פורמט עלון זה נקבע ע״י משרד הבריאות ותוכנו נבדק ואושר ע״י משרד הבריאות בתאריך , 03/03/2016
ועודכן בהתאם להוראות משרד הבריאות בתאריך15/01/2017

## 1 NAME OF THE MEDICINAL PRODUCT

**INTELENCE** 100 mg, tablets.
**INTELENCE** 200 mg, tablets.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

**INTELENCE** 100 mg:
Each tablet contains 100 mg of etravirine.
Excipient with known effect: Each tablet contains 160 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

**INTELENCE** 200 mg:
Each tablet contains 200 mg of etravirine.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

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

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

INTELENCE, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients, including those with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance.

Treatment history and, when available, resistance testing, should guide the use of INTELENCE. In patients who have experienced virological failure on an NNRTI- and nucleoside or nucleotide reverse transcriptase inhibitor (N[t]RTI)-containing regimen, INTELENCE is not recommended for use in combination with N(t)RTIs only.

### 4.2 Posology and method of administration

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

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

Posology
Adults

The recommended dose of INTELENCE for adults is 200 mg (two 100 mg tablets) taken orally twice daily (b.i.d.), following a meal (see section 5.2).

Children (less than 12 years of age) and adolescents (12 to 17 years of age)
Treatment with INTELENCE is not approved in Israel in children and adolescents.

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.

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).

Pregnancy and postpartum
Based on limited data available, no dose adjustment is required during pregnancy and postpartum (see section 5.2).

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.
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

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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 drug reactions have been reported with INTELENCE; 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 INTELENCE (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 INTELENCE. Most frequently, rash was mild to moderate, occurred in the second week of therapy and was infrequent after week 4. Rash was mostly self-limiting and generally

resolved within 1 to 2 weeks on continued therapy . When prescribing INTELENCE to females, prescribers should be aware that the incidence of rash was higher in females (see section 4.8).

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 reaction 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 medications 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. INTELENCE 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) 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 simeprevir, 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 100 mg

Each tablet contains 160 mg of lactose. 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 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. 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.1. The table is not all-inclusive.

***Interaction table****
Interactions between etravirine and co-administered medicinal products are listed in table.1 (increase is indicated as "↑", decrease as "↓", no change as "↔", not done as "ND", confidence interval as ""CI.").

| **Table 1: 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<br>400 mg once daily | didanosine<br>AUC ↔ 0.99 (0.79-1.25)<br>$C_{min}$ ND<br>$C_{max}$ ↔ 0.91 (0.58-1.42)<br>etravirine<br>AUC ↔ 1.11 (0.99-1.25)<br>$C_{min}$ ↔ 1.05 (0.93-1.18)<br>$C_{max}$ ↔ 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<br>245 mg once daily[b] | tenofovir<br>AUC ↔ 1.15 (1.09-1.21)<br>$C_{min}$ ↑ 1.19 (1.13-1.26)<br>$C_{max}$ ↑ 1.15 (1.04-1.27)<br>etravirine<br>AUC ↓ 0.81 (0.75-0.88)<br>$C_{min}$ ↓ 0.82 (0.73-0.91)<br>$C_{max}$ ↓ 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). | Etravirine can be used with these NRTIs without dose adjustment. |
| *NNRTIs* | | |
| Efavirenz<br>Nevirapine<br>Rilpivirine | Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE with efavirenz or nevirapine may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of INTELENCE.<br>Concomitant use of INTELENCE 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 INTELENCE 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. |
| Nelfinavir | Not studied. INTELENCE is expected to increase nelfinavir plasma concentrations. | It is not recommended to co-administer INTELENCE with nelfinavir. |

