INTELENCE®

etravirine

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

INTELENCE etravirine 100 mg tablets.

INTELENCE etravirine 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg tablet contains 100 mg of etravirine.

Each 200 mg tablet contains 200 mg of etravirine.

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

Excipient with known effect:

Each 100 mg tablet contains 160 mg lactose.

For the full list of excipients, see **section 6.1**.

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.

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 48-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 **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

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**).

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.

Special populations

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 **sections 4.4** and **5.2**).

Renal impairment:

No dose adjustment is required in patients with renal impairment (see **sections 4.4** and **5.2**).

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**).

Elderly:

Limited information is available in this population (see **sections 4.4** and **5.2**).

Pregnancy:

No dose adjustment is required during pregnancy and postpartum (see **sections 5.2** and **4.4**).

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

Transmission of HIV

Patients should be advised that current antiretroviral therapy does not cure HIV. Appropriate precautions to prevent 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**).

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 1-2 weeks on continued therapy. The incidence of rash was higher in females (see **section 4.8**).

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**).

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**).

Patients with co-existing conditions

Liver 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 **sections 4.2** and **5.2**).

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 **sections 4.2** and **5.2**).

Special populations

Children

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

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 **sections 4.2** and **5.2**).

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 a weak 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 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.

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)		

Concomitant Drug Class: Drug Name	**Effect on Concentration of Etravirine or Concomitant Drug**	**Clinical Comment**
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)		
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 can be used without dose adjustments.
lopinavir/ritonavir (melt extrusion tablet)	↓ etravirine ↔ lopinavir	The combination of INTELENCE and lopinavir/ritonavir (melt extrusion tablet) 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	Concomitant use of INTELENCE with maraviroc may cause significant decrease in the plasma concentration of maraviroc. When INTELENCE is co-administered with maraviroc in the absence of potent CYP34 inhibitor (e.g., a boosted PI), the

Concomitant Drug Class: Drug Name	**Effect on Concentration of Etravirine or Concomitant Drug**	**Clinical Comment**
		recommended dose of maraviroc is 600 mg b.i.d. no dose adjustment for INTELENCE is needed.
maraviroc/darunavir/ritonavir	↑ maraviroc ↔ etravirine	When INTELENCE is co-administered with maraviroc in the presence of a potent CYP3A inhibitor (e.g., a boosted PI), refer to the applicable prescribing information of maraviroc for the recommended dose, treating INTELENCE as a CYP3A inducer (such as efavirenz). No dose adjustment for INTELENCE is needed.
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		
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} 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.
elvitegravir/ritonavir	↔ elvitegravir ↔ ritonavir ↔ etravirine	The combination of INTELENCE and elvitegravir/ritonavir can be used without dose adjustments.
raltegravir	↔ etravirine ↓ raltegravir	The combination of INTELENCE and raltegravir can be used without dose adjustments.
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, lidocaine (systemic), mexiletine, propafenone, quinidine	↓ antiarrhythmics	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

Concomitant Drug Class: Drug Name	**Effect on Concentration of Etravirine or Concomitant Drug**	**Clinical Comment**
		recommended that the international normalized ratio (INR) be monitored when warfarin is combined with INTELENCE.
Antifungals: fluconazole, ↑ etravirine ↑ voriconazole itraconazole, ketoconazole, posaconazole, voriconazole	↑ etravirine ↔ fluconazole ↑ etravirine ↑ voriconazole ↓ itraconazole ↓ ketoconazole ↔ posaconazole ↑ voriconazole	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. The combination of INTELENCE and voriconazole can be used without dose adjustments. Posaconazole, a potent inhibitor of CYP3A4, may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE. The combination of INTELENCE and these antifungals can be used without dose adjustments.
Antiinfectives: azithromycin clarithromycin	↔ etravirine ↔ azithromycin ↑ etravirine ↓ clarithromycin ↑ 14-OH-clarithromycin	Based on the renal elimination pathway of azithromycin, no drug interactions are expected between azithromycin and INTELENCE. 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	↔ etravirine ↓ artemether ↓ 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.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Etravirine or Concomitant Drug**	**Clinical Comment**
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	↑ AUC, ↓ C_{min} boceprevir ↓ etravirine	The combination of INTELENCE and boceprevir can be used without dose adjustments. 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.
daclatasvir	↓ daclatasvir	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.
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,	↔ etravirine ↑ fluvastatin, ↓ lovastatin,	No interaction between pravastatin and INTELENCE is expected.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Etravirine or Concomitant Drug**	**Clinical Comment**
pravastatin, rosuvastatin, simvastatin	↔ pitavastatin, ↔ pravastatin, ↑ rosuvastatin, ↓ simvastatin	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		

4.6 Fertility, pregnancy and lactation

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 effect on reproductive function and fertility.

