749/mm^3	3.5%	4.3%
Grade 4	< 500/mm^3	1.5%	3.1%
LIPIDS AND GLUCOSE			
Total cholesterol		8.1%	5.3%
Grade 3	> 7.77 mmol/L	8.1%	5.3%
Low density lipoprotein		7.2%	6.6%
Grade 3	> 4.9 mmol/L	7.2%	6.6%
Triglycerides		9.2%	5.8%
Grade 3	8.49-13.56 mmol/L	5.7%	4.0%
Grade 4	> 13.56 mmol/L	3.5%	1.8%
Elevated Glucose Levels		3.5%	2.3%
Grade 3	13.89-27.75 mmol/L	3.5%	2.2%
Grade 4	> 27.75 mmol/L	0%	0.2%
HEPATIC PARAMETERS			
Alanine amino transferase		3.7%	2.0%
Grade 3	5.1-10 x ULN	2.7%	1.7%
Grade 4	> 10 x ULN	1.0%	0.3%
Aspartate amino transferase		3.2%	2.0%
Grade 3	5.1-10 x ULN	2.7%	1.7%
Grade 4	> 10 x ULN	0.5%	0.3%

ULN = Upper Limit of Normal
BR = Background Regimen

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 **section 4.4. Special warnings and precautions for use**).

Immune reconstitution inflammatory 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 inflammatory syndrome). Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported in the context of Immune Reconstitution syndrome (see **4.4. Special warnings and precautions for use**).

Additional information on special population

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 2.9% in the placebo arm discontinued because of liver or biliary system disorders. Standard clinical monitoring of patients with chronic hepatitis is considered adequate.

Postmarketing experiences

The following events have been identified during the 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.

Immune system disorders

Fatal cases of toxic epidermal necrolysis have been reported. Severe 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 **4.4. Special warnings and precautions for use**).

Musculoskeletal and connective tissue disorders

Rhabdomyolysis

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 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. Emesis is not recommended due to the risks of aspiration. Administration of activated charcoal may be used to remove unabsorbed active substance when it is expected that there is drug still in the upper gastrointestinal tract; for most overdoses this is within 1 hour of ingestion. Charcoal aspiration can be fatal, so the risk versus benefit of using activated charcoal should be considered. Please refer to the current Therapeutic Guidelines. Since etravirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: J05AG04.

Mechanism of action

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Etravirine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Etravirine can bind in at least two 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 repositioning and reorientation (translation and rotation) within the pocket. Etravirine does not inhibit the human DNA polymerases α, β and γ *in vitro*.

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 protease inhibitors (PIs) amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir, and saquinavir; the nucleoside and nucleotide reverse transcriptase inhibitors [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 vitro

Etravirine-resistant strains were selected in cell culture from wild-type HIV-1 of different origins and subtypes, and from NNRTI resistant HIV-1. Reduced susceptibility to

etravirine generally required multiple substitutions in the reverse transcriptase (RT), with the following observed most frequently: L100I, E138K, E138G, V179I, Y181C, and M230I.

In the Phase III 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 in vitro

In a panel of HIV-1/HXB2 mutants with well-defined single or multiple amino acid substitutions in the RT associated with NNRTI resistance, including the most commonly found K103N, 56/65 isolates with a single substitution, 18/40 with a double substitution, and 6/21 with a triple substitution remained susceptible to etravirine (≤3-fold change in EC_{50}). The single amino acid substitutions with highest resistance to etravirine were Y181I (13-fold change in EC_{50}) and Y181V (17-fold change). Mutant strains with a single NNRTI resistance-associated substitution (K101P, K101Q, E138Q, M230L) had cross-resistance between etravirine and efavirenz. Highest levels of resistance were observed with the combination of substitutions V179F + Y181C (187-fold change), V179F + Y181I (123-fold change), or V179F + Y181C + F227C (888-fold change).