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| *HIV PIs - Boosted with low-dose ritonavir* | | |
| Atazanavir/ritonavir 300/100 mg once daily | atazanavir<br>AUC ↓ 0.86 (0.79-0.93)<br>$C_{min}$ ↓ 0.62 (0.55-0.71)<br>$C_{max}$ ↔ 0.97 (0.89-1.05)<br>etravirine<br>AUC ↑ 1.30 (1.18-1.44)<br>$C_{min}$ ↑ 1.26 (1.12-1.42)<br>$C_{max}$ ↑ 1.30 (1.17-1.44) | INTELENCE and atazanavir/ritonavir can be used without dose adjustment. |
| Darunavir/ritonavir 600/100 mg twice daily | darunavir<br>AUC ↔ 1.15 (1.05-1.26)<br>$C_{min}$ ↔ 1.02 (0.90-1.17)<br>$C_{max}$ ↔ 1.11 (1.01-1.22)<br>etravirine<br>AUC ↓ 0.63 (0.54-0.73)<br>$C_{min}$ ↓ 0.51 (0.44-0.61)<br>$C_{max}$ ↓ 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 | amprenavir<br>AUC ↑ 1.69 (1.53-1.86)<br>$C_{min}$ ↑ 1.77 (1.39-2.25)<br>$C_{max}$ ↑ 1.62 (1.47-1.79)<br>etravirine<br>AUC ↔[a]<br>$C_{min}$ ↔[a]<br>$C_{max}$ ↔[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 | lopinavir<br>AUC ↔ 0.87 (0.83-0.92)<br>$C_{min}$ ↓ 0.80 (0.73-0.88)<br>$C_{max}$ ↔ 0.89 (0.82-0.96)<br>etravirine<br>AUC ↓ 0.65 (0.59-0.71)<br>$C_{min}$ ↓ 0.55 (0.49-0.62)<br>$C_{max}$ ↓ 0.70 (0.64-0.78) | INTELENCE and lopinavir/ritonavir can be used without dose adjustments. |
| Saquinavir/ritonavir 1,000/100 mg twice daily | saquinavir<br>AUC ↔ 0.95 (0.64-1.42)<br>$C_{min}$ ↓ 0.80 (0.46-1.38)<br>$C_{max}$ ↔ 1.00 (0.70-1.42)<br>etravirine<br>AUC ↓ 0.67 (0.56-0.80)<br>$C_{min}$ ↓ 0.71 (0.58-0.87)<br>$C_{max}$ ↓ 0.63 (0.53-0.75) | INTELENCE and saquinavir/ritonavir can be used without dose adjustments. |
| Tipranavir/ritonavir 500/200 mg twice daily | tipranavir<br>AUC ↑ 1.18 (1.03-1.36)<br>$C_{min}$ ↑ 1.24 (0.96-1.59)<br>$C_{max}$ ↑ 1.14 (1.02-1.27)<br>etravirine<br>AUC ↓ 0.24 (0.18-0.33)<br>$C_{min}$ ↓ 0.18 (0.13-0.25)<br>$C_{max}$ ↓ 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* | | |

