

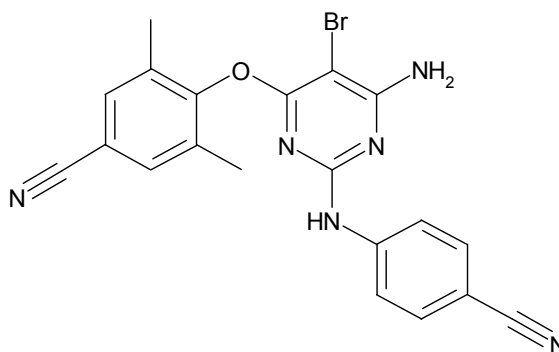
# INTELENCE<sup>®</sup>

## PRODUCT INFORMATION

### NAME OF THE MEDICINE

Etravirine

Etravirine has the following chemical structure:



C<sub>20</sub>H<sub>15</sub>BrN<sub>6</sub>O

MW 435.3

CAS Registry No: 269055-15-4

### DESCRIPTION

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

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

Each 100 mg tablet contains 100 mg of etravirine together with the inactive ingredients: microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, hypromellose, croscarmellose sodium and 160 mg of lactose monohydrate. Each 200 mg tablet contains 200 mg etravirine together with the inactive ingredients microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, hypromellose and croscarmellose sodium.

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

Etravirine is a white to slightly yellowish-brown powder that is practically insoluble in water over a wide pH range. It is very soluble in propylene glycol and slightly soluble in ethanol. Etravirine is soluble in polyethylene glycol (PEG) 400 and freely soluble in some organic solvents (e.g. N,N-dimethylformamide and tetrahydrofuran).

The chemical name for etravirine is 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)-amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile.

## PHARMACOLOGY

### Pharmacodynamics

#### Mechanism of action

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Etravirine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Etravirine can bind in at least two conformationally distinct modes. Within a given binding mode, torsional flexibility of etravirine permits access to numerous conformational variants, while the compact design of etravirine permits repositioning and reorientation (translation and rotation) within the pocket. Etravirine does not inhibit the human DNA polymerases  $\alpha$ ,  $\beta$  and  $\gamma$  *in vitro*.

#### Antiviral activity *in vitro*

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

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

The EC<sub>50</sub> value of etravirine for HIV-1 increases by a median factor of 5.8 in the presence of human serum.

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

#### Resistance *in vitro*

Etravirine-resistant strains were selected in cell culture from wild-type HIV-1 of different origins and subtypes, and from NNRTI resistant HIV-1. Reduced susceptibility to etravirine generally required multiple substitutions in the reverse transcriptase (RT), with the following observed most frequently: L100I, E138K, E138G, V179I, Y181C, and M230I.

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

### Cross-resistance *in vitro*

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

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

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

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

### Resistance *in vivo*

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

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

Number of INTELENCE RAMs	Patients Re-Using or Not Using Enfuvirtide	
	INTELENCE + BR %; (n/N)	Placebo + BR %; (n/N)
0	74.1% (117/158)	42.7% (61/143)
1	61.3% (73/119)	38.6% (59/153)
2	64.1% (41/64)	26.2% (16/61)
$\geq 3$	38.3% (23/60)	28.2% (11/39)

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

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

Baseline etravirine phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline etravirine phenotype are shown in Table 2. These baseline phenotype groups are based on the select subject populations in DUET-1 and DUET-2 and are not meant to represent definitive clinical susceptibility breakpoints for INTELENCE. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to etravirine in treatment-experienced patients.

<b>Table 2: Response to INTELENCE by Baseline Etravirine Phenotype: Non VF-excluded* population of the Pooled DUET studies - 'ENF re-using or ENF not using' patients</b>				
Baseline Etravirine Phenotype (fold change ranges)	Mean (SE) change in viral load from baseline at Week 48		Proportion of patients with <50 copies/mL at Week 48 % (n/N)	
	INTELENCE + BR N=400	Placebo + BR N=391	INTELENCE + BR N=400 %; (n/N)	Placebo + BR N=391 %; (n/N)
All ranges	-2.37 (1.31)	-1.38 (1.49)	63% 253/400	37% 145/391
0 – ≤3	-2.58 (1.16)	-1.47 (1.46)	70% 188/267	43% 112/262
>3 – ≤13	-2.20 (1.39)	-1.33 (1.57)	53% 39/74	29% 22/77
>13	-1.64 (1.51)	-1.04 (1.46)	44% 26/59	21% 11/52