The antiviral activity of etravirine in cell culture against 35 of 39 HIV-1 strains with multiple amino acid substitutions associated with resistance to N(t)RTIs and/or PIs was comparable to that observed against wild type HIV-1.

In a panel of 6171 clinical isolates resistant to at least one NNRTI, 37.3% were resistant to etravirine, and 78.8%, 87.4% and 95.3% were resistant to delavirdine, efavirenz and nevirapine, respectively (resistance defined as a fold-change > the respective biological cut-off for the assay)

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

Resistance *in vivo*

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 **Table 5**). These individual mutations occurred in the presence of other NNRTI RAMs. V179F was never present without Y181C.

Table 5: 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%	26.2%

	(41/64)	(16/61)
≥3	38.3% (23/60)	28.2% (11/39)

n = number of patients with observations; N = Total number of patients

* non-VF excluded = The population analysed was all patients excluding those that discontinued for reasons other than virologic failure

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 **Table 6**. These baseline phenotype groups are based on the select subject populations in DUET-1 and DUET-2 and are not meant to represent definitive clinical susceptibility breakpoints for INTELENCE. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to etravirine in treatment-experienced patients.

Table 6: Response to INTELENCE by Baseline Etravirine Phenotype: Non VF-excluded* population of the Pooled DUET studies - 'ENF re-using or ENF not using' patients

	Mean (SE) change in viral load from baseline at Week 48		**Proportion of patients with <50 copies/mL at Week 48 % (n/N)**	
Baseline Etravirine Phenotype (fold change ranges)	**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; VF = Virological Failure; ENF = enfuvirtide

* non-VF excluded = The population analyzed was all patients excluding those that discontinued for reasons other than virologic failure

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

Clinical trials

The evidence of efficacy of INTELENCE is based on the analyses of 48-week data from 2 ongoing, randomised, double-blinded, placebo-controlled, Phase III trials DUET-1 (TMC125-C206) and DUET-2 (TMC125-C216). The primary objective of the trials was to

show the superiority of TMC125 compared to placebo as part of an antiretroviral therapy (ART) containing TMC114/RTV and an investigator-selected OBR, in the proportion of subjects with undetectable plasma viral load values (< 50 copies/mL) at Week 24

The primary efficacy parameter of the DUET-1 and DUET-2 trials was the proportion of subjects with confirmed undetectable viral load (< 50 copies/mL) at Week 24 according to the TLOVR (time to loss of virologic response) imputation algorithm.

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 background regimen (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 drugs (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). In the pooled analysis for DUET-1 and DUET-2, demographics and baseline characteristics were balanced between the INTELENCE arm and the placebo arm. **Table 7** describes the demographic and baseline disease characteristics of the patients in the INTELENCE arm and patients in the placebo arm.

Table 7: Demographic and Baseline Disease Characteristics of Patients in the DUET-1 and DUET-2 Trials (Pooled Analysis)

	DUET 1 and DUET 2 Trials	
	INTELENCE + BR N=599	**Placebo + BR N=604**
Demographic Characteristics		
Median Age, years (range)	46 (18-77)	45 (18-72)
Sex		
Male	90.0%	88.6%
Female	10.0%	11.4%
Race		
White	70.1%	69.8%
Black	13.2%	13.0%
Hispanic	11.3%	12.2%
Asian	1.3%	0.6%