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| Atazanavir/cobicistat<br>Darunavir/cobicistat | Not studied. 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. |
| *CCR5 Antagonists* | | |
| Maraviroc<br>300 mg twice daily | <u>maraviroc</u><br>AUC ↓ 0.47 (0.38-0.58)<br>$C_{min}$ ↓ 0.61 (0.53-0.71)<br>$C_{max}$ ↓ 0.40 (0.28-0.57)<br><u>etravirine</u><br>AUC ↔ 1.06 (0.99-1.14)<br>$C_{min}$ ↔ 1.08 (0.98-1.19)<br>$C_{max}$ ↔ 1.05 (0.95-1.17) | The recommended dose for maraviroc when combined with INTELENCE in the presence of potent CYP3A inhibitors (e.g. boosted PIs) is 150 mg b.i.d. except for fosamprenavir/ritonavir (maraviroc dose 300 mg b.i.d.). No dose adjustment for INTELENCE is necessary.<br>See also section 4.4. |
| Maraviroc/darunavir/ritonavir<br>150/600/100 mg twice daily | <u>maraviroc*</u><br>AUC ↑ 3.10 (2.57-3.74)<br>$C_{min}$ ↑ 5.27 (4.51-6.15)<br>$C_{max}$ ↑ 1.77 (1.20-2.60)<br>* compared to maraviroc 150 mg b.i.d. | |
| *Fusion Inhibitors* | | |
| Enfuvirtide<br>90 mg twice daily | <u>etravirine</u>*<br>AUC ↔[a]<br>$C_{0h}$ ↔[a]<br>Enfuvirtide concentrations not studied and no effect is expected.<br>* based on population pharmacokinetic analyses | No interaction is expected for either INTELENCE or enfuvirtide when co-administered. |
| *Integrase Strand Transfer Inhibitors* | | |
| Dolutegravir<br>50 mg once daily | <u>dolutegravir</u><br>AUC ↓ 0.29 (0.26-0.34)<br>$C_{min}$ ↓ 0.12 (0.09-0.16)<br>$C_{max}$ ↓ 0.48 (0.43-0.54)<br><u>etravirine</u><br>AUC ↔[a]<br>$C_{min}$ ↔[a]<br>$C_{max}$ ↔[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.<br><br>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. |
| Dolutegravir + darunavir/ritonavir<br>50 mg once daily + 600/100 mg twice daily | <u>dolutegravir</u><br>AUC↓ 0.75 (0.69-0.81)<br>$C_{min}$ ↓ 0.63 (0.52-0.77)<br>$C_{max}$ ↓ 0.88 (0.78-1.00)<br><u>etravirine</u><br>AUC ↔[a]<br>$C_{min}$ ↔[a]<br>$C_{max}$ ↔[a] | |
| Dolutegravir + Lopinavir/ritonavir<br>50 mg once daily + 400/100 mg twice daily | <u>dolutegravir</u><br>AUC↔ 1.11(1.02-1.20)<br>$C_{min}$ ↑ 1.28 (1.13-1.45)<br>$C_{max}$ ↔ 1.07 (1.02-1.13)<br><u>etravirine</u><br>AUC ↔[a]<br>$C_{min}$ ↔[a]<br>$C_{max}$ ↔[a] | |

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| Raltegravir<br>400 mg twice daily | <u>raltegravir</u><br>AUC ↓ 0.90 (0.68-1.18)<br>$C_{min}$ ↓ 0.66 (0.34-1.26)<br>$C_{max}$ ↓ 0.89 (0.68-1.15)<br><u>etravirine</u><br>AUC ↔ 1.10 (1.03-1.16)<br>$C_{min}$ ↔ 1.17 (1.10-1.26)<br>$C_{max}$ ↔ 1.04 (0.97-1.12) | INTELENCE and raltegravir can be used without dose adjustments. |
| **ANTIARRHYTHMICS** | | |
| Digoxin<br>0.5 mg single dose | <u>digoxin</u><br>AUC ↑ 1.18 (0.90-1.56)<br>$C_{min}$ ND<br>$C_{max}$ ↑ 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<br>Bepridil<br>Disopyramide<br>Flecainide<br>Lidocaine (systemic)<br>Mexiletine<br>Propafenone<br>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<br>500 mg twice daily | <u>clarithromycin</u><br>AUC ↓ 0.61 (0.53-0.69)<br>$C_{min}$ ↓ 0.47 (0.38-0.57)<br>$C_{max}$ ↓ 0.66 (0.57-0.77)<br><u>14-OH-clarithromycin</u><br>AUC ↑ 1.21 (1.05-1.39)<br>$C_{min}$ ↔ 1.05 (0.90-1.22)<br>$C_{max}$ ↑ 1.33 (1.13-1.56)<br><u>etravirine</u><br>AUC ↑ 1.42 (1.34-1.50)<br>$C_{min}$ ↑ 1.46 (1.36-1.58)<br>$C_{max}$ ↑ 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. INTELENCE 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<br>Phenobarbital<br>Phenytoin | Not studied. Carbazamepine, phenobarbital and phenytoin are expected to decrease plasma concentrations of etravirine. | Combination not recommended. |

