SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

INTELENCE 200 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of etravirine.

Excipient with known effect

Each tablet contains less than 1 mmol sodium (23 mg), and is essentially sodium-free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white, biconvex, oblong tablet debossed with “T200” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

INTELENCE, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients and in antiretroviral treatment-experienced paediatric patients from 2 years of age (see sections 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

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

Adults

The recommended dose of etravirine for adults is 200 mg (one 200 mg tablet or two 100 mg tablets) taken orally twice daily following a meal (see section 5.2).

Paediatric population (2 years to less than 18 years of age)

The recommended dose of etravirine for paediatric patients (2 years to less than 18 years of age and weighing at least 10 kg) is based on body weight (see table below). INTELENCE tablet(s) should be taken orally, following a meal (see section 5.2).

Table 1: Recommended dose of etravirine for paediatric patients 2 years to less than 18 years of age

Body weight	Dose	Tablets
≥ 10 to < 20 kg	100 mg twice daily	four 25 mg tablets twice daily or one 100 mg tablet twice daily
≥ 20 to < 25 kg	125 mg twice daily	five 25 mg tablets twice daily or one 100 mg tablet and one 25 mg tablet twice daily
≥ 25 to < 30 kg	150 mg twice daily	six 25 mg tablets twice daily or one 100 mg tablet and two 25 mg tablets twice daily
≥ 30 kg	200 mg twice daily	eight 25 mg tablets twice daily or two 100 mg tablets twice daily or one 200 mg tablet twice daily

Missed dose

If the patient misses a dose of INTELENCE within 6 hours of the time it is usually taken, the patient should take it following a meal as soon as possible and then take the next dose at the regularly scheduled time. If a patient misses a dose by more than 6 hours of the time it is usually taken, the patient should not take the missed dose and simply resume the usual dosing schedule.

If a patient vomits within 4 hours of taking the medicine, another dose of INTELENCE should be taken following a meal as soon as possible. If a patient vomits more than 4 hours after taking the medicine, the patient does not need to take another dose until the next regularly scheduled time.

Elderly

There is limited information regarding the use of INTELENCE in patients > 65 years of age (see section 5.2), therefore caution should be used in this population.

Hepatic impairment

No dose adjustment is suggested in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B); INTELENCE should be used with caution in patients with moderate hepatic impairment. The pharmacokinetics of etravirine have not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Therefore, INTELENCE is not recommended in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is required in patients with renal impairment (see section 5.2).

Paediatric population (less than 2 years of age)

INTELENCE should not be used in children less than 2 years of age. Currently available data for children between 1 and 2 years old are described in sections 4.8, 5.1 and 5.2 and suggest that the benefits do not outweigh the risks in this age group. No data are available for children less than 1 year of age.

Method of administration

Oral use.

Patients should be instructed to swallow the tablet(s) whole with a liquid such as water. Patients who are unable to swallow the tablet(s) whole may disperse the tablet(s) in a glass of water (see section 4.4).

For instructions on dispersion of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with elbasvir/grazoprevir (see section 4.5).

4.4 Special warnings and precautions for use

INTELENCE should optimally be combined with other antiretrovirals that exhibit activity against the patient's virus (see section 5.1).

A decreased virologic response to etravirine was observed in patients with viral strains harbouring 3 or more among the following mutations V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, and G190A/S (see section 5.1).

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results.

No data other than drug-drug interaction data (see section 4.5) are available when etravirine is combined with raltegravir or maraviroc.

Severe cutaneous and hypersensitivity reactions

Severe cutaneous adverse reactions have been reported with etravirine. In clinical trials, Stevens-Johnson Syndrome and erythema multiforme have been rarely

(< 0.1%) reported. Treatment with INTELENCE should be discontinued if a severe cutaneous reaction develops.

The clinical data are limited and an increased risk of cutaneous reactions in patients with a history of NNRTI-associated cutaneous reactions cannot be excluded. Caution should be observed in such patients, especially in case of history of a severe cutaneous drug reaction.

Cases of severe hypersensitivity syndromes, including DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and TEN (toxic epidermal necrolysis), sometimes fatal, have been reported with the use of etravirine (see section 4.8). The DRESS syndrome is characterised by rash, fever, eosinophilia and systemic involvement (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and eosinophilia). Time to onset is usually around 3-6 weeks and the outcome in most cases is favourable upon discontinuation and after initiation of corticosteroid therapy.

Patients should be informed to seek medical advice if severe rash or hypersensitivity reactions occur. Patients who are diagnosed with a hypersensitivity reaction whilst on therapy must discontinue INTELENCE immediately.

Delay in stopping INTELENCE treatment after the onset of severe rash may result in a life-threatening reaction.

Patients who have stopped treatment due to hypersensitivity reactions should not restart therapy with INTELENCE.

Rash

Rash has been reported with etravirine. 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. When prescribing INTELENCE to females, prescribers should be aware that the incidence of rash was higher in females (see section 4.8).

Paediatric population

For children who cannot swallow the tablet(s) whole, the tablet(s) may be dispersed in liquid. This should only be considered if the child is likely to take the entire dose of the tablet(s) in liquid (see sections 4.2 and 6.6). The importance of consuming the entire dose needs to be highlighted to the child and his/her caregiver to avoid too low exposure and lack of virologic response. In case of any doubt that a child will take the entire dose of the tablet(s) dispersed in liquid, treatment with another antiretroviral product needs to be considered.

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 etravirine. The type and incidence of adverse reactions in patients > 55 years of age were similar to the ones in younger patients (see sections 4.2 and 5.2).

Pregnancy

Given the increased etravirine exposure during pregnancy, caution should be applied for those pregnant patients that require concomitant medicinal products or have comorbidities that may further increase etravirine exposure.

Patients with coexisting conditions

Hepatic impairment

Etravirine is primarily metabolised and eliminated by the liver and highly bound to plasma proteins. Effects on unbound exposure could be expected (has not been studied) and therefore caution is advised in patients with moderate hepatic impairment. Etravirine has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and its use is therefore not recommended in this group of patients (see sections 4.2 and 5.2).

Co-infection with HBV (hepatitis B virus) or HCV (hepatitis C virus)

Caution should be exercised in patients co-infected with hepatitis B or C virus due to the current limited data available. A potential increased risk of liver enzymes increase cannot be excluded.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Immune reconstitution syndrome

In HIV infected patients with severe immune deficiency at the time of initiation 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 reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.8).

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Interactions with medicinal products

It is not recommended to combine etravirine with tipranavir/ritonavir, due to a marked pharmacokinetic interaction (76% decrease of etravirine AUC) that could significantly impair the virologic response to etravirine.

The combination of etravirine with daclatasvir, atazanavir/cobicistat or darunavir/cobicistat is not recommended (see section 4.5).

For further information on interactions with medicinal products see section 4.5.

Lactose intolerance and lactase deficiency

INTELENCE 25 mg tablets

Each tablet contains 40 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTELENCE 100 mg tablets

Each tablet contains 160 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that affect etravirine exposure

Etravirine is metabolised by CYP3A4, 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 etravirine 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 etravirine 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. 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 alter their adverse events profile.

Known and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in table 2. The table is not all-inclusive.