	DUET 1 and DUET 2 Trials	
	INTELENCE + BR N=599	**Placebo + BR N=604**
Other	4.1%	4.5%
Baseline Disease Characteristics		
Median Baseline Plasma HIV-1 RNA (range), log_{10} copies/mL	4.8 (2.7-6.8)	4.8 (2.2-6.5)
Percentage of Patients with Baseline Viral Load:		
< 30,000 copies/mL	27.5%	28.8%
≥ 30,000 copies/mL and< 100,000 copies/mL	34.4%	35.3%
≥ 100,000 copies/mL	38.1%	35.9%
Median Baseline CD4+ Cell Count (range), cells/mm^3	99 (1-789)	109 (0-912)
Percentage of Patients with Baseline CD4+ Cell Count:		
< 50 cells/mm^3	35.6%	34.7%
≥ 50 cells/mm^3 and < 200 cells/mm^3	34.8%	34.5%
≥ 200 cells/mm^3	29.6%	30.8%
Median (range) Number of Primary PI Mutations[a]	4 (0-7)	4 (0-7)
Percentage of Patients with Previous Use of NNRTIs:		
0	8.2%	7.9%
1	46.9%	46.7%
>1	44.9%	45.4%
Percentage of Patients with Previous Use of the following NNRTIs:		
Efavirenz	70.3%	72.5%
Nevirapine	57.1%	58.6%
Delavirdine	13.7%	12.7%
Median (range) Number of NNRTI RAMs[b]	2 (0-5)	2 (0-4)
Median Fold Change of the Virus for the Following NNRTIs:		
Delavirdine	27.4	26.4
Efavirenz	63.9	46.1
Etravirine	1.6	1.5
Nevirapine	74.3	74.3
Percentage of Patients with Previous Use of Enfuvirtide	39.6%	41.9%

	DUET 1 and DUET 2 Trials	
	INTELENCE + BR N=599	**Placebo + BR N=604**

RAMs = Resistance-Associated Mutations

BR = Background Regimen

FC = fold change in EC_{50}

[a] IAS-USA primary PI mutations [November 2005]: D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, V82A/F/L/S/T, I84V, N88S, L90M

[b] Tibotec NNRTI RAMs [March 2007]: A98G, L100I, K101E/P/Q, K103H/N/S/T, V106A/M, V108I, E138G/K/Q, V179D/E/F/G/I, Y181C/I/V, Y188C/H/L, G190A/C/E/Q/S, H221Y, P225H, F227C/L, M230I/L, P236L, K238N/T, Y318F

Efficacy results at 48 weeks for patients in the INTELENCE arm and patients in the placebo arm for the total study population (pooled DUET-1 and DUET-2) are shown in **Table 8**.

Table 8: Outcomes of Treatment at Week 48 of the DUET-1 and DUET-2 Trials (Pooled Analysis)

	DUET-1 and DUET-2 Trials		
	Total Study Population		
	INTELENCE + BR N=599	**Placebo + BR N=604**	**Treatment difference (95% CI)[c]**
Virologic Responders Confirmed Undetectable Viral Load (< 50 HIV-1 RNA copies/mL) at Week 48[a,d]	60.6%	39.7%	20.9% (15.3%; 26.4%)[d]
Virologic failures	29.5%	49.7%	-20.1% (-25.5%; -14.7%)
≥ 50 HIV-1 RNA copies/mL and < 400 HIV-1 RNA copies/mL	5.8%	3.3%	2.5% (0.2%; 4.9%)
≥ 400 HIV-1 RNA copies/mL	6.3%	20.0%	-13.7% (-17.4%; -9.9%)
Rebound[b]	7.8%	9.3%	-1.4 (-4.6%; 1.7%)
Discontinued due to virologic failure before Week 48	9.5%	17.1%	-7.5% (-11.3%; -3.7%)
Death	1.8%	3.3%	-1.5% (-3.3%; 0.3%)
Discontinuation due to adverse events	5.2%	2.3%	2.9% (0.7%; 5.0%)
Discontinuation due to other reasons	2.8%	5.0%	-2.1% (-4.3%; 0.1%)

[a] Patients achieved virologic response (two consecutive viral loads < 50 copies/mL) and maintained it through week 48

[b] Patients with an initial response (confirmed viral load < 50 copies/mL), but with at least two consecutive values > 50 copies/mL before Week 48

[c] Confidence interval around observed difference of response rates

[d] P-value < 0.001 from logistic regression model including stratification factors

BR = Background Regimen

The proportion of patients with confirmed viral load < 50 copies/mL at all time points up to Week 48, in the overall population according to the (Time to Loss of Virologic Response) TLOVR imputation algorithm, is presented in **Figure 1**.