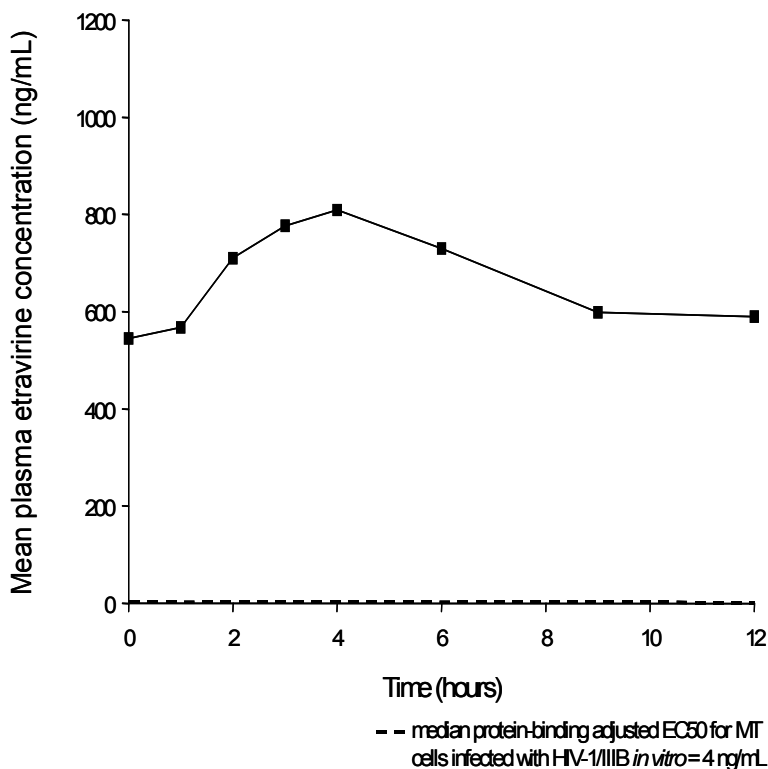
n = number of patients with observations; N = Total number of patients; VF = Virological Failure; ENF = enfuvirtide  
\* non-VF excluded = The population analyzed was all patients excluding those that discontinued for reasons other than virologic failure

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

## Pharmacokinetics

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

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



### Absorption

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

### *Effect of food on absorption*

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

### Distribution

Etravirine is approximately 99.9% bound to plasma proteins, primarily to albumin (99.6%) and  $\alpha$ 1-acid glycoprotein (94.5-97.7%) at physiological concentrations *in vitro*. The distribution of etravirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

### Metabolism

*In vitro* experiments with human liver microsomes (HLMs) and *E. coli* systems expressing recombinant human CYP enzymes indicate that etravirine primarily undergoes oxidative metabolism by the hepatic cytochrome CYP450 (CYP3A) system and, to a lesser extent, by the CYP2C family followed by glucuronidation.

### Elimination

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

### Special Populations

#### *Children and adolescents*

The pharmacokinetics of etravirine in paediatric patients are under investigation. There are insufficient data at this time to recommend a dose (see **DOSAGE AND ADMINISTRATION**).

#### *Elderly*

Population pharmacokinetic analysis in HIV-infected patients showed that etravirine pharmacokinetics are not considerably different in the age range (18 to 77 years) evaluated (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**).

#### *Gender*

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

#### *Race*

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

#### *Renal impairment*

The pharmacokinetics of etravirine have not been studied in patients with renal insufficiency. Results from a mass balance study with radioactive <sup>14</sup>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 **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

#### *Hepatic impairment*

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

#### *Hepatitis B and/or Hepatitis C Virus Co-infection*

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

## **CLINICAL TRIALS**

The evidence of efficacy of INTELENCE is based on the analyses of 48-week data from 2 ongoing, randomised, double-blinded, placebo-controlled, Phase III trials DUET-1 (TMC125-C206) and DUET-2 (TMC125-C216). The primary objective of the trials was to show the superiority of TMC125 compared to placebo as part of an antiretroviral therapy (ART) containing TMC114/RTV and an investigator-selected OBR, in the proportion of subjects with undetectable plasma viral load values (< 50copies/mL) at Week 24

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

These trials were identical in design, and similar efficacy for INTELENCE was seen in each trial. The results below are pooled data from the two trials.

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

At 48 weeks, the virologic response rate was evaluated in patients receiving INTELENCE (200 mg b.i.d.) in addition to a BR versus patients receiving placebo in addition to a BR. The BR consisted of darunavir/ritonavir 600/100 mg b.i.d. and at least 2 other investigator-selected antiretroviral drugs (N[t]RTIs with or without ENF). 45.6% of patients in the INTELENCE arm and 46.9% of patients in the placebo arm used ENF in the underlying antiretroviral therapy. 25.5% of patients in the INTELENCE arm used ENF for the first time (*de novo*), compared with 26.5% of patients in the placebo arm. 20.0% of patients in the INTELENCE arm re-used ENF, compared with 20.4% of patients in the placebo arm. Virologic response was defined as achieving a confirmed undetectable viral load (< 50 HIV-1 RNA copies/mL). In the pooled analysis for DUET-1 and DUET-2, demographics and baseline characteristics were balanced between the INTELENCE arm and the placebo arm. Table 3 describes the demographic and baseline disease characteristics of the patients in the INTELENCE arm and patients in the placebo arm.