Interaction table

Interactions between etravirine and co-administered medicinal products are listed in table 2 (increase is indicated as "↑", decrease as "↓", no change as "↔", not done as "ND", confidence interval as "CI").

Table 2: Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	**Effects on drug levels Least Squares Mean Ratio (90% CI; 1.00 = No effect)**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
NRTIs		
Didanosine 400 mg once daily	didanosine AUC ↔ 0.99 (0.79-1.25) C_{min} ND C_{max} ↔ 0.91 (0.58-1.42) etravirine AUC ↔ 1.11 (0.99-1.25) C_{min} ↔ 1.05 (0.93-1.18) C_{max} ↔ 1.16 (1.02-1.32)	No significant effect on didanosine and etravirine PK parameters is seen. INTELENCE and didanosine can be used without dose adjustments.
Tenofovir disoproxil 245 mg once daily[b]	tenofovir AUC ↔ 1.15 (1.09-1.21) C_{min} ↑ 1.19 (1.13-1.26) C_{max} ↑ 1.15 (1.04-1.27) etravirine AUC ↓ 0.81 (0.75-0.88) C_{min} ↓ 0.82 (0.73-0.91) C_{max} ↓ 0.81 (0.75-0.88)	No significant effect on tenofovir and etravirine PK parameters is seen. INTELENCE and tenofovir can be used without dose adjustments.
Other NRTIs	Not studied, but no interaction expected based on the primary renal elimination route for other NRTIs (e.g., abacavir, emtricitabine, lamivudine, stavudine and zidovudine).	INTELENCE can be used with these NRTIs without dose adjustment.
NNRTIs		
Efavirenz Nevirapine Rilpivirine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of etravirine with efavirenz or nevirapine may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of etravirine. Concomitant use of etravirine with rilpivirine may cause a decrease in the plasma concentration of rilpivirine and loss of therapeutic effect of rilpivirine.	It is not recommended to co-administer INTELENCE with other NNRTIs.
HIV Protease Inhibitors (PIs) – Unboosted (i.e. without co-administration of low-dose ritonavir)		
Indinavir	Concomitant use of etravirine with indinavir may cause a significant decrease in the plasma concentration of indinavir and loss of therapeutic effect of indinavir.	It is not recommended to co-administer INTELENCE with indinavir.
HIV PIs – Boosted with low-dose ritonavir		
Atazanavir/ritonavir 300/100 mg once daily	atazanavir AUC ↓ 0.86 (0.79-0.93) C_{min} ↓ 0.62 (0.55-0.71) C_{max} ↔ 0.97 (0.89-1.05) etravirine AUC ↑ 1.30 (1.18-1.44) C_{min} ↑ 1.26 (1.12-1.42) C_{max} ↑ 1.30 (1.17-1.44)	INTELENCE and atazanavir/ritonavir can be used without dose adjustment.

Darunavir/ritonavir 600/100 mg twice daily	<u>darunavir</u> AUC ↔ 1.15 (1.05-1.26) C_{min} ↔ 1.02 (0.90-1.17) C_{max} ↔ 1.11 (1.01-1.22) <u>etravirine</u> AUC ↓ 0.63 (0.54-0.73) C_{min} ↓ 0.51 (0.44-0.61) C_{max} ↓ 0.68 (0.57-0.82)	INTELENCE and darunavir/ritonavir can be used without dose adjustments (see also section 5.1).
Fosamprenavir/ ritonavir 700/100 mg twice daily	<u>amprenavir</u> AUC ↑ 1.69 (1.53-1.86) C_{min} ↑ 1.77 (1.39-2.25) C_{max} ↑ 1.62 (1.47-1.79) <u>etravirine</u> AUC ↔[a] C_{min} ↔[a] C_{max} ↔[a]	Amprenavir/ritonavir and fosamprenavir/ritonavir may require dose reduction when co-administered with INTELENCE. Using the oral solution may be considered for dose reduction.
Lopinavir/ritonavir (tablet) 400/100 mg twice daily	<u>lopinavir</u> AUC ↔ 0.87 (0.83-0.92) C_{min} ↓ 0.80 (0.73-0.88) C_{max} ↔ 0.89 (0.82-0.96) <u>etravirine</u> AUC ↓ 0.65 (0.59-0.71) C_{min} ↓ 0.55 (0.49-0.62) C_{max} ↓ 0.70 (0.64-0.78)	INTELENCE and lopinavir/ritonavir can be used without dose adjustments.
Saquinavir/ritonavir 1,000/100 mg twice daily	<u>saquinavir</u> AUC ↔ 0.95 (0.64-1.42) C_{min} ↓ 0.80 (0.46-1.38) C_{max} ↔ 1.00 (0.70-1.42) <u>etravirine</u> AUC ↓ 0.67 (0.56-0.80) C_{min} ↓ 0.71 (0.58-0.87) C_{max} ↓ 0.63 (0.53-0.75)	INTELENCE and saquinavir/ritonavir can be used without dose adjustments.
Tipranavir/ritonavir 500/200 mg twice daily	<u>tipranavir</u> AUC ↑ 1.18 (1.03-1.36) C_{min} ↑ 1.24 (0.96-1.59) C_{max} ↑ 1.14 (1.02-1.27) <u>etravirine</u> AUC ↓ 0.24 (0.18-0.33) C_{min} ↓ 0.18 (0.13-0.25) C_{max} ↓ 0.29 (0.22-0.40)	It is not recommended to co-administer tipranavir/ritonavir and INTELENCE (see section 4.4).
HIV PIs – Boosted with cobicistat		
Atazanavir/cobicistat Darunavir/cobicistat	Not studied. Co-administration of etravirine 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.

CCR5 Antagonists		
Maraviroc 300 mg twice daily Maraviroc/darunavir/ ritonavir 150/600/100 mg twice daily	<u>maraviroc</u> AUC ↓ 0.47 (0.38-0.58) C_{min} ↓ 0.61 (0.53-0.71) C_{max} ↓ 0.40 (0.28-0.57) <u>etravirine</u> AUC ↔ 1.06 (0.99-1.14) C_{min} ↔ 1.08 (0.98-1.19) C_{max} ↔ 1.05 (0.95-1.17) <u>maraviroc*</u> AUC ↑ 3.10 (2.57-3.74) C_{min} ↑ 5.27 (4.51-6.15) C_{max} ↑ 1.77 (1.20-2.60) * compared to maraviroc 150 mg twice daily	The recommended dose for maraviroc when combined with INTELENCE and a PI is 150 mg twice daily, except for fosamprenavir/ritonavir which is not recommended with maraviroc. No dose adjustment for INTELENCE is necessary. See also section 4.4.
Fusion Inhibitors		
Enfuvirtide 90 mg twice daily	<u>etravirine*</u> AUC ↔[a] C_{0h} ↔[a] Enfuvirtide concentrations not studied and no effect is expected. * based on population pharmacokinetic analyses	No interaction is expected for either INTELENCE or enfuvirtide when co-administered.
Integrase Strand Transfer Inhibitors		
Dolutegravir 50 mg once daily Dolutegravir + darunavir/ritonavir 50 mg once daily + 600/100 mg twice daily Dolutegravir + Lopinavir/ritonavir 50 mg once daily + 400/100 mg twice daily	<u>dolutegravir</u> AUC ↓ 0.29 (0.26-0.34) C_{min} ↓ 0.12 (0.09-0.16) C_{max} ↓ 0.48 (0.43-0.54) <u>etravirine</u> AUC ↔[a] C_{min} ↔[a] C_{max} ↔[a] <u>dolutegravir</u> AUC↓ 0.75 (0.69-0.81) C_{min} ↓ 0.63 (0.52-0.77) C_{max} ↓ 0.88 (0.78-1.00) <u>etravirine</u> AUC ↔[a] C_{min} ↔[a] C_{max} ↔[a] <u>dolutegravir</u> AUC↔ 1.11(1.02-1.20) C_{min} ↑ 1.28 (1.13-1.45) C_{max} ↔ 1.07 (1.02-1.13) <u>etravirine</u> AUC ↔[a] C_{min} ↔[a] C_{max} ↔[a]	Etravirine significantly reduced plasma concentrations of dolutegravir. 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. INTELENCE should only be used with dolutegravir when co-administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir. This combination can be used without dose adjustment.
Raltegravir 400 mg twice daily	<u>raltegravir</u> AUC ↓ 0.90 (0.68-1.18) C_{min} ↓ 0.66 (0.34-1.26) C_{max} ↓ 0.89 (0.68-1.15) <u>etravirine</u> AUC ↔ 1.10 (1.03-1.16) C_{min} ↔ 1.17 (1.10-1.26) C_{max} ↔ 1.04 (0.97-1.12)	INTELENCE and raltegravir can be used without dose adjustments.