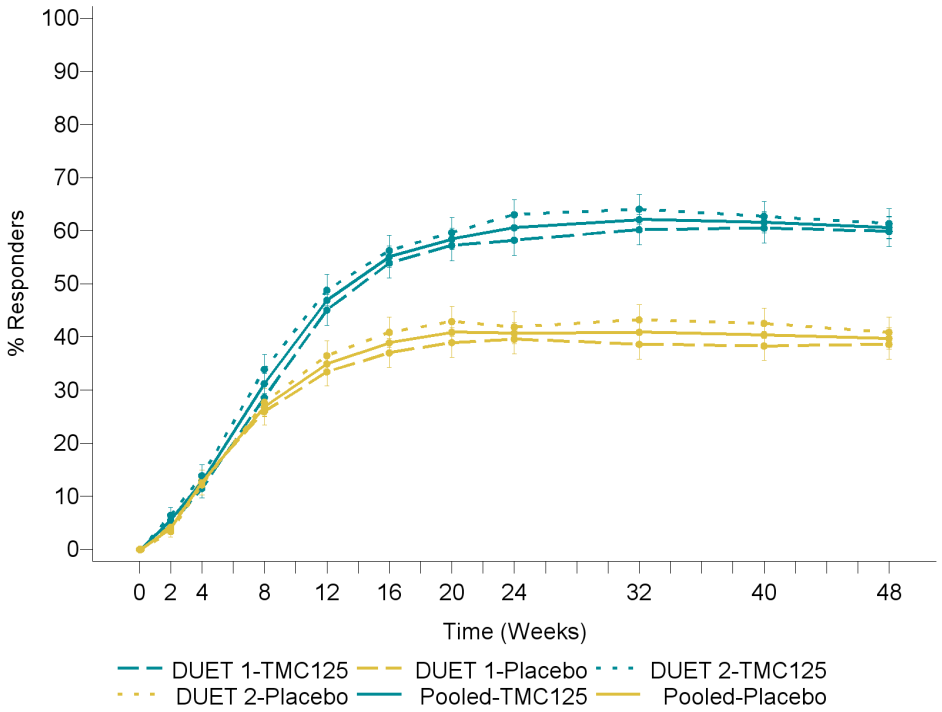


Figure 1: Proportion of Virologic Responders (< 50 Copies/mL; TLOVR Imputed), Overall in the DUET-1 and DUET-2 Trials

In the total study population, through 48 weeks of treatment, the proportion of patients with < 400 HIV-1 RNA copies/mL in the arm receiving INTELENCE was 71.5% compared with 47.4% in the placebo arm. At Week 48, the mean decrease in plasma HIV-1 RNA from baseline at Week 48 were –2.25 $\log_{10}$ copies/mL in the arm receiving INTELENCE and –1.49 $\log_{10}$ copies/mL for the placebo arm. The change from Baseline in $\log_{10}$ viral load at all time points is also presented graphically in **Figure 2**. Similar results were seen across the 2 DUET studies.