<b>Table 3: Demographic and Baseline Disease Characteristics of Patients in the DUET-1 and DUET-2 Trials (Pooled Analysis)</b>		
	<b>DUET 1 and DUET 2 Trials</b>	
	<b>INTELENCE + BR N=599</b>	<b>Placebo + BR N=604</b>
<b>Demographic Characteristics</b>		
Median Age, years (range)	46 (18-77)	45 (18-72)
Sex		
Male	90.0%	88.6%
Female	10.0%	11.4%
Race		
White	70.1%	69.8%
Black	13.2%	13.0%
Hispanic	11.3%	12.2%
Asian	1.3%	0.6%
Other	4.1%	4.5%
<b>Baseline Disease Characteristics</b>		
Median Baseline Plasma HIV-1 RNA (range), log <sub>10</sub> copies/mL	4.8 (2.7-6.8)	4.8 (2.2-6.5)
Percentage of Patients with Baseline Viral Load:		
< 30,000 copies/mL	27.5%	28.8%
≥ 30,000 copies/mL and < 100,000 copies/mL	34.4%	35.3%
≥ 100,000 copies/mL	38.1%	35.9%
Median Baseline CD4+ Cell	99	109

Count (range), cells/mm <sup>3</sup>	(1-789)	(0-912)
Percentage of Patients with Baseline CD4+ Cell Count:		
< 50 cells/mm <sup>3</sup>	35.6%	34.7%
≥ 50 cells/mm <sup>3</sup>		
and < 200 cells/mm <sup>3</sup>	34.8%	34.5%
≥ 200 cells/mm <sup>3</sup>	29.6%	30.8%
Median (range) Number of Primary PI Mutations <sup>a</sup>	4 (0-7)	4 (0-7)
Percentage of Patients with Previous Use of NNRTIs:		
0	8.2%	7.9%
1	46.9%	46.7%
>1	44.9%	45.4%
Percentage of Patients with Previous Use of the following NNRTIs:		
Efavirenz	70.3%	72.5%
Nevirapine	57.1%	58.6%
Delavirdine	13.7%	12.7%
Median (range) Number of NNRTI RAMs <sup>b</sup>	2 (0-5)	2 (0-4)
Median Fold Change of the Virus for the Following NNRTIs:		
Delavirdine	27.4	26.4
Efavirenz	63.9	46.1
Etravirine	1.6	1.5
Nevirapine	74.3	74.3
Percentage of Patients with Previous Use of Enfuvirtide	39.6%	41.9%
RAMs = Resistance-Associated Mutations BR = Background Regimen FC = fold change in EC <sub>50</sub> <sup>a</sup> IAS-USA primary PI mutations [November 2005]: D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, V82A/F/L/S/T, I84V, N88S, L90M <sup>b</sup> Tibotec NNRTI RAMs [March 2007]: A98G, L100I, K101E/P/Q, K103H/N/S/T, V106A/M, V108I, E138G/K/Q, V179D/E/F/G/I, Y181C/I/V, Y188C/H/L, G190A/C/E/Q/S, H221Y, P225H, F227C/L, M230I/L, P236L, K238N/T, Y318F		

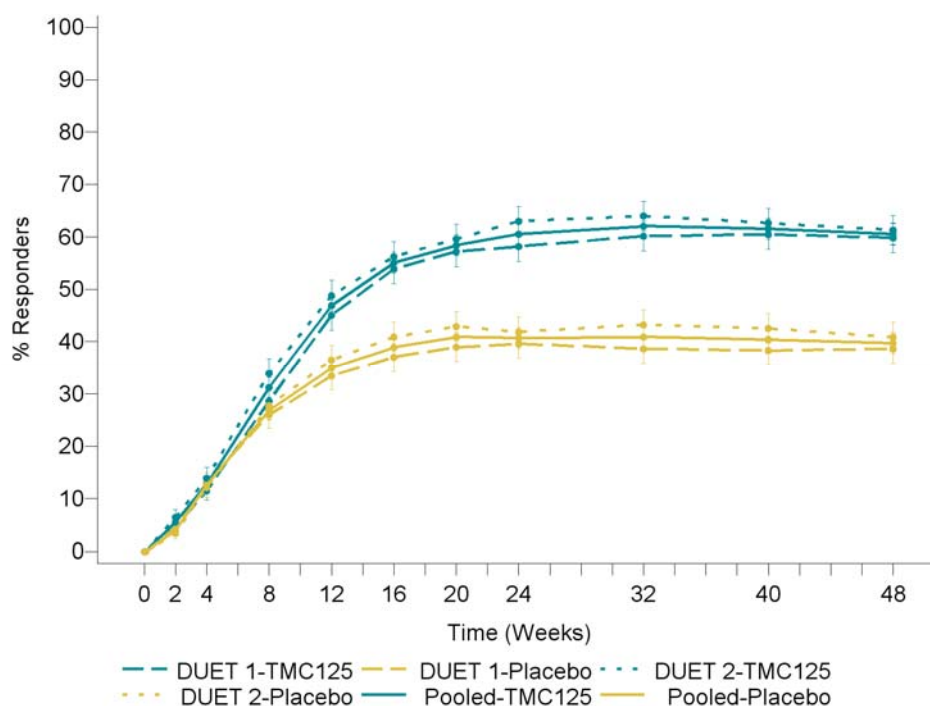
Efficacy results at 48 weeks for patients in the INTELENCE arm and patients in the placebo arm for the total study population (pooled DUET-1 and DUET-2) are shown in Table 4.