Reproduction studies conducted with etravirine have shown no teratogenicity in rats and rabbits at doses up to 1000 mg/kg/day in rats and up to 375 mg/kg/day in rabbits. The plasma exposures (AUC values) were equivalent in both species to 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**). There were no relevant clinical findings in the mothers or in the newborns in this trial.

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 **sections 5.2** and **4.2**).

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.

Effects on fertility

No human data on the effect of etravirine on fertility are available. In the rat pre- and postnatal development study, development and reproductive performance of offspring was not affected by maternal treatment with etravirine (at doses up to 500 mg/kg/day). Plasma exposures achieved in rats were equivalent to those obtained in humans at the recommended clinical dose.

4.7 Effect on ability to drive or operate machinery

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**).

4.8 Undesirable effects

Adverse drug 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% in the placebo arm), hypertriglyceidaemia (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**). 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 **Table 4**: 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 Subjects 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%
Dyslipidemia	1.0%	0.3%
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 subjects per treatment group

Treatment-emergent ADRs occurring in less than 1% of subjects (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 disorder, 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 subjects. 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 subjects treated with INTELENCE are presented in **Table 4**.

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

		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	1.2%	1.0%
Creatinine		**2.0**	**1.7**
Grade 3	>1.9-3.4 x ULN	2.0	1.5
Grade 4	>3.4 x ULN	0	0.2
Lipase		**2.7%**	**1.7%**
Grade 3	> 3-5 x ULN	1.7%	1.2%
Grade 4	> 5xULN	1.0%	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			

		Pooled DUET-1 and DUET-2 Trials	
Laboratory Parameter Preferred Term, %	**DAIDS Toxicity Range**	**INTELENCE + BR N=599**	**Placebo + BR N=604**
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%	4.5%
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			

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**).

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 **section 4.4**).

Additional information on special population

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

In the pooled analysis for DUET-1 and DUET-2, the safety profile in co-infected patients (n=140) was comparable between the INTELENCE arm and the placebo arm. 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 **section 4.4**).

Musculoskeletal and connective tissue disorders

Rhabdomyolysis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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. Since etravirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors, ATC code: J05AG04

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.

Etravirine is soluble in polyethylene glycol (PEG) 400 and freely soluble in some organic solvents (e.g. N,N-dimethylformamide and tetrahydrofuran).

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.

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 EC50 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 EC50 values ranging from 0.7 to 21.7 nM. These EC50 values are well below the 50% cellular toxicity concentration range of 15 to > 100 µM.

The EC50 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 vitro*

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-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 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*

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.

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 Subjects 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

	Subjects Re-Using or Not Using Enfuvirtide	
Number of INTELENCE RAMs	**INTELENCE + BR %; (n/N)**	**Placebo + BR %; (n/N)**
0	47.1% (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 subjects with observations; N = Total number of subjects

* non-VF excluded = The population analysed was all subjects 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' subjects

	Mean (SE) change in viral load from baseline at Week 48		Proportion of subjects 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=403 %; (n/N)**	**Placebo + BR N=391 %; (n/N)**
All ranges	-2.37 (1.16)	-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 subjects with observations; N = Total number of subjects

* non-VF excluded = The population analyzed was all subjects 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). 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 subjects 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 subjects 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 subjects in DUET-1 and 591 subjects in DUET-2 who had completed 48 weeks of treatment or discontinued earlier.