ANTIARRHYTHMICS		
Digoxin 0.5 mg single dose	<u>digoxin</u> AUC ↑ 1.18 (0.90-1.56) C_{min} ND C_{max} ↑ 1.19 (0.96-1.49)	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	Not studied. INTELENCE is expected to decrease plasma concentrations of these antiarrhythmics.	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with INTELENCE.
ANTIBIOTICS		
Azithromycin	Not studied. Based on the biliary elimination pathway of azithromycin, no drug interactions are expected between azithromycin and INTELENCE.	INTELENCE and azithromycin can be used without dose adjustments.
Clarithromycin 500 mg twice daily	<u>clarithromycin</u> AUC ↓ 0.61 (0.53-0.69) C_{min} ↓ 0.47 (0.38-0.57) C_{max} ↓ 0.66 (0.57-0.77) <u>14-OH-clarithromycin</u> AUC ↑ 1.21 (1.05-1.39) C_{min} ↔ 1.05 (0.90-1.22) C_{max} ↑ 1.33 (1.13-1.56) <u>etravirine</u> AUC ↑ 1.42 (1.34-1.50) C_{min} ↑ 1.46 (1.36-1.58) C_{max} ↑ 1.46 (1.38-1.56)	Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.
ANTICOAGULANTS		
Warfarin	Not studied. Etravirine is expected to increase plasma concentrations of warfarin.	It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with INTELENCE.
ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	Not studied. Carbazamepine, phenobarbital and phenytoin are expected to decrease plasma concentrations of etravirine.	Combination not recommended.
ANTIFUNGALS		
Fluconazole 200 mg once in the morning	<u>fluconazole</u> AUC ↔ 0.94 (0.88-1.01) C_{min} ↔ 0.91 (0.84-0.98) C_{max} ↔ 0.92 (0.85-1.00) <u>etravirine</u> AUC ↑ 1.86 (1.73-2.00) C_{min} ↑ 2.09 (1.90-2.31) C_{max} ↑ 1.75 (1.60-1.91)	INTELENCE and fluconazole can be used without dose adjustments.

Itraconazole Ketoconazole Posaconazole	Not studied. 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 etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by etravirine.	INTELENCE and these antifungals can be used without dose adjustments.
Voriconazole 200 mg twice daily	voriconazole AUC ↑ 1.14 (0.88-1.47) C_{min} ↑ 1.23 (0.87-1.75) C_{max} ↓ 0.95 (0.75-1.21) etravirine AUC ↑ 1.36 (1.25-1.47) C_{min} ↑ 1.52 (1.41-1.64) C_{max} ↑ 1.26 (1.16-1.38)	INTELENCE and voriconazole can be used without dose adjustments.
ANTIMALARIALS		
Artemether/ Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	artemether AUC ↓ 0.62 (0.48-0.80) C_{min} ↓ 0.82 (0.67-1.01) C_{max} ↓ 0.72 (0.55-0.94) dihydroartemisinin AUC ↓ 0.85 (0.75-0.97) C_{min} ↓ 0.83 (0.71-0.97) C_{max} ↓ 0.84 (0.71-0.99) lumefantrine AUC ↓ 0.87 (0.77-0.98) C_{min} ↔ 0.97 (0.83-1.15) C_{max} ↔ 1.07 (0.94-1.23) etravirine AUC ↔ 1.10 (1.06-1.15) C_{min} ↔ 1.08 (1.04-1.14) C_{max} ↔ 1.11 (1.06-1.17)	Close monitoring of antimalarial response is warranted when co-administering INTELENCE and artemether/lumefantrine as a significant decrease in exposure of artemether and its active metabolite, dihydroartemisinin, may result in decreased antimalarial efficacy. No dose adjustment is needed for INTELENCE.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Not studied. Rifampicin and rifapentine are expected to decrease plasma concentrations of etravirine. INTELENCE should be used in combination with a boosted PI. Rifampicin is contraindicated in combination with boosted Pis.	Combination not recommended.

Rifabutin 300 mg once daily	With an associated boosted PI: No interaction study has been performed. Based on historical data, a decrease in etravirine exposure may be expected whereas an increase in rifabutin exposure and especially in 25-O-desacetyl-rifabutin may be expected. With no associated boosted PI (out of the recommended indication for etravirine): <u>rifabutin</u> AUC ↓ 0.83 (0.75-0.94) C_{min} ↓ 0.76 (0.66-0.87) C_{max} ↓ 0.90 (0.78-1.03) <u>25-O-desacetyl-rifabutin</u> AUC ↓ 0.83 (0.74-0.92) C_{min} ↓ 0.78 (0.70-0.87) C_{max} ↓ 0.85 (0.72-1.00) <u>etravirine</u> AUC ↓ 0.63 (0.54-0.74) C_{min} ↓ 0.65 (0.56-0.74) C_{max} ↓ 0.63 (0.53-0.74)	The combination of INTELENCE with a boosted PI and rifabutin should be used with caution due to the risk of decrease in etravirine exposure and the risk of increase in rifabutin and 25-O-desacetyl-rifabutin exposures. Close monitoring for virologic response and for rifabutin related adverse reactions is recommended. Please refer to the product information of the associated boosted PI for the dose adjustment of rifabutin to be used.
BENZODIAZEPINES		
Diazepam	Not studied. Etravirine is expected to increase plasma concentrations of diazepam.	Alternatives to diazepam should be considered.
CORTICOSTEROIDS		
Dexamethasone (systemic)	Not studied. Dexamethasone is expected to decrease plasma concentrations of etravirine	Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for chronic use.
OESTROGEN-BASED CONTRACEPTIVES		
Ethinylestradiol 0.035 mg once daily Norethindrone 1 mg once daily	<u>ethinylestradiol</u> AUC ↑ 1.22 (1.13-1.31) C_{min} ↔ 1.09 (1.01-1.18) C_{max} ↑ 1.33 (1.21-1.46) <u>norethindrone</u> AUC ↔ 0.95 (0.90-0.99) C_{min} ↓ 0.78 (0.68-0.90) C_{max} ↔ 1.05 (0.98-1.12) <u>etravirine</u> AUC ↔[a] C_{min} ↔[a] C_{max} ↔[a]	The combination of oestrogen- and/or progesterone-based contraceptives and INTELENCE can be used without dose adjustment.
HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS		
Ribavirin	Not studied, but no interaction expected based on the renal elimination pathway of ribavirin.	The combination of INTELENCE and ribavirin can be used without dose adjustments.
Daclatasvir	Not studied. Co-administration of etravirine with daclatasvir may decrease daclatasvir concentrations.	Co-administration of Intelence and daclatasvir is not recommended.