	DUET-1 and DUET-2 Trials		
	Total Study Population		
	INTELENCE + BR N=599	Placebo + BR N=604	Treatment difference (95% CI) <sup>c</sup>
<b>Virologic Responders</b> Confirmed Undetectable Viral Load (< 50 HIV-1 RNA copies/mL) at Week 48 <sup>a,d</sup>	60.6%	39.7%	20.9% (15.3%; 26.4%) <sup>d</sup>
<b>Virologic failures</b>	29.5%	49.7%	-20.1% (-25.5%; -14.7%)

≥ 50 HIV-1 RNA copies/mL and < 400 HIV-1 RNA copies/mL	5.8%	3.3%	2.5% (0.2%; 4.9%)
≥ 400 HIV-1 RNA copies/mL	6.3%	20.0%	-13.7% (-17.4%; -9.9%)
Rebound <sup>b</sup>	7.8%	9.3%	-1.4 (-4.6%; 1.7%)
Discontinued due to virologic failure before Week 48	9.5%	17.1%	-7.5% (-11.3%; -3.7%)
<b>Death</b>	1.8%	3.3%	-1.5% (-3.3%; 0.3%)
<b>Discontinuation due to adverse events</b>	5.2%	2.3%	2.9% (0.7%; 5.0%)
<b>Discontinuation due to other reasons</b>	2.8%	5.0%	-2.1% (-4.3%; 0.1%)

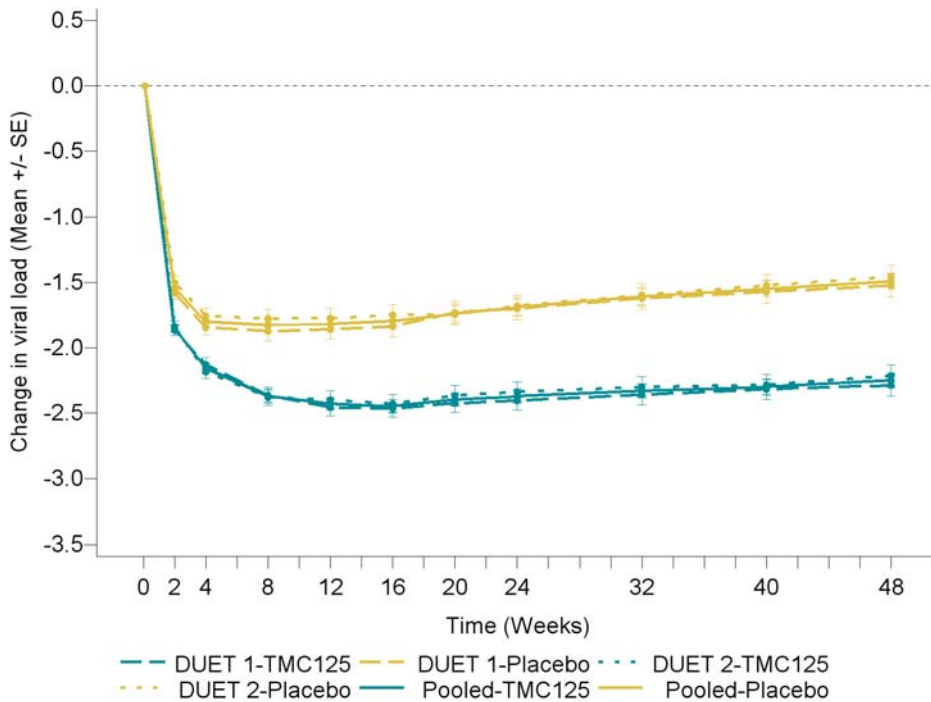
<sup>a</sup>Patients achieved virologic response (two consecutive viral loads < 50 copies/mL) and maintained it through week 48  
<sup>b</sup>Patients with an initial response (confirmed viral load < 50 copies/mL), but with at least two consecutive values > 50 copies/mL before Week 48  
<sup>c</sup>Confidence interval around observed difference of response rates  
<sup>d</sup>P-value < 0.001 from logistic regression model including stratification factors  
BR = Background Regimen

The proportion of patients with confirmed viral load < 50 copies/mL at all time points up to Week 48, in the overall population according to the (Time to Loss of Virologic Response) TLOVR imputation algorithm, is presented in Figure 2.