At 48 weeks, the virologic response rate was evaluated in subjects receiving INTELENCE (200 mg b.i.d.) in addition to a BR versus subjects 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 subjects in the INTELENCE arm and 46.9% of subjects in the placebo arm used ENF in the underlying antiretroviral therapy. 25.5% of subjects in the INTELENCE arm used ENF for the first time (de novo), compared with 26.5% of subjects in the placebo arm. 20.0% of subjects in the INTELENCE arm re-used ENF, compared with 20.4% of subjects 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 subjects in the INTELENCE arm and subjects in the placebo arm.

Table 7: Demographic and Baseline Disease Characteristics of Subjects 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%
Other	4.1%	4.5%
Baseline Disease Characteristics		
Median Baseline Plasma HIV-1 RNA (range), log_{10} copies/mL	4.8 (2.7-6.8)	4.8 (2.2-6.5)
Percentage of Subjects with Baseline Viral Load:		
< 30,000 copies/mL	27.5%	28.8%
≥ 30,000 copies/mL and< 100,000 copies/mL	34.4%	35.3%
≥ 100,000 copies/mL	38.1%	35.9%
Median Baseline CD4+ Cell Count (range), cells/mm^3	99 (1-789)	109 (0-912)

	DUET 1 and DUET 2 Trials	
	INTELENCE + BR N=599	**Placebo + BR N=604**
Percentage of Subjects with Baseline CD4+ Cell Count:		
< 50 cells/mm^3	35.6%	34.7%
≥ 50 cells/mm^3 and < 200 cells/mm^3	34.8%	34.5%
≥ 200 cells/mm^3	29.6%	30.8%
Median (range) Number of Primary PI Mutations[a]	4 (0-7)	4 (0-7)
Percentage of Subjects with Previous Use of NNRTIs:		
0	8.2%	7.9%
1	46.9%	46.7%
>1	44.9%	45.4%
Percentage of Subjects with Previous Use of the following NNRTIs:	70.3%	72.5%
Efavirenz	57.1%	58.6%
Nevirapine	13.7%	12.7%
Delavirdine		
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 Subjects with Previous Use of Enfuvirtide	39.6%	41.9%

RAMs = Resistance-Associated Mutations

FC = fold change in EC50

[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 subjects in the INTELENCE arm and subjects 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%)[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 24	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]Subjects achieved virologic response (two consecutive viral loads < 50 copies/mL) and maintained it through week 48

[b]Subjects 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 models including stratification factors

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

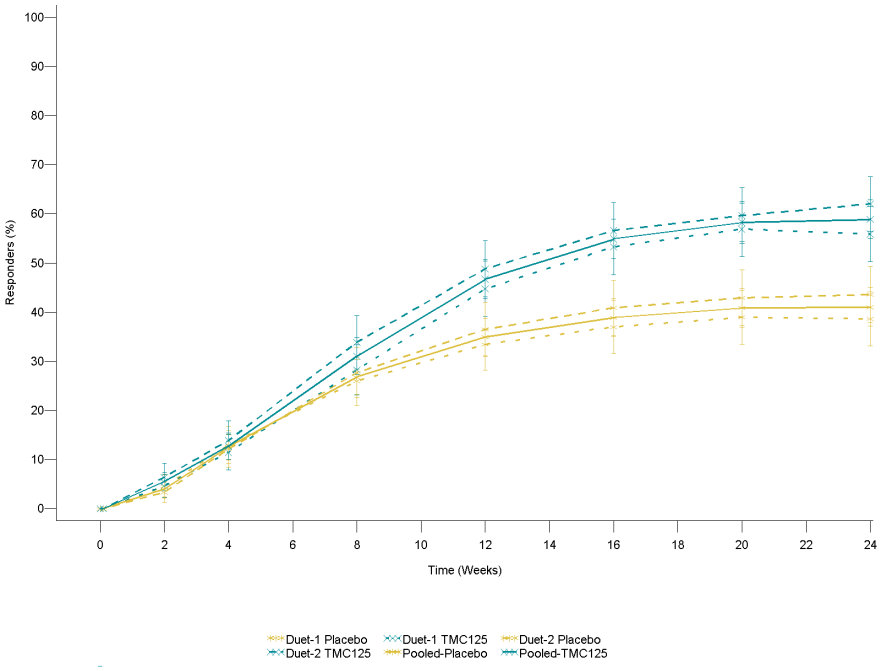


Figure 1: Proportion of Virologic Responders (< 50 Copies/mL; TLOVR Imputed), Overall in the DUET-1 and DUET-2 Trials

In the total study population, through 48 weeks of treatment, the proportion of subjects 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.