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| **ANTIFUNGALS** | | |
| Fluconazole<br>200 mg once in the morning | fluconazole<br>AUC ↔ 0.94 (0.88-1.01)<br>$C_{min}$ ↔ 0.91 (0.84-0.98)<br>$C_{max}$ ↔ 0.92 (0.85-1.00)<br>etravirine<br>AUC ↑ 1.86 (1.73-2.00)<br>$C_{min}$ ↑ 2.09 (1.90-2.31)<br>$C_{max}$ ↑ 1.75 (1.60-1.91) | INTELENCE and fluconazole can be used without dose adjustments. |
| Itraconazole<br>Ketoconazole<br>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 INTELENCE may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE. | INTELENCE and these antifungals can be used without dose adjustments. |
| Voriconazole<br>200 mg twice daily | voriconazole<br>AUC ↑ 1.14 (0.88-1.47)<br>$C_{min}$ ↑ 1.23 (0.87-1.75)<br>$C_{max}$ ↓ 0.95 (0.75-1.21)<br>etravirine<br>AUC ↑ 1.36 (1.25-1.47)<br>$C_{min}$ ↑ 1.52 (1.41-1.64)<br>$C_{max}$ ↑ 1.26 (1.16-1.38) | INTELENCE and voriconazole can be used without dose adjustments. |
| **ANTIMALARIALS** | | |
| Artemether/<br>Lumefantrine<br>80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours | artemether<br>AUC ↓ 0.62 (0.48-0.80)<br>$C_{min}$ ↓ 0.82 (0.67-1.01)<br>$C_{max}$ ↓ 0.72 (0.55-0.94)<br>dihydroartemisinin<br>AUC ↓ 0.85 (0.75-0.97)<br>$C_{min}$ ↓ 0.83 (0.71-0.97)<br>$C_{max}$ ↓ 0.84 (0.71-0.99)<br>lumefantrine<br>AUC ↓ 0.87 (0.77-0.98)<br>$C_{min}$ ↔ 0.97 (0.83-1.15)<br>$C_{max}$ ↔ 1.07 (0.94-1.23)<br>etravirine<br>AUC ↔ 1.10 (1.06-1.15)<br>$C_{min}$ ↔ 1.08 (1.04-1.14)<br>$C_{max}$ ↔ 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<br>Rifapentine | Not studied. Rifampicin and rifapentine are expected to decrease plasma concentrations of etravirine.<br>INTELENCE should be used in combination with a boosted PI. Rifampicin is contraindicated in combination with boosted PIs. | Combination not recommended. |

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| Rifabutin<br>300 mg once daily | With an associated boosted PI:<br>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.<br><br>With no associated boosted PI (out of the recommended indication for etravirine):<br><u>rifabutin</u><br>AUC ↓ 0.83 (0.75-0.94)<br>$C_{min}$ ↓ 0.76 (0.66-0.87)<br>$C_{max}$ ↓ 0.90 (0.78-1.03)<br><u>25-O-desacetyl-rifabutin</u><br>AUC ↓ 0.83 (0.74-0.92)<br>$C_{min}$ ↓ 0.78 (0.70-0.87)<br>$C_{max}$ ↓ 0.85 (0.72-1.00)<br><u>etravirine</u><br>AUC ↓ 0.63 (0.54-0.74)<br>$C_{min}$ ↓ 0.65 (0.56-0.74)<br>$C_{max}$ ↓ 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.<br>Close monitoring for virologic response and for rifabutin related adverse reactions is recommended.<br>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<br>0.035 mg once daily<br>Norethindrone<br>1 mg once daily | <u>ethinylestradiol</u><br>AUC ↑ 1.22 (1.13-1.31)<br>$C_{min}$ ↔ 1.09 (1.01-1.18)<br>$C_{max}$ ↑ 1.33 (1.21-1.46)<br><u>norethindrone</u><br>AUC ↔ 0.95 (0.90-0.99)<br>$C_{min}$ ↓ 0.78 (0.68-0.90)<br>$C_{max}$ ↔ 1.05 (0.98-1.12)<br><u>etravirine</u><br>AUC ↔[a]<br>$C_{min}$ ↔[a]<br>$C_{max}$ ↔[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. |