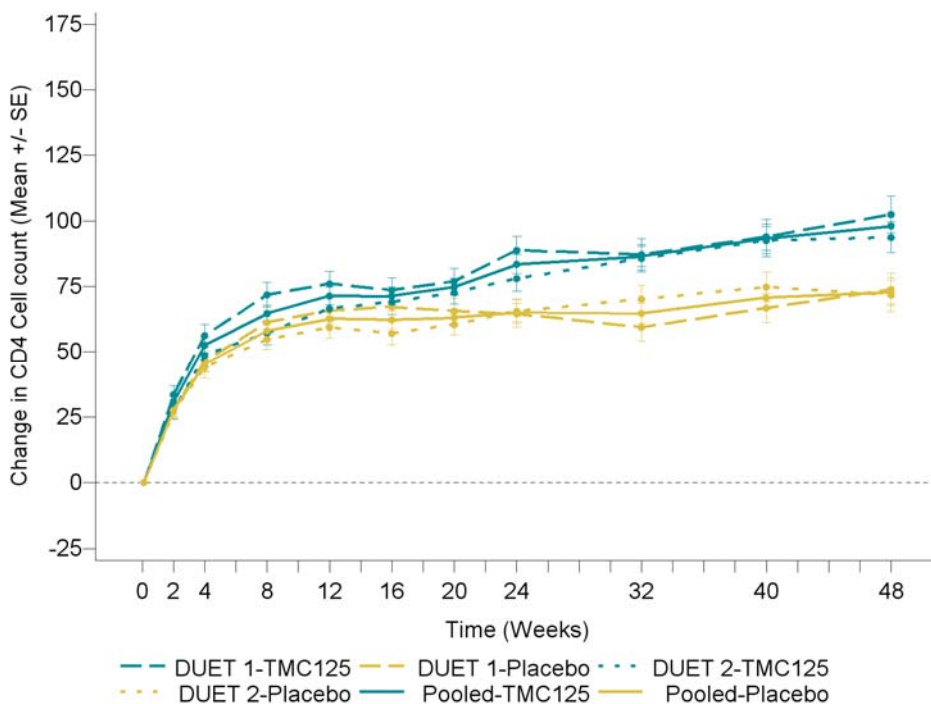
**Figure 2: Proportion of Virologic Responders (< 50 Copies/mL; TLOVR Imputed), Overall in the DUET-1 and DUET-2 Trials**

In the total study population, through 48 weeks of treatment, the proportion of patients with < 400 HIV-1 RNA copies/mL in the arm receiving INTELENCE was 71.5% compared with 47.4% in the placebo arm. At Week 48, the mean decrease in plasma HIV-1 RNA from baseline at Week 48 were  $-2.25 \log_{10}$  copies/mL in the arm receiving INTELENCE and  $-1.49 \log_{10}$  copies/mL for the placebo arm. The change from Baseline in  $\log_{10}$  viral load at all time points is also presented graphically in Figure 3. Similar results were seen across the 2 DUET studies.



**Figure 3: Change from Baseline in Log<sub>10</sub> Viral Load, Overall in the DUET-1 and DUET-2 Trials**

INTELENCE also showed an additional benefit over placebo in CD4+ cell count increase from baseline: 98.2 x 10<sup>6</sup> cells/L versus 72.9 x 10<sup>6</sup> cells/L, respectively. A graphical presentation of the mean change in CD4 cell count from Baseline is provided in Figure 4.



**Figure 4: Change from Baseline in CD4 Cell Count (x 10<sup>6</sup>/L) (Imputed [NC = F]) in the DUET-1 and DUET-2 Trials**

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

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

Since there was a significant interaction effect between treatment and ENF, the primary analysis was done for 2 ENF strata (patients re-using or not using ENF versus patients using ENF *de novo*). The week 48 results from the pooled analysis of DUET-1 and DUET-2 demonstrated that the INTELENCE arm was superior to the placebo arm irrespective of whether ENF was used *de novo* or not. In the population of patients who either re-used or did not use ENF; the proportion of patients with < 50 HIV-1 RNA copies/mL in this subgroup was 57.0% in the INTELENCE arm and 33.0% in the placebo arm (a difference (95%CI) of 24.0% (17.6%;30.3%) ). In the group of patients that used ENF *de novo*, 71.2% of patients in the INTELENCE arm reached < 50 HIV-1 RNA copies/mL compared to 58.5% of patients in the placebo arm (a difference (95%CI) of 12.7% (2.3%;23.2%) ).

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

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

In the population of patients using ENF *de novo*, through 48 weeks of treatment, the proportion of patients with a decrease in HIV-1 RNA versus baseline of > 1.0 log<sub>10</sub> in the arm receiving INTELENCE compared to placebo was 83.0% and 74.8%, respectively. In addition, the mean decrease in plasma HIV-1 RNA from baseline at Week 48 was -2.60 log<sub>10</sub> copies/mL in the arm receiving INTELENCE and -2.22 log<sub>10</sub> copies/mL for the placebo arm. The CD4+ cell count increase from baseline was 134.5 x 10<sup>6</sup> cells/L in the INTELENCE arm versus 111.4 x 10<sup>6</sup> cells/L in the placebo arm.

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

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

## INDICATIONS

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

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

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

## **CONTRAINDICATIONS**

Hypersensitivity to etravirine or to any of the excipients.

## **PRECAUTIONS**

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

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

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

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

### **Severe Skin Rash and Hypersensitivity Reactions**

Severe, potentially life-threatening, and fatal skin reactions have been reported with INTELENCE; Stevens-Johnson Syndrome and toxic epidermal necrolysis have been rarely (< 0.1%) reported. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and infrequently organ dysfunction, including hepatic failure.

Most frequently, rash was mild to moderate, occurred in the second week of therapy and was infrequent after week 4. Rash was mostly self-limiting and generally resolved within 1-2 weeks on continued therapy (see **ADVERSE EFFECTS**).