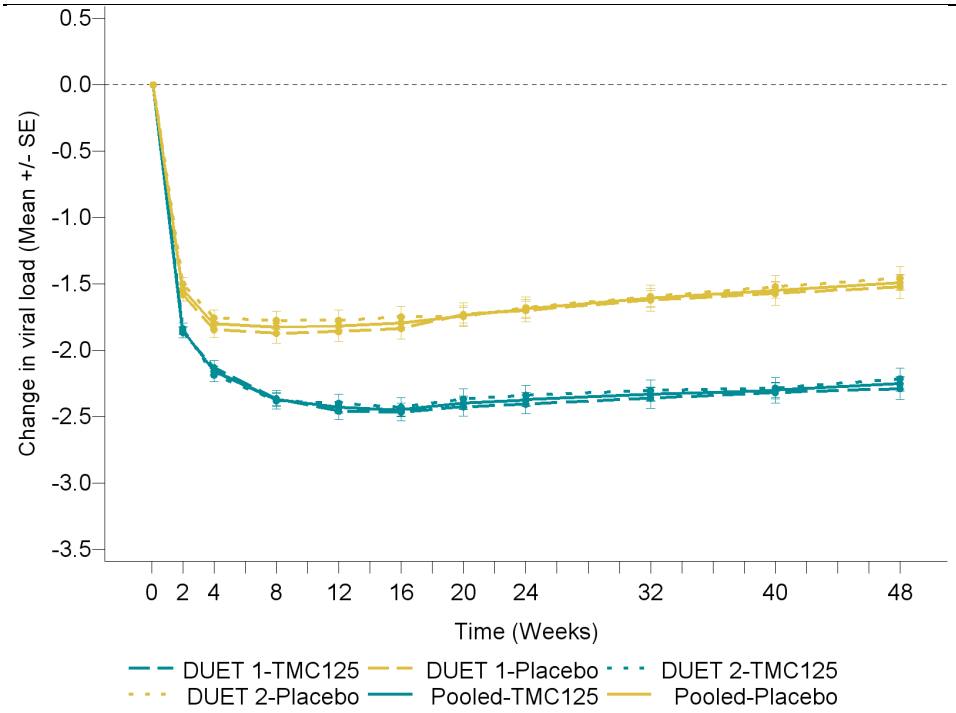


Figure 2: Change from Baseline in Log_{10} Viral Load, Overall in the DUET-1 and DUET-2 Trials

INTELENCE also showed an additional benefit over placebo in CD4+ cell count increase from baseline: 98.2 x 10^6 cells/L versus 72.9 x 10^6 cells/L, respectively. A graphical presentation of the mean change in CD4 cell count from Baseline is provided in **Figure 3**.

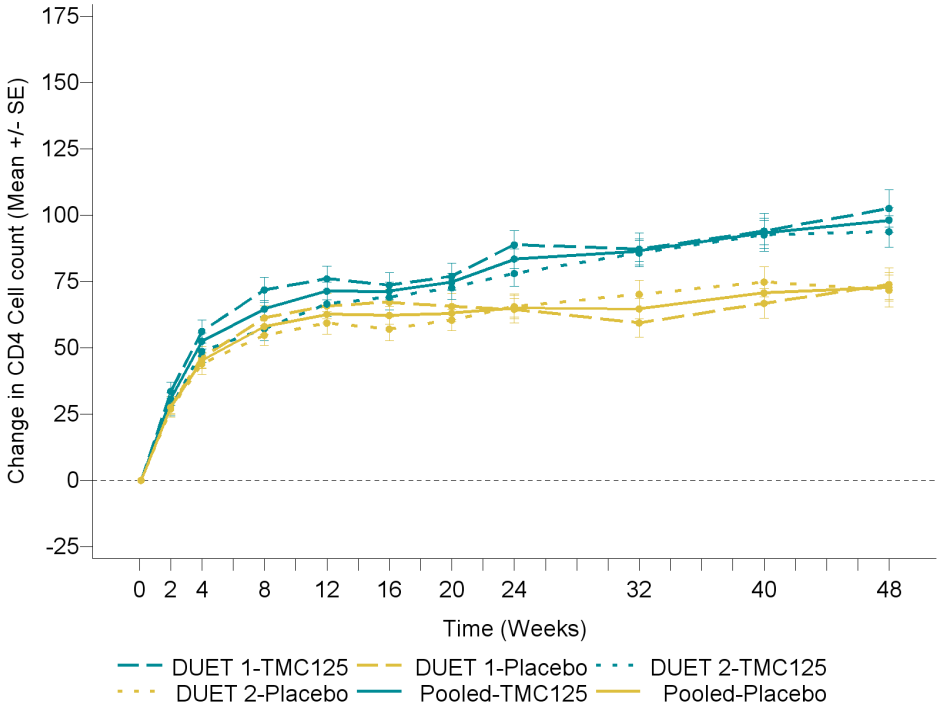


Figure 3: Change from Baseline in CD4 Cell Count (x 10^6/L) (Imputed [NC = F]) in the DUET-1 and DUET-2 Trials