| | | |
|---|---|---|
| Boceprevir<br>800 mg 3 times daily + etravirine 200 mg every 12 hours | boceprevir<br>AUC ↑ 1.10 (0.94-1.28)<br>$C_{max}$ ↑ 1.10 (0.94-1.29)<br>$C_{min}$ ↓ 0.88 (0.66-1.17)<br>etravirine<br>AUC ↓ 0.77 (0.66-0.91)<br>$C_{max}$ ↓ 0.76 (0.68-0.85)<br>$C_{min}$ ↓ 0.71 (0.54-0.95) | The clinical significance of the reductions in etravirine pharmacokinetic parameters and boceprevir $C_{min}$ in the setting of the combination therapy with HIV antiretroviral medicines which also affect the pharmacokinetics of etravirine and/or boceprevir has not been directly assessed. Increased clinical and laboratory monitoring for HIV and HCV suppression is recommended. |
| Daclatasvir | Not studied. Co-administration of INTELENCE with daclatasvir may decrease daclatasvir concentrations. | Co-administration of Intelence and daclatasvir is not recommended. |
| Elbasvir/grazoprevir | Not studied. Co-administration of INTELENCE 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). |
| Simeprevir | Not studied. Concomitant use of INTELENCE with simeprevir may decrease plasma concentrations of simeprevir. | Co-administration of Intelence and simeprevir is not recommended. |
| | | |
| **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<br>40 mg once daily | atorvastatin<br>AUC ↓ 0.63 (0.58-0.68)<br>$C_{min}$ ND<br>$C_{max}$ ↑ 1.04 (0.84-1.30)<br>2-OH-atorvastatin<br>AUC ↑ 1.27 (1.19-1.36)<br>$C_{min}$ ND<br>$C_{max}$ ↑ 1.76 (1.60-1.94)<br>etravirine<br>AUC ↔ 1.02 (0.97-1.07)<br>$C_{min}$ ↔ 1.10 (1.02-1.19)<br>$C_{max}$ ↔ 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<br>Lovastatin<br>Pravastatin<br>Rosuvastatin<br>Simvastatin | Not studied. No interaction between pravastatin and INTELENCE is expected.<br>Lovastatin, rosuvastatin and simvastatin are CYP3A4 substrates and co-administration with INTELENCE may result in lower plasma concentrations of the HMG Co-A reductase inhibitor. Fluvastatin, and rosuvastatin are metabolised by CYP2C9 and co-administration with INTELENCE may result in higher plasma concentrations of the HMG Co-A reductase inhibitor. | Dose adjustments for these HMG Co-A reductase inhibitors may be necessary. |

| | | |
|---|---|---|
| **$H_2$-RECEPTOR ANTAGONISTS** | | |
| Ranitidine<br>150 mg twice daily | <u>etravirine</u><br>AUC ↓ 0.86 (0.76-0.97)<br>$C_{min}$ ND<br>$C_{max}$ ↓ 0.94 (0.75-1.17) | INTELENCE can be co-administered with $H_2$-receptor antagonists without dose adjustments. |
| **IMMUNOSUPPRESSANTS** | | |
| Cyclosporin<br>Sirolimus<br>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<br>individual dose ranging from 60 mg to 130 mg once daily | <u>R(-) methadone</u><br>AUC ↔ 1.06 (0.99-1.13)<br>$C_{min}$ ↔ 1.10 (1.02-1.19)<br>$C_{max}$ ↔ 1.02 (0.96-1.09)<br><u>S(+) methadone</u><br>AUC ↔ 0.89 (0.82-0.96)<br>$C_{min}$ ↔ 0.89 (0.81-0.98)<br>$C_{max}$ ↔ 0.89 (0.83-0.97)<br><u>etravirine</u><br>AUC ↔[a]<br>$C_{min}$ ↔[a]<br>$C_{max}$ ↔[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<br>Tadalafil<br>Vardenafil | <u>sildenafil</u><br>AUC ↓ 0.43 (0.36-0.51)<br>$C_{min}$ ND<br>$C_{max}$ ↓ 0.55 (0.40-0.75)<br><u>N-desmethyl-sildenafil</u><br>AUC ↓ 0.59 (0.52-0.68)<br>$C_{min}$ ND<br>$C_{max}$ ↓ 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<br>40 mg once daily | <u>etravirine</u><br>AUC ↑ 1.41 (1.22-1.62)<br>$C_{min}$ ND<br>$C_{max}$ ↑ 1.17 (0.96-1.43) | INTELENCE can be co-administered with proton pump inhibitors without dose adjustments. |

| **SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)** | | |
|---|---|---|
| Paroxetine<br>20 mg once daily | paroxetine<br>AUC ↔ 1.03 (0.90-1.18)<br>$C_{min}$ ↓ 0.87 (0.75-1.02)<br>$C_{max}$ ↔ 1.06 (0.95-1.20)<br>etravirine<br>AUC ↔ 1.01 (0.93-1.10)<br>$C_{min}$ ↔ 1.07 (0.98-1.17)<br>$C_{max}$ ↔ 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.