Discontinue INTELENCE immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping INTELENCE treatment after the onset of severe rash may result in life-threatening reaction.

### **Fat redistribution**

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

### **Immune reconstitution inflammatory syndrome**

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary (see **ADVERSE EFFECTS**).

### **Patients with co-existing conditions**

#### **Liver impairment**

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). The pharmacokinetics of INTELENCE have not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see **DOSAGE AND ADMINISTRATION** and **PHARMACOKINETICS**).

#### **Renal impairment**

Since the renal clearance of etravirine is negligible (< 1.2%), a decrease in total body clearance is not expected in patients with renal impairment. No special precautions or dose adjustments are required in patients with renal impairment. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see **DOSAGE AND ADMINISTRATION** and **PHARMACOKINETICS**).

#### **Effects on fertility**

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

#### **Use in Pregnancy**

##### **Category B1**

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

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

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

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

#### **Use in Lactation**

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

## Children

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

## Elderly

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

## Carcinogenicity

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

## Genotoxicity

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

## Interactions with Other Medicines

### **Medicinal products that affect etravirine exposure**

Etravirine is metabolised by cytochrome P450 (CYP) 3A4, CYP2C9 and CYP2C19 followed by glucuronidation of the metabolites by uridine diphosphate glucuronosyl transferase (UDPGT). Medicinal products that induce CYP3A4, CYP2C9, or CYP2C19 may increase the clearance of etravirine resulting in lowered plasma concentrations of etravirine. Co-administration of INTELENCE and medicinal products that inhibit CYP3A4, CYP2C9, or CYP2C19 may decrease the clearance of etravirine and may result in increased plasma concentrations of etravirine.

### **Medicinal products that are affected by the use of etravirine**

Etravirine is an inducer of CYP3A4. Co-administration of INTELENCE with medicinal products primarily metabolised by CYP3A4 may result in decreased plasma concentrations of such medicinal products, which could decrease or shorten their therapeutic effects. Etravirine is an inhibitor of CYP2C9 and CYP2C19. Etravirine is also a weak inhibitor of P-glycoprotein but not a substrate. Co-administration with medicinal products primarily metabolised by CYP2C9 or CYP2C19 or transported by P-glycoprotein may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect or adverse events profile.

Drugs that are not recommended for co-administration with INTELENCE are included in Table 5. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

<b>Table 5: Drugs That Should Not Be Co-administered With INTELENCE</b>	
<b>Concomitant Drug Class: Drug Name</b>	<b>Clinical Comment</b>
<b>HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>	
NNRTIs	It is not recommended to co-administer INTELENCE with other NNRTIs.
<b>HIV-Antiviral Agents: Protease Inhibitors (PIs) – Unboosted (i.e., without co-administration of low-dose ritonavir)</b>	
atazanavir, unboosted	Concomitant use of INTELENCE with unboosted atazanavir may cause a significant decrease in the plasma concentration of atazanavir. It is not recommended to co-administer unboosted atazanavir and INTELENCE.
Ritonavir, full dose	Concomitant use of INTELENCE with full-dose ritonavir (600 mg b.i.d.) may cause a significant decrease in the plasma concentration of etravirine. This may result in loss of therapeutic effect of INTELENCE. It is not recommended to co-administer full-dose ritonavir (600 mg b.i.d.) with INTELENCE.
Other Unboosted PIs	Other Unboosted PIs: It is not recommended to co-administer INTELENCE with other unboosted PIs (including indinavir and saquinavir).
<b>HIV-Antiviral Agents: Protease Inhibitors (PIs) – Boosted (with co-administration of low-dose ritonavir)</b>	
tipranavir/ritonavir	Concomitant use of INTELENCE with tipranavir/low-dose ritonavir may cause a significant decrease in the plasma concentration of etravirine. This may result in loss of therapeutic effect of INTELENCE. It is not recommended to co-administer tipranavir/low-dose ritonavir and INTELENCE.
<b>Other Agents</b>	
<b>Anticonvulsants:</b> carbamazepine, phenobarbital, phenytoin	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE should not be used in combination with carbamazepine, phenobarbital, or phenytoin as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE.
<b>Antimycobacterials:</b> rifampin, rifapentine	Rifampin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE should not be used in combination with rifampin or rifapentine as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE.
<b>Herbal Products:</b> St. John's wort ( <i>Hypericum perforatum</i> )	INTELENCE should not be used concomitantly with products containing St. John's wort because co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE.