Elbasvir/grazoprevir	Not studied. Co-administration of etravirine with elbasvir/grazoprevir may decrease elbasvir and grazoprevir concentrations, leading to reduced therapeutic effect of elbasvir/grazoprevir.	Co-administration is contraindicated (see section 4.3).
HERBAL PRODUCTS		
St John's wort (*Hypericum perforatum*)	Not studied. St John's wort is expected to decrease the plasma concentrations of etravirine.	Combination not recommended.
HMG CO-A REDUCTASE INHIBITORS		
Atorvastatin 40 mg once daily	atorvastatin AUC ↓ 0.63 (0.58-0.68) C_{min} ND C_{max} ↑ 1.04 (0.84-1.30) 2-OH-atorvastatin AUC ↑ 1.27 (1.19-1.36) C_{min} ND C_{max} ↑ 1.76 (1.60-1.94) etravirine AUC ↔ 1.02 (0.97-1.07) C_{min} ↔ 1.10 (1.02-1.19) C_{max} ↔ 0.97 (0.93-1.02)	The combination of INTELENCE and atorvastatin can be given without any dose adjustments, however, the dose of atorvastatin may need to be altered based on clinical response.
Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin	Not studied. No interaction between pravastatin and etravirine is expected. Lovastatin, rosuvastatin and simvastatin are CYP3A4 substrates and co-administration with etravirine may result in lower plasma concentrations of the HMG Co-A reductase inhibitor. Fluvastatin, and rosuvastatin are metabolised by CYP2C9 and co-administration with etravirine may result in higher plasma concentrations of the HMG Co-A reductase inhibitor.	Dose adjustments for these HMG Co-A reductase inhibitors may be necessary.
H_2-RECEPTOR ANTAGONISTS		
Ranitidine 150 mg twice daily	etravirine AUC ↓ 0.86 (0.76-0.97) C_{min} ND C_{max} ↓ 0.94 (0.75-1.17)	INTELENCE can be co-administered with H_2-receptor antagonists without dose adjustments.
IMMUNOSUPPRESSANTS		
Cyclosporin Sirolimus Tacrolimus	Not studied. Etravirine is expected to decrease plasma concentrations of cyclosporine, sirolimus and tacrolimus.	Co-administration with systemic immunosuppressants should be done with caution because plasma concentrations of cyclosporin, sirolimus and tacrolimus may be affected when co-administered with INTELENCE.

NARCOTIC ANALGESICS		
Methadone individual dose ranging from 60 mg to 130 mg once daily	<u>R(-) methadone</u> AUC ↔ 1.06 (0.99-1.13) C_{min} ↔ 1.10 (1.02-1.19) C_{max} ↔ 1.02 (0.96-1.09) <u>S(+) methadone</u> AUC ↔ 0.89 (0.82-0.96) C_{min} ↔ 0.89 (0.81-0.98) C_{max} ↔ 0.89 (0.83-0.97) <u>etravirine</u> AUC ↔[a] C_{min} ↔[a] C_{max} ↔[a]	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 50 mg single dose Tadalafil Vardenafil	<u>sildenafil</u> AUC ↓ 0.43 (0.36-0.51) C_{min} ND C_{max} ↓ 0.55 (0.40-0.75) <u>N-desmethyl-sildenafil</u> AUC ↓ 0.59 (0.52-0.68) C_{min} ND C_{max} ↓ 0.75 (0.59-0.96)	Concomitant use of PDE-5 inhibitors with INTELENCE may require dose adjustment of the PDE-5 inhibitor to attain the desired clinical effect.
PLATELET AGGREGGATION INHIBITORS		
Clopidogrel	*In vitro* data show that etravirine has inhibitory properties on CYP2C19. It is therefore possible that etravirine may inhibit the metabolism of clopidogrel to its active metabolite by such inhibition of CYP2C19 *in vivo*. The clinical relevance of this interaction has not been demonstrated.	As a precaution it is recommended that concomitant use of etravirine and clopidogrel should be discouraged.
PROTON PUMP INHIBITORS		
Omeprazole 40 mg once daily	<u>etravirine</u> AUC ↑ 1.41 (1.22-1.62) C_{min} ND C_{max} ↑ 1.17 (0.96-1.43)	INTELENCE can be co-administered with proton pump inhibitors without dose adjustments.
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)		
Paroxetine 20 mg once daily	<u>paroxetine</u> AUC ↔ 1.03 (0.90-1.18) C_{min} ↓ 0.87 (0.75-1.02) C_{max} ↔ 1.06 (0.95-1.20) <u>etravirine</u> AUC ↔ 1.01 (0.93-1.10) C_{min} ↔ 1.07 (0.98-1.17) C_{max} ↔ 1.05 (0.96-1.15)	INTELENCE can be co-administered with paroxetine without dose adjustments.

[a] Comparison based on historic control.

[b] Study was conducted with tenofovir disoproxil fumarate 300 mg once daily

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

<u>Paediatric population</u>

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women, and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the foetus.

Placental transfer has been seen in pregnant rats, but it is not known whether placental transfer of etravirine also occurs in pregnant women. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Based on animal data the malformative risk is unlikely in humans. The clinical data do not raise safety concern but are very limited.

Breast-feeding

Etravirine is excreted in human milk.

Because of the potential for adverse events in nursing infants, women should be instructed not to breastfeed if they are receiving INTELENCE.

It is recommended that women living with HIV do not breastfeed in order to avoid transmission of HIV.

Fertility

No human data on the effect of etravirine on fertility are available. In rats, there was no effect on mating or fertility with etravirine treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

INTELENCE has minor influence on the ability to drive and use machines. No studies on the effects of INTELENCE on the ability to drive or operate machines have been performed. Adverse reactions such as somnolence and vertigo have been reported in etravirine-treated patients and should be considered when assessing a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequent (incidence ≥ 10%) adverse reactions of all intensities reported for etravirine were rash, diarrhoea, nausea and headache. In the Phase III studies, the rates of discontinuation due to any adverse reaction were 7.2% in patients receiving etravirine. The most common adverse reaction leading to discontinuation was rash.