As primary analysis method, the Cochran-Mantel-Haenszel test controlling for the stratification factors (use of ENF in the underlying ART, previous use of darunavir, and baseline plasma viral load) was applied to test the difference between the treatment groups at 24 weeks.

Because the effect of the INTELENCE treatment was expected to be different between subjects who were using ENF *de novo* in the optimised background regimen (OBR) and the subjects who were not using or re-using ENF, it was first tested whether there was a significant interaction effect between INTELENCE and ENF use.

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 in this subgroup was 57.0% in the INTELENCE arm and 33.0% in the placebo arm (a difference (95%CI) of 24.0% (17.6%;30.3%)). 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 (95%CI) of 12.7% (2.3%;23.2%)).

At week 48, 35 patients (5.8%) in the INTELENCE arm reached the endpoint of AIDS-defining illness or death compared to 59 (9.8%) patients in the placebo arm.

In the population of patients who either re-used or did not use ENF, through 48 weeks of treatment, the proportion of patients with a decrease in HIV-1 RNA versus baseline of > 1.0 $\log_{10}$ in the arm receiving INTELENCE compared to placebo was 71.3% and 42.9%, respectively. In addition, the mean decrease in plasma HIV-1 RNA from baseline at Week 48 was -2.13 $\log_{10}$ copies/mL in the arm receiving INTELENCE and –1.23 $\log_{10}$ copies/mL for the placebo arm. INTELENCE also showed an additional benefit over placebo in CD4+ cell count increase from baseline: 85.7 x 10^6 cells/L versus 59.2 x 10^6 cells/L, respectively.

In the population of patients using ENF *de novo*, through 48 weeks of treatment, the proportion of patients with a decrease in HIV-1 RNA versus baseline of > 1.0 $\log_{10}$ in the arm receiving INTELENCE compared to placebo was 83.0% and 74.8%, respectively. In addition, the mean decrease in plasma HIV-1 RNA from baseline at Week 48 was –2.60 $\log_{10}$ copies/mL in the arm receiving INTELENCE and -2,22 $\log_{10}$ copies/mL for the placebo arm. The CD4+ cell count increase from baseline was 134.5 x 10^6 cells/L in the INTELENCE arm versus 111.4 x 10^6 cells/L in the placebo arm.