Paediatric population

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 INTELENCE 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

It is not known whether etravirine is excreted in human milk.

As a general rule, it is recommended that mothers infected by HIV do not breast-feed their babies under any circumstances 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 no or negligible influence on the ability to drive and use machines. Adverse drug reactions such as somnolence and vertigo have been reported in INTELENCE treated subjects at incidences similar to placebo (see section 4.8). There is no evidence that INTELENCE may alter the patient's ability to drive and operate machines, however, the adverse drug reaction profile should be taken into account.

## 4.8 Undesirable effects

Summary of the safety profile

The safety assessment is based on all data from 1,203 patients in the Phase III placebo-controlled trials DUET-1 and DUET-2 in antiretroviral treatment-experienced HIV-1 infected adult patients, 599 of whom received INTELENCE (200 mg b.i.d.) (see section 5.1). In these pooled trials, the median exposure for patients in the INTELENCE arm was 52.3 weeks.

The most frequently reported adverse drug reactions (ADRs) (incidence ≥ 10% in the INTELENCE arm) of all intensities occurring in the Phase III studies were rash (19.2% in the INTELENCE arm versus 10.9% in the placebo arm), diarrhoea (18.0% in the INTELENCE arm versus 23.5% in the placebo arm), nausea (14.9% in the INTELENCE arm versus 12.7% in the placebo arm) and headache (10.9% in the INTELENCE arm versus 12.7% in the placebo arm). The rates of discontinuation due to any adverse reaction were 7.2% in patients receiving INTELENCE and 5.6% in patients receiving placebo. The most common ADR 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) (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).

Tabulated list of adverse reactions

ADRs of moderate intensity or greater (≥ grade 2) reported in patients treated with INTELENCE are summarised in table 2 (background regimen is indicated as "BR"). Laboratory abnormalities considered ADRs are included in a paragraph below table 2. The ADRs are listed by system organ class (SOC) and frequency. Within each frequency grouping, ADRs 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 and very rare ADRs cannot be detected based on the number of patients included in the DUET trials.

**Table 2: DUET-1 and DUET-2 trials**

| **System Organ Class (SOC)** | **Frequency Category** | **ADRs (INTELENCE + BR versus Placebo + BR)** |
|---|---|---|
| Blood and lymphatic system disorders | common | thrombocytopaenia (1.3% vs 1.5%), anaemia (4.0% vs 3.8%) |
| Immune system disorders | uncommon | immune reconstitution syndrome (0.2% vs 0.3%), drug hypersensitivity (0.8% vs 1.2%) |