Tabulated list of adverse reactions

Adverse reactions reported in patients treated with etravirine are summarised in Table 3. The adverse reactions are listed by system organ class (SOC) and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

Table 3: Adverse reactions observed with etravirine in clinical trials and post-marketing experience

System Organ Class (SOC)	Frequency category	Adverse Reaction
Blood and lymphatic system disorders	common	thrombocytopaenia, anaemia, decreased neutrophils
	uncommon	decreased white blood cell count
Immune system disorders	common	drug hypersensitivity
	uncommon	immune reconstitution syndrome
Metabolism and nutrition disorders	common	diabetes mellitus, hyperglycaemia, hypercholesterolaemia, increased low density lipoprotein (LDL), hypertriglyceridaemia, hyperlipidaemia, dyslipidaemia, anorexia
Psychiatric disorders	common	anxiety, insomnia, sleep disorders
	uncommon	confusional state, disorientation, nightmares, nervousness, abnormal dreams
Nervous system disorders	very common	headache
	common	peripheral neuropathy, paraesthesia, hypoaesthesia, amnesia, somnolence
	uncommon	convulsion, syncope, tremor, hypersomnia, disturbance in attention
Eye disorders	common	blurred vision
Ear and labyrinth disorders	uncommon	vertigo
Cardiac disorders	common	myocardial infarction
	uncommon	atrial fibrillation, angina pectoris
Vascular disorders	common	hypertension
	rare	haemorrhagic stroke[a]
Respiratory, thoracic and mediastinal disorders	common	exertional dyspnoea
	uncommon	bronchospasm
Gastrointestinal disorders	very common	diarrhoea, nausea
	common	gastrooesophageal reflux disease, vomiting, abdominal pain, abdominal distension, flatulence, gastritis, constipation, dry mouth, stomatitis, lipase increased, blood amylase increased
	uncommon	pancreatitis, haematemesis, retching
Hepatobiliary disorders	common	increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST)
	uncommon	hepatitis, hepatic steatosis, cytolytic hepatitis, hepatomegaly
Skin and subcutaneous tissue disorders	very common	rash
	common	night sweats, dry skin, prurigo
	uncommon	angioneurotic oedema[a], swelling face, hyperhidrosis
	rare	Stevens-Johnson Syndrome[a], erythema multiforme[a]
	very rare	toxic epidermal necrolysis[a], DRESS[b]
Renal and urinary disorders	common	renal failure, blood creatinine increased
Reproductive system and breast disorders	uncommon	gynaecomastia
General disorders and administration site conditions	common	fatigue
	uncommon	sluggishness

[a] These adverse reactions were observed in other clinical trials than DUET-1 and DUET-2.
[b] These adverse reactions have been identified through postmarketing experience with etravirine.

Description of selected adverse reactions

Rash

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 etravirine arm in the DUET trials (rash ≥ grade 2 was reported in 9/60 [15.0%] women versus 51/539 [9.5%] men; discontinuations due to rash were reported in 3/60 [5.0%] women versus 10/539 [1.9%] men) (see section 4.4). There was no gender difference in severity or treatment discontinuation due to rash. The clinical data are limited and an increased risk of cutaneous reactions in patients with a history of NNRTI-associated cutaneous reaction cannot be excluded (see section 4.4).

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

Immune reconstitution syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy. The frequency of this is unknown (see section 4.4).

Paediatric population (1 year to less than 18 years of age)

The safety assessment in children and adolescents is based on two single-arm trials. PIANO (TMC125-C213) is a Phase II trial in which 101 antiretroviral treatment-experienced HIV-1 infected paediatric patients 6 years to less than 18 years of age received INTELENCE in combination with other antiretroviral agents. TMC125-C234/IMPAACT P1090 is a Phase I/II trial in which 26 antiretroviral treatment-experienced HIV-1 infected paediatric patients aged 1 years to less than 6 years received INTELENCE in combination with other antiretroviral agents (see section 5.1).

In PIANO and TMC125-C234/IMPAACT P1090, the frequency, type and severity of adverse reactions in paediatric patients were comparable to those observed in adults. In PIANO, rash was reported more frequently in female subjects than in male subjects (rash ≥ grade 2 was reported in 13/64 [20.3%] females versus 2/37 [5.4%] males; discontinuations due to rash were reported in 4/64 [6.3%] females versus 0/37 [0%] males) (see section 4.4). Most often, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was mostly self-limiting and generally resolved within 1 week on continued therapy.

In a postmarketing retrospective cohort study aiming at substantiating the long-term safety profile of etravirine in HIV-1-infected children and adolescents receiving etravirine with other HIV-1 antiretrovirals (N = 182), Stevens-Johnson Syndrome was reported at a higher incidence (1%) than has been reported in adult clinical trials (< 0.1%).

Other special populations

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

In the pooled analysis for DUET-1 and DUET-2, the incidence of hepatic events tended to be higher in co-infected subjects treated with etravirine compared to co-infected subjects in the placebo group. INTELENCE should be used with caution in these patients (see also sections 4.4 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medical 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There are no data with regard to symptomatic overdose with etravirine, but it is possible that the most frequent adverse reactions of etravirine, i.e. rash, diarrhoea, nausea, and headache would be the most common symptoms noted. There is no specific antidote for overdose with etravirine. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Etravirine is an NNRTI of human immunodeficiency virus type 1 (HIV-1). Etravirine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and

DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site.

Antiviral activity *in vitro*

Etravirine exhibits activity against wild type HIV-1 in T-cell lines and primary cells with median EC_{50} values ranging from 0.9 to 5.5 nM. Etravirine demonstrates activity against HIV-1 group M (subtypes A, B, C, D, E, F, and G) and HIV-1 group O primary isolates with EC_{50} values ranging from 0.3 to 1.7 nM and from 11.5 to 21.7 nM, respectively. Although etravirine demonstrates *in vitro* activity against wild type HIV-2 with median EC_{50} values ranging from 5.7 to 7.2 µM, treatment of HIV-2 infection with etravirine is not recommended in the absence of clinical data. Etravirine retains activity against HIV-1 viral strains resistant to nucleoside reverse transcriptase and/or protease inhibitors. In addition, etravirine demonstrates a fold change (FC) in $EC_{50} \leq 3$ against 60% of 6,171 NNRTI-resistant clinical isolates.

Resistance

Etravirine efficacy in relation to NNRTI resistance at baseline has mainly been analysed with etravirine given in combination with darunavir/ritonavir (DUET-1 and DUET-2). Boosted protease inhibitors, like darunavir/ritonavir, show a higher barrier to resistance compared to other classes of antiretrovirals. The breakpoints for reduced efficacy with etravirine (> 2 etravirine-associated mutations at baseline, see clinical results section) applies when etravirine is given in combination with a boosted protease inhibitor. This breakpoint might be lower in antiretroviral combination therapy not including a boosted protease inhibitor.

In the Phase III trials DUET-1 and DUET-2, mutations that developed most commonly in patients with virologic failure to the etravirine containing regimen were V108I, V179F, V179I, Y181C and Y181I, which usually emerged in a background of multiple other NNRTI resistance-associated mutations (RAMs). In all the other trials conducted with etravirine in HIV-1 infected patients, the following mutations emerged most commonly: L100I, E138G, V179F, V179I, Y181C and H221Y.

Cross-resistance

Following virologic failure of an etravirine-containing regimen it is not recommended to treat patients with efavirenz and/or nevirapine.

Clinical efficacy and safety

Treatment-experienced adult patients

Pivotal studies

The evidence of efficacy of etravirine is based on 48-week data from 2 Phase III trials DUET-1 and DUET-2. These trials were identical in design and similar efficacy for etravirine was seen in each trial. The results below are pooled data from the two trials.