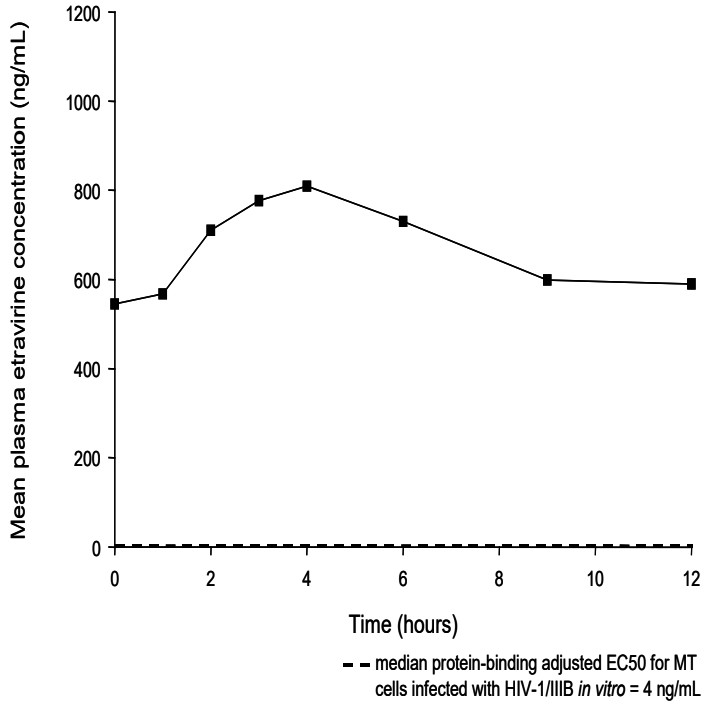
The added benefit of etravirine when combined with a PI is not only observed with darunavir/ritonavir, as this was also seen when it was combined with LPV/rtv in a randomised, controlled, partially blind, Phase IIb trial, TMC125-C223. Patients included had documented genotypic evidence of resistance (either at screening or historically) to currently available NNRTIs, at least 3 primary PI mutations at screening and previous NRTI experience. Patients were randomised to the control arm (standard of care regimen consisting of at least 3 approved drugs {NRTIs and/or PIs and/or enfurvitide in any combination}), INTELENCE 400 mg b.i.d. or INTELENCE 800 mg b.i.d in a 1:2:2 ratio. The 800 mg dose used in this study is equivalent to the 200 mg dose used in the Phase III studies.

Results from this trial showed responses in the INTELENCE treatment group were statistically superior to the control group. This clinical evidence confirmed the *in vitro* virologic profile of the compound and demonstrated that INTELENCE is an active and potent treatment option for patients with NNRTI resistance.

5.2 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.

Figure 4: Mean Steady-State Plasma Concentration-Time Profile of Etravirine 200 mg b.i.d. at Week 4 in HIV-1 Infected Patients (N=25) [integrated data from DUET-1 and DUET-2 substudies]



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%), after a croissant (20%), or fasted (51%). Therefore, to achieve optimal exposure, INTELENCE should be taken following a meal (see **section 4.2 Dose and method of administration**).

Distribution

Etravirine is approximately 99.9% bound to plasma proteins, primarily to albumin (99.6%) and α1-acid glycoprotein (94.5-97.7%) at physiological concentrations *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) and *E. coli* systems expressing recombinant human CYP enzymes indicate that etravirine primarily undergoes oxidative metabolism by the hepatic cytochrome CYP450 (CYP3A) system and, to a lesser extent, by the CYP2C family followed by glucuronidation.

Excretion

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 faeces. Unchanged etravirine was not detected in urine. The terminal elimination half-life of etravirine was approximately 30-40 hours.

Special Populations

Children and adolescents

The pharmacokinetics of etravirine in paediatric patients are under investigation. There are insufficient data at this time to recommend a dose (see **section 4.2 Dose and method of 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 **section 4.2 Dose and method of administration** and **section 4.4 Special warnings and precautions for use**).

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.

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 haemodialysis or peritoneal dialysis (see **section 4.2 Dose and method of administration** and **section 4.4 Special warnings and precautions for use**).

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 **section 4.2 Dose and method of administration** and **section 4.4 Special warnings and precautions for use**).

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 **section 4.8 Adverse effects (Undesirable effects)**), no dose adjustment is necessary in patients co-infected with hepatitis B and/or C virus.

Pregnancy and Postpartum

Study TMC114HIV3015 evaluated etravirine 200 mg twice daily in combination with other antiretroviral medicinal products in pregnant women during the second and third trimesters of pregnancy and postpartum.

Fifteen participants were enrolled, median (range) of maternal age was 26 (30 – 34) years, 11 were Black/African American, 2 were Hispanic and 2 were White. Median (range) BMI was 30.48 (23.4 to 47.5) kg/m^2. All had Class A disease according to the CDC Classification System for HIV Infection 1993.