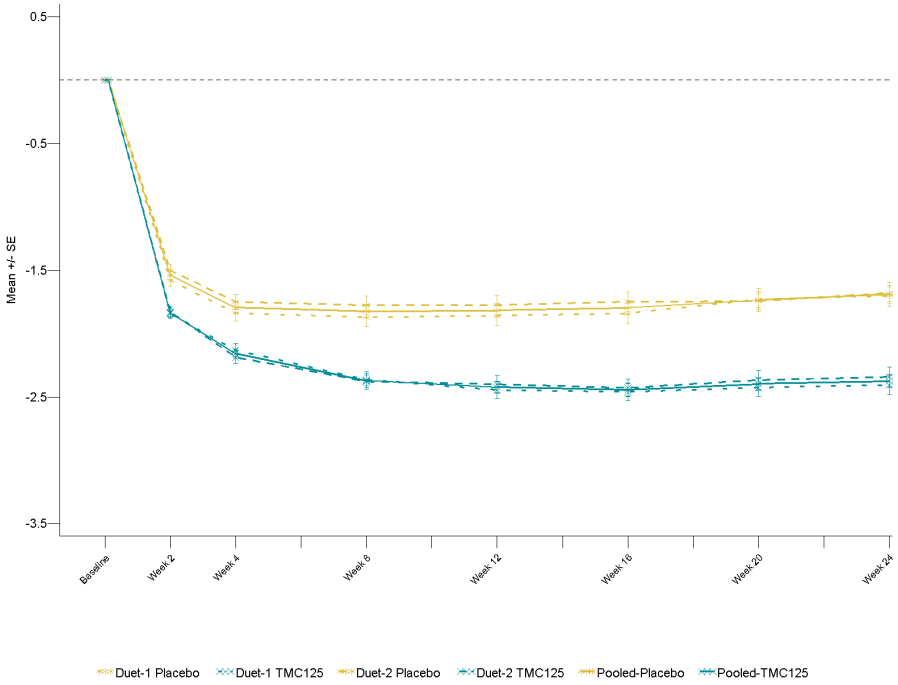


Figure 2: Change from Baseline in Log_{10} Viral Load, Overall in the DUET-1 and DUET-2 Trials

INTELENCE also showed an additional benefit over placebo in CD4+ cell count increase from baseline: 98.2 x 10^6 cells/L versus 77.9 x 10^6 cells/L, respectively. A graphical presentation of the mean change in CD4 cell count from Baseline is provided in **Figure 3**.