Trial characteristics

- Design: randomised (1:1), double-blinded, placebo-controlled.
- Treatment: Etravirine vs. placebo, in addition to a background regimen (BR) including darunavir/ritonavir (DRV/rtv), investigator-selected N(t)RTIs and optional enfuvirtide (ENF).
- Main inclusion criteria:
    - HIV-1 plasma viral load > 5,000 HIV-1 RNA copies/ml at screening

- 1 or more NNRTI resistance-associated mutations (RAMs) at screening or from prior genotypic analysis (i.e., archived resistance)
- 3 or more primary PI mutations at screening
- on a stable antiretroviral regimen for at least 8 weeks.

- Stratification: Randomisation was stratified by the intended use of ENF in the BR, previous use of darunavir and screening viral load.
- Virologic response was defined as achieving a confirmed undetectable viral load (< 50 HIV-1 RNA copies/ml).

Summary of efficacy results

Table 4: DUET-1 and DUET-2 pooled 48-week data

	Etravirine + BR N = 599	**Placebo + BR N = 604**	**Treatment difference (95% CI)**
Baseline characteristics			
Median plasma HIV-1 RNA	4.8 $\log_{10}$ copies/ml	4.8 $\log_{10}$ copies/ml	
Median CD4 cell count	99 x 10^6 cells/l	109 x 10^6 cells/l	
Outcomes			
Confirmed undetectable viral load (< 50 HIV-1 RNA copies/ml)[a] n (%)			
Overall	363 (60.6%)	240 (39.7%)	20.9% (15.3%; 26.4%)[d]
de novo ENF	109 (71.2%)	93 (58.5%)	12.8% (2.3%; 23.2%)[f]
Not *de novo* ENF	254 (57.0%)	147 (33.0%)	23.9% (17.6%; 30.3%)[f]
< 400 HIV-1 RNA copies/ml[a] n (%)	428 (71.5%)	286 (47.4%)	24.1% (18.7%; 29.5%)[d]
HIV-1 RNA $\log_{10}$ mean change from baseline ($\log_{10}$ copies/ml)[b]	-2.25	-1.49	-0.6 (-0.8; -0.5)[c]
CD4 cell count mean change from baseline (x 10^6/l)[b]	+98.2	+72.9	24.4 (10.4; 38.5)[c]
Any AIDS defining illness and/or death n (%)	35 (5.8%)	59 (9.8%)	-3.9% (-6.9%; -0.9%)[e]

[a] Imputations according to the TLOVR algorithm (TLOVR = Time to Loss of Virologic Response).

[b] Non-completer is failure (NC = F) imputation.

[c] Treatment differences are based on Least Square Means from an ANCOVA model including the stratification factors. P-value < 0.0001 for mean decrease in HIV-1 RNA; P-value = 0.0006 for mean change in CD4 cell count.

[d] Confidence interval around observed difference of response rates; P-value < 0.0001 from logistic regression model, including stratification factors.

[e] Confidence interval around observed difference of response rates; P-value = 0.0408.

[f] Confidence interval around observed difference of response rates; P-value from CMH test controlling for stratification factors = 0.0199 for *de novo*, and < 0.0001 for not *de novo*.

Since there was a significant interaction effect between treatment and ENF, the primary analysis was done for 2 ENF strata (patients reusing 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 etravirine arm was superior to the placebo arm irrespective of whether ENF was used *de novo* (p = 0.0199) or not

($p < 0.0001$). Results of this analysis (week 48 data) by ENF stratum are shown in table 4.

Significantly fewer patients in the etravirine arm reached a clinical endpoint (AIDS-defining illness and/or death) as compared to the placebo arm ($p = 0.0408$).

A subgroup analysis of the virologic response (defined as a viral load < 50 HIV-1 RNA copies/ml) at week 48 by baseline viral load and baseline CD4 count (pooled DUET data) is presented in table 5.

Table 5: DUET-1 and DUET-2 pooled data

Subgroups	**Proportion of subjects with HIV-1 RNA < 50 copies/ml at week 48**	
	Etravirine + BR N = 599	**Placebo + BR N = 604**
Baseline HIV-1 RNA		
< 30,000 copies/ml	75.8%	55.7%
≥ 30,000 and < 100,000 copies/ml	61.2%	38.5%
≥ 100,000 copies/ml	49.1%	28.1%
Baseline CD4 count (x 10^6/l)		
< 50	45.1%	21.5%
≥ 50 and < 200	65.4%	47.6%
≥ 200 and < 350	73.9%	52.0%
≥ 350	72.4%	50.8%

Note: Imputations according to the TLOVR algorithm (TLOVR = Time to Loss of Virologic Response)

Baseline genotype or phenotype and virologic outcome analyses

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, (etravirine RAMs) was associated with a decreased virologic response to etravirine (see table 6). These individual mutations occurred in the presence of other NNRTI RAMs. V179F was never present without Y181C.

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results.

Table 6: Proportion of subjects with < 50 HIV-1 RNA copies/ml at week 48 by baseline number of etravirine RAMs in the non-viral failure excluded population of pooled DUET-1 and DUET-2 trials

Baseline number of Etravirine RAMs*	**Etravirine arms N = 549**	
	Reused/not used ENF	*de novo* ENF
All ranges	63.3% (254/401)	78.4% (109/139)
0	74.1% (117/158)	91.3% (42/46)
1	61.3% (73/119)	80.4% (41/51)
2	64.1% (41/64)	66.7% (18/27)
≥ 3	38.3% (23/60)	53.3% (8/15)
	Placebo arms N = 569	
All ranges	37.1% (147/396)	64.1% (93/145)

* Etravirine RAMs = V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S
Note: all patients in the DUET trials received a background regimen consisting of darunavir/rtv, investigator-selected NRTIs and optional enfuvirtide.

The presence of K103N alone, 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 etravirine. Furthermore, the presence of this mutation alone did not affect the response in the etravirine arm. Additional data is required to conclude on the influence of K103N when associated with other NNRTIs mutations.

Data from the DUET studies suggest that baseline fold change (FC) in EC_{50} to etravirine was a predictive factor of virologic outcome, with gradually decreasing responses observed above FC 3 and FC 13.

FC subgroups are based on the select patient populations in DUET-1 and DUET-2 and are not meant to represent definitive clinical susceptibility breakpoints for etravirine.

Exploratory head to head comparison with protease inhibitor in protease inhibitor naïve patients (trial TMC125-C227)

TMC125-C227 was an exploratory, randomised, active-controlled open-label trial, which investigated the efficacy and safety of etravirine in a treatment regimen, which is not approved under the current indication. In the TMC125-C227 study, etravirine (N = 59) was administered with 2 investigator-selected NRTIs (i.e. without a ritonavir-boosted PI) and compared to an investigator-selected combination of a PI with 2 NRTIs (N = 57). The trial population included PI-naïve, NNRTI-experienced patients with evidence of NNRTI resistance.

At week 12, virologic response was greater in the control-PI arm (-2.2 $\log_{10}$ copies/ml from baseline; n = 53) compared to the etravirine arm (-1.4 $\log_{10}$ copies/ml from baseline; n = 40). This difference between treatment arms was statistically significant.