Lower apparent clearance (CL/F) was documented during the second and third trimesters of pregnancy compared to 6-12 weeks post-partum. Higher geometric mean values for total etravirine C_{max}, AUC_{12h} and C_{min} were observed during pregnancy compared to postpartum (**Table 9**). The differences were less pronounced for unbound etravirine exposure.

Table 9: 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	13	10[a]
C_{min}, ng/mL	269 ± 182	383 ± 210	349 ± 103
	284	346	371
C_{max}, ng/mL	569 ± 261	774 ± 300	785 ± 238
	528	828	694
AUC12h, h*ng/mL	5004 ± 2521	6617 ± 2766	6846 ± 1482
	5246	6836	6028
CL/F, L/h	61.5 ± 56.7	35.9 ± 17.0	30.4 ± 6.19
	38.3	29.3	33.2

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

Each participant served as her own control and for intra-individual comparisons, 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 compared to postpartum, and 1.1-, 1.4- and 1.2-fold higher, respectively, during the 3rd trimester of pregnancy compared to postpartum.

The ratio of individual cord/maternal intra-partum etravirine plasma concentrations ranged from 18.83% to 63.41%; with %CV of 35.5 (see **4.2 Dose and method of administration** and **section 4.4 Special warnings and precautions for use**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Etravirine has tested negative in the *in vitro* Ames reverse mutation assay, in the *in vitro* chromosomal aberration assay in human lymphocytes, and in the *in vitro* clastogenicity

genotoxicity assay mouse lymphoma, assay, tested both in the absence and presence of a metabolic activation system. Etravirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Carcinogenicity

Etravirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 50, 200/100 and 400/200/100 mg/kg were administered to mice and doses of 70/50, 200/150/100 and 600/200/100 (males) and 70, 200/150 and 600/200/150 (females) mg/kg were administered to rats. Doses were reduced due to increased mortality. Etravirine was not carcinogenic in rats and in male mice. In female mice the incidence of hepatocellular adenomas and carcinomas was statistically significantly increased at all doses. 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 considered to be of limited relevance to humans. At the highest tested doses, the systemic exposures (based on AUC) to etravirine were between 0.8- and 0.9 fold (mice) and between 0.2- and 1.1 -fold (rats), relative to those observed in humans at the recommended therapeutic dose (200 mg b.i.d.)

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose,

Colloidal anhydrous silica,

Magnesium stearate,

Hypromellose,

Croscarmellose sodium

Lactose monohydrate (100 mg tablets only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.

6.5 NATURE AND CONTENTS OF CONTAINER

INTELENCE 100 mg tablets are provided in high-density polyethylene (HDPE) plastic bottles containing 120 tablets and 3 desiccant pouches, fitted with a polypropylene (PP) child resistant closure*.

INTELENCE 200 mg tablets are provided in high-density polyethylene (HDPE) plastic bottles containing 60 tablets and 3 desiccant pouches, fitted with a polypropylene (PP) child resistant closure.

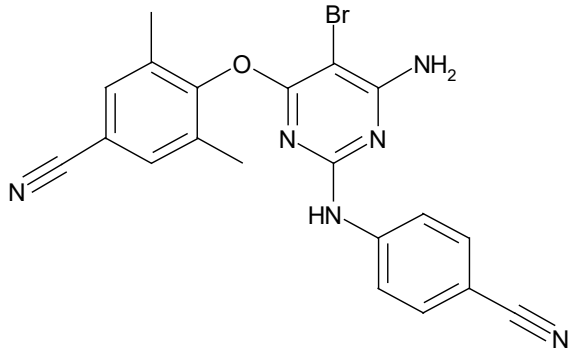
*Not currently marketed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



CAS: 269055-15-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

19 December 2008

10. DATE OF REVISION

19 July 2024

Summary table of changes

Section changed	Summary of new information
4.4	Editorial update to move text up for better readability. Amendment of statement related to transmission of HIV to others