| | | |
|---|---|---|
| Metabolism and nutrition disorders | common | diabetes mellitus (1.3% vs 0.2%), hyperglycaemia (1.5% vs 0.7%), hypercholesterolaemia (4.3% vs 3.6%), hypertriglyceridaemia (6.3% vs 4.3%), hyperlipidaemia (2.5% vs 1.3%) |
| | uncommon | anorexia (0.8% vs 1.5%), dyslipidaemia (0.8% vs 0.3%) |
| Psychiatric disorders | common | anxiety (1.7% vs 2.6%), insomnia (2.7% vs 2.8%) |
| | uncommon | confusional state (0.2% vs 0.2%), disorientation (0.2% vs 0.3%), nightmares (0.2% vs 0.2%), sleep disorders (0.5% vs 0.5%), nervousness (0.2% vs 0.3%), abnormal dreams (0.2% vs 0.2%) |
| Nervous system disorders | common | peripheral neuropathy (3.8% vs 2.0%), headache (3.0% vs 4.5%) |
| | uncommon | convulsion (0.5% vs 0.7%), syncope (0.3% vs 0.3%), amnesia (0.3% vs 0.5%), tremor (0.2% vs 0.3%), somnolence (0.7% vs 0.5%), paraesthesia (0.7% vs 0.7%), hypoaesthesia (0.5% vs 0.2%), hypersomnia (0.2% vs 0%), disturbance in attention (0.2% vs 0.2%) |
| Eye disorders | uncommon | blurred vision (0.7% vs 0%) |
| Ear and labyrinth disorders | uncommon | vertigo (0.2% vs 0.5%) |
| Cardiac disorders | common | myocardial infarction (1.3% vs 0.3%) |
| | uncommon | atrial fibrillation (0.2% vs 0.2%), angina pectoris (0.5% vs 0.3%) |
| Vascular disorders | common | hypertension (3.2% vs 2.5%) |
| Respiratory, thoracic and mediastinal disorders | uncommon | bronchospasm (0.2% vs 0%), exertional dyspnoea (0.5% vs 0.5%) |
| Gastrointestinal disorders | common | gastrooesophageal reflux disease (1.8% vs 1.0%), diarrhoea (7.0% vs 11.3%), vomiting (2.8% vs 2.8%), nausea (5.2% vs 4.8%), abdominal pain (3.5% vs 3.1%), flatulence (1.5% vs 1.0%), gastritis (1.5% vs 1.0%) |
| | uncommon | pancreatitis (0.7% vs 0.3%), haematemesis (0.2% vs 0%), stomatitis (0.2% vs 0.2%), constipation (0.3% vs 0.5%), abdominal distension (0.7% vs 1.0%), dry mouth (0.3% vs 0%), retching (0.2% vs 0%) |
| Hepatobiliary disorders | uncommon | hepatitis (0.2% vs 0.3%), hepatic steatosis (0.3% vs 0%), cytolytic hepatitis (0.3% vs 0%), hepatomegaly (0.5% vs 0.2%) |
| Skin and subcutaneous tissue disorders | very common | rash (10.0% vs 3.5%) |
| | common | night sweats (1.0% vs 1.0%) |

| | | |
|---|---|---|
| | uncommon | swelling face (0.3% vs 0%), hyperhidrosis (0.5% vs 0.2%), prurigo (0.7% vs 0.5%), dry skin (0.3% vs 0.2%) |
| Renal and urinary disorders | common | renal failure (2.7% vs 2.0%) |
| Reproductive system and breast disorders | uncommon | gynaecomastia (0.2% vs 0%) |
| General disorders and administration site conditions | common | fatigue (3.5% vs 4.6%) |
| | uncommon | sluggishness (0.2% vs 0%) |

Additional ADRs of at least moderate intensity observed in other trials were angioneurotic oedema, erythema multiforme and haemorrhagic stroke, each reported in no more than 0.5% of patients. Stevens-Johnson Syndrome (rare; < 0.1%) and toxic epidermal necrolysis (very rare; < 0.01%) have been reported during clinical development with INTELENCE.

*Laboratory abnormalities*
Treatment emergent clinical laboratory abnormalities (grade 3 or 4), considered ADRs, reported in ≥ 2% of patients in the INTELENCE arm versus the placebo arm, respectively, were increases in amylase (8.9% vs 9.4%), creatinine (2.0% vs 1.7%), lipase (3.4% vs 2.6%), total cholesterol (8.1% vs 5.3%), low density lipoprotein (LDL) (7.2% vs 6.6%), triglycerides (9.2% vs 5.8%), glucose (3.5% vs 2.4%), alanine aminotransferase (ALT) (3.7% vs 2.0%), aspartate amino transferase (AST) (3.2% vs 2.0%) and decreases in neutrophils (5.0% vs 7.4%) and white blood cell count (2.0% vs 4.3%).

Description of selected adverse reactions
*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) 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).

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 INTELENCE 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).