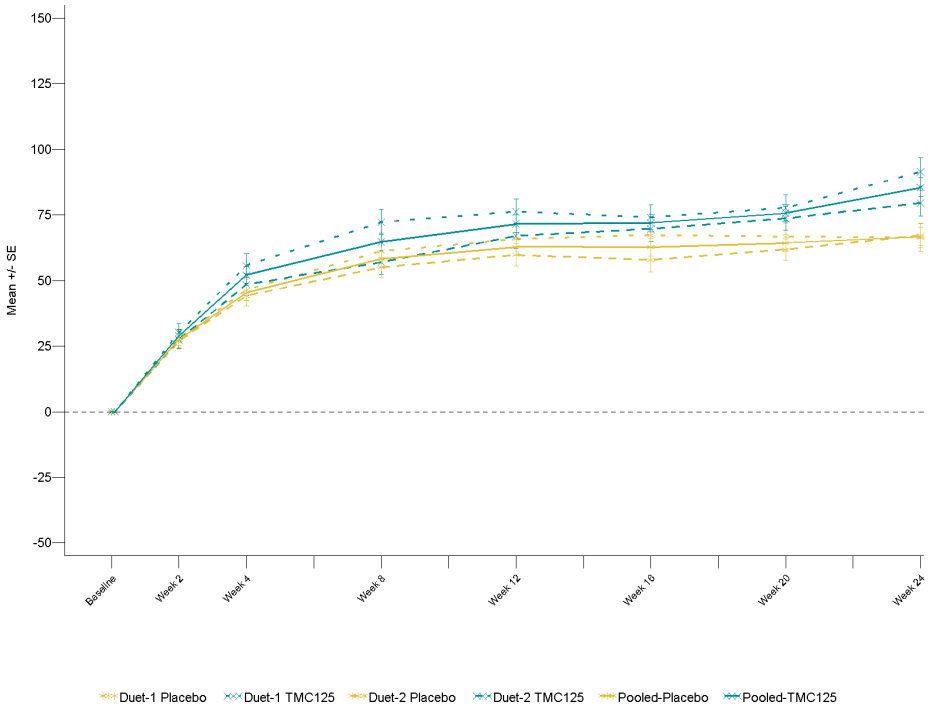


Figure 3: Change from Baseline in CD4 Cell Count (x 10^6/L) (Imputed [NC = F]) in the DUET-1 and DUET-2 Trials

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 compared to 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).

In the population of subjects who either re-used or did not use ENF, through 48 weeks of treatment, the proportion of subjects 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 subjects using ENF de novo, through 48 weeks of treatment, the proportion of subjects 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 111.5 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. Subjects 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. Subjects 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.

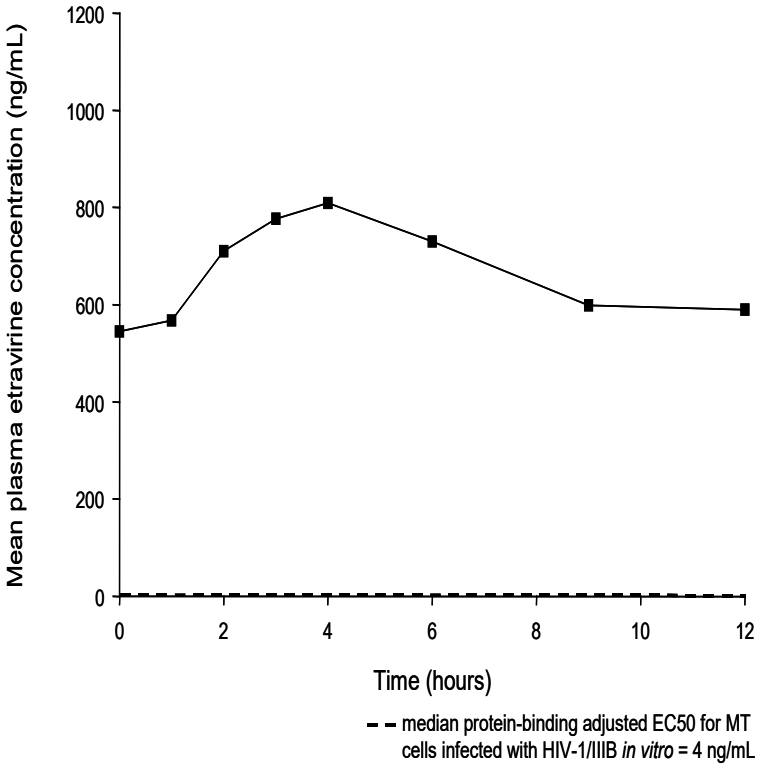
Patient-reported outcomes:

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.

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 Subjects (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**).

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 CYP450 (CYP3A) 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 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**).

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 **sections 4.2** and **4.4**).

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 **sections 4.4** and **4.2**).

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 **sections 4.4** and **4.2**).

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**), no dose adjustment is necessary in patients co-infected with hepatitis B and/or C virus.

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. 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.

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 (see **sections 4.4** and **4.2**).

5.3 Preclinical safety data

Carcinogenicity

Long-term carcinogenicity studies of etravirine in rodents are ongoing.

Genotoxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Colloidal anhydrous silica

Magnesium stearate

Hypromellose

Croscarmellose sodium

Lactose monohydrate (100 mg tablets only).

Silicified microcrystalline cellulose (200 mg tablets only).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

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 New Zealand.

6.6 Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

2 July 2009 (100 mg tablets)

22 December 2011 (200 mg tablets)

10. DATE OF REVISION OF TEXT

06 April 2023

Summary table of changes

Section changes	Summary of new information
4.4	Addition of HIV heading and further details on HIV transmission