Based on these trial results, etravirine is not recommended for use in combination with N(t)RTIs only in patients who have experienced virological failure on an NNRTI- and N(t)RTI-containing regimen.

Paediatric population

Treatment-experienced paediatric patients (6 years to less than 18 years of age)

PIANO is a single-arm, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of etravirine in 101 antiretroviral treatment-experienced HIV-1 infected paediatric patients 6 years to less than 18 years of age and weighing at least 16 kg. The study enrolled patients on a stable but virologically failing antiretroviral treatment regimen, with a confirmed HIV-1 RNA plasma viral load $\geq$ 500 copies/ml. Sensitivity of the virus to etravirine at screening was required.

The median baseline plasma HIV-1 RNA was 3.9 $\log_{10}$ copies/ml, and the median baseline CD4 cell count was 385 x 10^6 cells/l.

Table 7: Virologic responses (ITT – TLOVR), change from baseline in log_{10} viral load (NC = F), and change from baseline in CD4 percentage and cell count (NC = F) at week 24 in the TMC125-C213 and pooled DUET studies

Study Age at screening Treatment group	**TMC125-C213 6 to < 12 years ETR N = 41**	**TMC125-C213 12 to < 18 years ETR N = 60**	**TMC125-C213 6 to < 18 years ETR N = 101**	**Pooled DUET Studies ≥ 18 years ETR N = 599**
Virologic parameters				
Viral load < 50 copies/ ml at week 24, n (%)	24 (58.5)	28 (46.7)	52 (51.5)	363 (60.6)
Viral load < 400 copies /ml at week 24, n (%)	28 (68.3)	38 (63.3)	66 (65.3)	445 (74.3)
≥ 1 log_{10} decrease from baseline at week 24, n (%)	26 (63.4)	38 (63.3)	64 (63.4)	475 (79.3)
Change from baseline in log_{10} viral load (copies/ml) at week 24, mean (SE) and median (range)	-1.62 (0.21) -1.68 (-4.3; 0.9)	-1.44 (0.17) -1.68 (-4.0; 0.7)	-1.51 (0.13) -1.68 (-4.3; 0.9)	-2.37 (0.05) -2.78 (-4.6; 1.4)
Immunologic parameters				
Change from baseline in CD4 cell count (x 10^6 cells/l), mean (SE) and median (range)	125 (33.0) 124 (-410; 718)	104 (17.5) 81 (-243; 472)	112 (16.9) 108 (-410; 718)	83.5 (3.64) 77.5 (-331; 517)
Change from baseline in CD4 percentage, median (range)	4% (-9; 20)	3% (-4; 14)	4% (-9; 20)	3% (-7; 23)

N = number of subjects with data; n = number of observations.

At week 48, 53.5% of all paediatric patients had a confirmed undetectable viral load < 50 HIV-1 RNA copies/ml according to the TLOVR algorithm. The proportion of paediatric patients with < 400 HIV-1 RNA copies/ml was 63.4%. The mean change in plasma HIV-1 RNA from baseline to week 48 was -1.53 log_{10} copies/ml, and the mean CD4 cell count increase from baseline was 156 x 10^6 cells/l.

Treatment-experienced paediatric patients (1 year to less than 6 years of age)

TMC125-C234/IMPAACT P1090 is a Phase I/II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of INTELENCE in 20 antiretroviral treatment-experienced HIV-1 infected pediatric patients 2 years to less than 6 years of age (Cohort I) and 6 antiretroviral treatment-experienced HIV-1 infected pediatric patients 1 year to less than 2 years of age (Cohort II). No patients have been enrolled in Cohort III (≥ 2 months to < 1 year). The study enrolled patients on a virologically failing antiretroviral treatment regimen for at least 8 weeks or on a treatment interruption of at least 4 weeks with a history of virologic failure while on an antiretroviral regimen, with a confirmed HIV-1 RNA plasma viral load greater than 1,000 copies/ml and with no evidence of phenotypic resistance to etravirine at screening.

Table 8 summarizes the virologic response results for the TMC125-C234/IMPAACT P1090 study.

Table 8: Virologic responses (ITT-FDA Snapshot*) at week 48 in the TMC125-C234/IMPAACT P1090 Study

	Cohort I ≥ 2 to < 6 years (N = 20)	**Cohort II ≥ 1 to < 2 years (N = 6)**
Baseline		
Plasma HIV-1 RNA	4.4 $\log_{10}$ copies/ml	4.4 $\log_{10}$ copies/ml
Median CD4+ cell count Median baseline CD4+ percentage	817.5 x 10^6 cells/l (27.6%)	1,491.5 x 10^6 cells/l (26.9%)
Week 48		
Virologic Response (plasma viral load < 400 HIV-1 RNA copies/ml)	16/20 (80.0%)	1/6 (16.7%)
Median change in plasma HIV-1 RNA from baseline to Week 48	-2.31 $\log_{10}$ copies/ml	-0.665 $\log_{10}$ copies/ml
Median CD4+ change from baseline	298.5 x 10^6 cells/l (5.15%)	0 x 10^6 cells/l (-2.2%)

N = number of subjects per treatment group.
* Intent-to-treat-FDA Snapshot approach.

Subgroup analyses showed that for subjects aged 2 to less than 6 years virologic response [HIV RNA < 400 copies/ml] was 100.0% [6/6] for subjects who swallowed the etravirine tablet whole, 100% [4/4] for subjects who took a combination of both etravirine dispersed in liquid and etravirine tablet whole and 60% [6/10] for subjects who took etravirine dispersed in liquid. Of the 4 subjects who did not show virologic response and took etravirine dispersed in liquid, 3 showed virologic failure and had adherence issues, and one discontinued prior to Week 48 for safety reasons.

The European Medicines Agency has deferred the obligation to submit the results of studies with INTELENCE in one or more subsets of the paediatric population in human immunodeficiency virus infection, as per Paediatric Investigation Plan (PIP) decision in the granted indication (see section 4.2 for information on paediatric use).

Pregnancy and postpartum

Etravirine (200 mg twice daily), evaluated in combination with other antiretroviral medicinal products 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 new clinically relevant safety findings in the mothers or in the newborns in this trial.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of etravirine have been evaluated in adult healthy subjects and in adult and paediatric treatment-experienced HIV-1 infected patients. Exposure to etravirine was lower (35-50%) in HIV-1 infected patients than in healthy subjects.

Table 9: Population pharmacokinetic estimates of etravirine 200 mg twice daily in HIV-1 infected adult subjects (integrated data from Phase III trials at week 48)*

Parameter	**Etravirine 200 mg twice daily N = 575**
AUC_{12h} (ng•h/ml)	
Geometric Mean ± Standard Deviation	4,522 ± 4,710
Median (Range)	4,380 (458 - 59,084)
C_{0h} (ng/ml)	
Geometric Mean ± Standard Deviation	297 ± 391
Median (Range)	298 (2 - 4,852)

* All HIV-1 infected subjects enrolled in Phase III clinical trials received darunavir/ritonavir 600/100 mg twice daily as part of their background regimen. Therefore, the pharmacokinetic parameter estimates shown in the table account for reductions in the pharmacokinetic parameters of etravirine due to co-administration of etravirine with darunavir/ritonavir.

Note: The median protein binding adjusted EC_{50} for MT4 cells infected with HIV-1/IIIB *in vitro* = 4 ng/ml.