Adverse drug reactions identified through post marketing experience with INTELENCE
Hypersensitivity reactions, including DRESS, have been reported with INTELENCE. These hypersensitivity reactions were characterised by rash, fever and sometimes organ 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) (see section 4.4).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

### 4.9 Overdose

There are no data with regard to symptomatic overdose with INTELENCE, but it is possible that the most frequent ADRs of INTELENCE, i.e. rash, diarrhoea, nausea, and headache would be the most common symptoms noted.
There is no specific antidote for overdose with INTELENCE. 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 INTELENCE 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 INTELENCE 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 INTELENCE 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 INTELENCE 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: INTELENCE vs. placebo, in addition to a background regimen 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 3: DUET-1 and DUET-2 pooled 48-week data** | | | |
|---|---|---|---|
| | INTELENCE + 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 INTELENCE 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 3.

Significantly fewer patients in the INTELENCE 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 4.

**Table 4: DUET-1 and DUET-2 pooled data**

| Subgroups | Proportion of subjects with HIV-1 RNA < 50 copies/ml at week 48 | |
|---|---|---|
| | INTELENCE + 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, (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.

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

| Baseline number of INTELENCE 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) |

* INTELENCE 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 INTELENCE. Furthermore, the presence of this mutation alone did not affect the response in the INTELENCE 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 INTELENCE.

*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 INTELENCE in a treatment regimen, which is not approved under the current indication. In the TMC125-C227 study, INTELENCE (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 INTELENCE arm (-1.4 $\log_{10}$ copies/ml from baseline; n = 40). This difference between treatment arms was statistically significant.

Based on these trial results, INTELENCE 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.

Pregnancy and postpartum
INTELENCE (200 mg b.i.d.), 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 treatment-experienced HIV-1 infected patients. Exposure to etravirine was lower (35-50%) in HIV-1 infected patients than in healthy subjects.

**Table 6: Population pharmacokinetic estimates of etravirine 200 mg b.i.d. in HIV-1-infected adult subjects (integrated data from Phase III trials at week 48)***

| Parameter | Etravirine 200 mg b.i.d. N = 575 |
|---|---|
| $AUC_{12h}$ (ng•h/ml) | |
| Geometric Mean ± Standard Deviation | 4522 ± 4710 |
| Median (Range) | 4380 (458 - 59084) |
| $C_{0h}$ (ng/ml) | |
| Geometric Mean ± Standard Deviation | 297 ± 391 |
| Median (Range) | 298 (2 - 4852) |

* All HIV-1-infected subjects enrolled in Phase III clinical trials received darunavir/ritonavir 600/100 mg b.i.d. 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 INTELENCE with darunavir/ritonavir.

Note: The median protein binding adjusted EC50 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 INTELENCE 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 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.

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

*Children and adolescents*

Treatment with INTELENCE in Israel is not approved in children and adolescents

*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 score 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 adviced 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 INTELENCE 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 b.i.d. 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 b.i.d.

as part of an antiretroviral regimen was generally higher during pregnancy compared with postpartum (see Table 9). The differences were less pronounced for unbound etravirine exposure. In women receiving etravirine 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.

**Table 9: Pharmacokinetic results of total etravirine after administration of etravirine 200 mg b.i.d. as part of an antiretroviral regimen, during the 2nd trimester of pregnancy, the 3rd trimester of pregnancy, and postpartum.**

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

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

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**INTELENCE™** 100 mg:
Hypromellose
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Colloidal anhydrous silica

**INTELENCE™** 200 mg:
Hypromellose
Silicified microcrystalline cellulose
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Colloidal anhydrous silica

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The expiary date of the product is indicated on the packaging materials.

### 6.4 Special precautions for storage

Do not store above 30ºC. Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.
After first opening-use up to 2 months.

### 6.5 Nature and contents of container

INTELENCE 100 mg
The bottle is a high-density polyethylene (HDPE) plastic bottle containing 120 tablets and 3 desiccant pouches, fitted with a polypropylene (PP) child resistant closure.
Each carton contains one bottle.

INTELENCE 200 mg
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 and other handling

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.

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.

**Manufacturer**: Janssen Cilag S.p.A., Via C. Janssen 04010, Borgo S. Michele Latina, Italy
**Registration holder**: J-C Health Care Ltd. Kibbutz Shefayim, 6099000