Absorption

An intravenous formulation of etravirine is unavailable, thus, the absolute bioavailability of etravirine 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, medicinal products that are known to increase gastric pH.

Effect of food on absorption

The systemic exposure (AUC) to etravirine was decreased by about 50% when etravirine was administered under fasting conditions, as compared to administration following a meal. Therefore, INTELENCE should be taken following a meal.

Distribution

Etravirine is approximately 99.9% bound to plasma proteins, primarily to albumin (99.6%) and α_1-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.

Biotransformation

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 in faeces is likely to be unabsorbed drug. Unchanged etravirine was not detected in urine. The terminal elimination half-life of etravirine was approximately 30-40 hours.

Special populations

Paediatric population (1 year to less than 18 years of age)

The pharmacokinetics of etravirine in 122 treatment-experienced HIV-1 infected paediatric patients, 1 year to less than 18 years of age, showed that the administered weight-based dosages resulted in etravirine exposure comparable to that in adults receiving etravirine 200 mg twice daily (see sections 4.2 and 5.2). The population pharmacokinetic estimates for etravirine AUC_{12h} and C_{0h} are summarised in the table below.

Table 10: Pharmacokinetic parameters for etravirine in treatment-experienced HIV-1 infected paediatric patients 1 year to less than 18 years of age (TMC125-C234/IMPAACT P1090 [48 week analysis, intensive PK] and PIANO [48 Weeks analysis, population PK])

Age Range (years)	**≥ 1 year to < 2 years (Cohort II)**	**≥ 2 years to < 6 years (Cohort I)**	**6 years to < 18 years**
Parameter	**Etravirine N = 6**	**Etravirine N = 15**	**Etravirine N = 101**
AUC_{12h} (ng•h/ml)			
Geometric Mean ± Standard Deviation	3,328 ± 3,138	3,824 ± 3,613	3,729 ± 4,305
Median (Range)	3,390 (1,148 - 9,989)	3,709 (1,221 - 12,999)	4,560 (62 - 28,865)
C_{0h} (ng/ml)			
Geometric Mean ± Standard Deviation	193 ± 186	203 ± 280	205 ± 342
Median (Range)	147 (0[a] - 503)	180 (54 - 908)	287 (2 - 2,276)

[a] One subject in Cohort II had etravirine predose concentrations below the detection limit at the intensive PK visit.

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, with 6 subjects aged 65 years or older (see sections 4.2 and 4.4).

Gender

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

Race

Population pharmacokinetic analysis of etravirine in HIV infected patients indicated no apparent difference in the exposure to etravirine between Caucasian, Hispanic and Black subjects. The pharmacokinetics in other races have not been sufficiently evaluated.

Hepatic impairment

Etravirine is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild (Child-Pugh Class A) hepatic impairment to 8 matched controls and 8 patients with moderate (Child-Pugh Class 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. However, unbound concentrations have not been assessed. Increased unbound exposure could be expected. No dose adjustment is suggested but caution is advised in patients with moderate hepatic impairment. INTELENCE has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and is therefore not recommended (see sections 4.2 and 4.4).

Hepatitis B and/or hepatitis C virus co-infection

Population pharmacokinetic analysis of the DUET-1 and DUET-2 trials showed reduced clearance (potentially leading to increased exposure and alteration of the safety profile) for etravirine in HIV-1 infected patients with hepatitis B and/or hepatitis C virus co-infection. In view of the limited data available in hepatitis B and/or C co-infected patients, particular caution should be paid when INTELENCE is used in these patients (see sections 4.4 and 4.8).

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).

Pregnancy and postpartum

Study TMC114HIV3015 evaluated etravirine 200 mg twice daily in combination with other antiretroviral medicinal products in 15 pregnant women during the second and third trimesters of pregnancy and postpartum. The total etravirine exposure after intake of etravirine 200 mg twice daily as part of an antiretroviral regimen was generally higher during pregnancy compared with postpartum (see Table 11). The differences were less pronounced for unbound etravirine exposure.

In women receiving etravirine 200 mg twice daily, 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.

Table 11: Pharmacokinetic results of total etravirine after administration of etravirine 200 mg twice daily 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 twice daily postpartum N = 10**	**Etravirine 200 mg twice daily 2nd trimester N = 13**	**Etravirine 200 mg twice daily 3rd trimester N = 10[a]**
C_{min}, ng/ml	269 ± 182 (284)	383 ± 210 (346)	349 ± 103 (371)
C_{max}, ng/ml	569 ± 261 (528)	774 ± 300 (828)	785 ± 238 (694)
$AUC_{12h,}$ h*ng /ml	5004 ± 2521 (5246)	6617 ± 2766 (6836)	6846 ± 1482 (6028)

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

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

5.3 Preclinical safety data

Animal toxicology studies have been conducted with etravirine in mice, rats, rabbits and dogs. In mice, the key target organs identified were the liver and the coagulation system. Haemorrhagic cardiomyopathy was only observed in male mice and was considered to be secondary to severe coagulopathy mediated via the vitamin K pathway. In the rat, the key target organs identified were the liver, the thyroid and the coagulation system. Exposure in mice was equivalent to human exposure while in rats it was below the clinical exposure at the recommended dose. In the dog, changes were observed in the liver and gall bladder at exposures approximately 8-fold higher than human exposure observed at the recommended dose (200 mg twice daily).

In a study conducted in rats, there were no effects on mating or fertility at exposure levels equivalent to those in humans at the clinically recommended dose. There was no teratogenicity with etravirine in rats and rabbits at exposures equivalent to those observed in humans at the recommended clinical dose. Etravirine had no effect on offspring development during lactation or post weaning at maternal exposures equivalent to those observed at the recommended clinical dose.

Etravirine was not carcinogenic in rats and in male mice. An increase in the incidences of hepatocellular adenomas and carcinomas were observed in female mice. The observed hepatocellular findings in female mice are generally considered to be rodent specific, associated with liver enzyme induction, and of limited relevance to humans. At the highest tested doses, the systemic exposures (based on AUC) to etravirine were 0.6-fold (mice) and between 0.2- and 0.7-fold (rats), relative to those observed in humans at the recommended therapeutic dose (200 mg twice daily).

In vitro and *in vivo* studies with etravirine revealed no evidence of a mutagenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose

Silicified microcrystalline cellulose

Microcrystalline cellulose

Colloidal anhydrous silica

Croscarmellose sodium

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6 weeks after opening the bottle.

6.4 Special precautions for storage

Store in the original bottle and keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.

6.5 Nature and contents of container

The bottle is a high-density polyethylene (HDPE) plastic bottle containing 60 tablets and 3 desiccant pouches, fitted with a polypropylene (PP) child resistant closure.

Each carton contains one bottle.

6.6 Special precautions for disposal

Patients who are unable to swallow the 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 liquid to cover the medicine,
- stir well until the water looks milky,
- if desired, add 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.

INTELENCE tablet(s) dispersed in liquid should be taken before other antiretroviral liquids that may need to be taken concomitantly.

The patient and his/her caregiver should be instructed to contact the prescribing physician if unable to swallow the entire dose when dispersed in liquid (see section 4.4).

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

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

7 MARKETING AUTHORISATION HOLDER

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