Established and other potentially significant drug interactions with INTELENCE are included in Table 6. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

<b>Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction</b>		
<b>Concomitant Drug Class: Drug Name</b>	<b>Effect on Concentration of Etravirine or Concomitant Drug</b>	<b>Clinical Comment</b>
<b><i>HIV-Antiviral Agents: Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N[t]RTIs)</i></b>		
didanosine	↔ etravirine ↔ didanosine	The combination of INTELENCE and didanosine can be used without dose adjustments. As didanosine is administered on an empty stomach, didanosine should be administered one hour before or two hours after INTELENCE (which should be administered following a meal).
tenofovir disoproxil fumarate	↓ etravirine ↔ tenofovir	The combination of INTELENCE and tenofovir disoproxil fumarate can be used without dose adjustments.
Other NRTIs: Based on the primarily renal elimination route for other NRTIs (e.g., abacavir, emtricitabine, lamivudine, stavudine, and zidovudine), no drug interactions are expected between these drugs and INTELENCE.		
<b><i>HIV-Antiviral Agents: Protease Inhibitors (PIs) – Unboosted (i.e., without co-administration of low-dose ritonavir)</i></b>		
nelfinavir	↑ nelfinavir	Concomitant use of INTELENCE with nelfinavir may cause an increase in the plasma concentrations of nelfinavir.
Fosamprenavir, unboosted	↑ amprenavir	Concomitant use of INTELENCE with unboosted fosamprenavir may cause an increase in the plasma concentrations of amprenavir.
<b><i>HIV-Antiviral Agents: Protease Inhibitors (PIs) – Boosted (with co-administration of low-dose ritonavir)</i></b>		
atazanavir/ritonavir	↑ etravirine ↓ atazanavir	The combination of INTELENCE and atazanavir/ritonavir can be used without dose adjustments.
darunavir/ritonavir	↓ etravirine ↔ darunavir	The combination of INTELENCE and darunavir/ritonavir can be used without dose adjustments.
fosamprenavir/ritonavir	↔ etravirine ↑ amprenavir	In the presence of etravirine, an increase of 69% for amprenavir exposure was observed when fosamprenavir/ritonavir was co-administered. Amprenavir and fosamprenavir/ritonavir may require dose adjustment when co-administered with INTELENCE.
lopinavir/ritonavir (soft gel capsule)	↑ etravirine ↓ lopinavir	The combination of INTELENCE and lopinavir/ritonavir can be used without dose adjustments.
saquinavir/ritonavir	↓ etravirine ↔ saquinavir	The combination of INTELENCE and saquinavir/ritonavir can be used without dose adjustments.
<b><i>HIV-Antiviral Agents: Dual Boosted Protease Inhibitors</i></b>		
lopinavir/saquinavir/	↔ etravirine	The combination of INTELENCE and

ritonavir	↓ lopinavir ↓ saquinavir	lopinavir/saquinavir/ritonavir can be used without dose adjustments.
<b>HIV-Antiviral Agents: CCR5 Antagonists</b>		
Maraviroc	↓ maraviroc ↔ etravirine	INTELENCE acts as a CYP3A inducer and may cause significant decrease in the plasma concentration of maraviroc. A mean decrease of 46.8% (90% CI 38.1, 57.6) has been demonstrated in maraviroc AUC <sub>12</sub> in a pharmacokinetic study in which maraviroc 300 mg and INTELENCE 200 mg were co-administered twice daily (Refer also to prescribing information for maraviroc). No dose adjustment for INTELENCE is needed.
Maraviroc/darunavir/ritonavir	↑ maraviroc ↔ etravirine	INTELENCE acts as a CYP3A inducer and maraviroc plasma concentrations are decreased by 47% when combined with INTELENCE. Maraviroc dose should be increased to 600 mg twice daily when co-administered with INTELENCE in the absence of a boosted HIV protease inhibitor or other potent CYP3A inhibitor. No dose adjustment for INTELENCE is necessary.  The potent CYP3A inhibitor effect of the boosted protease inhibitor darunavir/ritonavir overrides the inducer effect of INTELENCE. Maraviroc plasma concentrations increased 310% when maraviroc 150 mg, INTELENCE 200 mg and darunavir/ritonavir 600/100 mg were co-administered twice daily. Maraviroc dose should be decreased to 150 mg twice daily when co-administered with INTELENCE in the presence of a boosted HIV protease inhibitor or other potent CYP3A inhibitor. No dose adjustment for INTELENCE is necessary.
<b>HIV-Antiviral Agents: Fusion Inhibitors</b>		
enfuvirtide	↔ etravirine ↔ enfuvirtide	No interaction is expected for either INTELENCE or enfuvirtide when co-administered.
<b>HIV-Antiviral Agents: Integrase Strand Transfer Inhibitors</b>		
raltegravir	↔ etravirine ↓ raltegravir	The combination of INTELENCE and raltegravir can be used without dose adjustments.
<b>Other Agents</b>		
<b>Antiarrhythmics:</b> Digoxin	↑ digoxin ↔ etravirine	The combination of INTELENCE and digoxin can be used without dose adjustments. It is recommended that digoxin levels be monitored when digoxin is combined with INTELENCE.

amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with INTELENCE.
<b>Anticoagulants:</b> warfarin		Warfarin concentrations may be affected when co-administered with INTELENCE. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with INTELENCE.
<b>Antifungals:</b> fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	↑ etravirine ↔ fluconazole ↓ itraconazole ↓ ketoconazole ↔ posaconazole ↑ voriconazole	Fluconazole and posaconazole are potent inhibitors of CYP3A4 and may increase plasma concentrations of INTELENCE. 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 INTELENCE. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE. Voriconazole is a CYP2C19 substrate and CYP3A4 and CYP2C inhibitor. Concomitant use of voriconazole and INTELENCE may increase plasma concentrations of both drugs.
<b>Antiinfectives:</b> azithromycin  clarithromycin	↔ etravirine ↔ azithromycin  ↑ etravirine ↓ clarithromycin ↑ 14-OH-clarithromycin	Based on the renal elimination pathway of azithromycin, no drug interactions are expected between azithromycin and INTELENCE.  Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against <i>Mycobacterium avium</i> complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.
<b>Antimycobacterials:</b> rifabutin	↓ etravirine ↓ rifabutin ↓ 25-O-desacetyl-rifabutin	The combination of INTELENCE and rifabutin can be used without dose adjustments.
<b>Antivirals:</b> ribavirin	↔ etravirine ↔ ribavirin	Based on the renal elimination pathway of ribavirin, no drug interactions are expected between ribavirin and INTELENCE.
<b>Benzodiazepines:</b> diazepam	↑ diazepam	Concomitant use of INTELENCE with diazepam may increase plasma concentrations of diazepam.

<b>Corticosteroids:</b> Dexamethasone (systemic)	↓ etravirine	Systemic dexamethasone induces CYP3A4 and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE. Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use.
<b>Estrogen-based Contraceptives:</b> ethinylestradiol norethindrone	↔ etravirine ↑ ethinylestradiol ↔ norethindrone	The combination of estrogen- and/or progesterone-based contraceptives and INTELENCE can be used without dose adjustment.
<b>HMG-CoA Reductase Inhibitors:</b> atorvastatin  fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	↔ etravirine ↓ atorvastatin ↑ 2-OH-atorvastatin  ↔ etravirine ↑ fluvastatin, ↓ lovastatin, ↔ pitavastatin, ↔ pravastatin, ↑ rosuvastatin, ↓ simvastatin	Atorvastatin plasma concentrations are decreased 37% and plasma concentrations of the active metabolite, 2-hydroxy-atorvastatin, are increased by 27% when combined with INTELENCE. Dose adjustment of atorvastatin may be necessary to tailor the clinical response when combined with INTELENCE.  No interaction between pravastatin and INTELENCE is expected.  Lovastatin, rosuvastatin, and simvastatin are CYP3A4 substrates and co-administration with INTELENCE may result in lower plasma concentrations of the HMG-CoA reductase inhibitor. Fluvastatin, rosuvastatin, and, to a lesser extent, pitavastatin are metabolized by CYP2C9 and co-administration with INTELENCE may result in higher plasma concentrations of the HMG-CoA reductase inhibitor. Dose adjustments for these HMG-CoA reductase inhibitors may be necessary.
<b>H<sub>2</sub>-Receptor Antagonists:</b> ranitidine	↓ etravirine	INTELENCE can be co-administered with H <sub>2</sub> -receptor antagonists without dose adjustments.
<b>Immunosuppressants:</b> cyclosporine, sirolimus, tacrolimus		Co-administration with systemic immunosuppressants should be done with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected when co-administered with INTELENCE.
<b>Narcotic Analgesics:</b> methadone	↔ etravirine ↔ R(-) methadone ↔ S(+) methadone	No changes in methadone dosage were required based on clinical status during or after the period of INTELENCE co-administration.
<b>Phosphodiesterase Type 5 (PDE-5) Inhibitors:</b> sildenafil, vardenafil, tadalafil	↓ sildenafil ↓ N-desmethyl-sildenafil	Sildenafil plasma concentrations are decreased by 57% and plasma concentrations of the active metabolite, N-desmethyl-sildenafil, are decreased by 41% when combined with INTELENCE. Concomitant use of PDE-5 inhibitors with INTELENCE may require dose

		adjustment of the PDE-5 inhibitor to attain the desired clinical effect.
<b>Platelet Aggregation Inhibitors:</b> <i>Clopidogrel</i>		<i>Activation of clopidogrel to its active metabolite may be decreased when clopidogrel is co administered with INTELENCE. Alternatives to clopidogrel should be considered.</i>
<b>Proton Pump Inhibitors:</b> omeprazole	↑ etravirine	INTELENCE can be co-administered with proton pump inhibitors without dose adjustments.
<b>Selective Serotonin Reuptake Inhibitors (SSRIs):</b> paroxetine	↔ etravirine ↔ paroxetine	INTELENCE can be co-administered with paroxetine without dose adjustments.
↑ = increases, ↓ = decreases, ↔ = no change		

## Effect on Ability to Drive or Operate Machinery

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

## ADVERSE EFFECTS

### Adverse Drug Reactions from Clinical Trials

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

The most frequently reported adverse drug reactions (ADRs) ( $\geq 5\%$ ) that were at least grade 2 in severity were rash (10.0% in the INTELENCE arm and 3.5% in the placebo arm), diarrhoea (7.0% in the INTELENCE arm and 11.3%), hypertriglyceridaemia (6.3% in the INTELENCE arm and 4.3% in the placebo arm) and nausea (5.2% in the INTELENCE arm and 4.8% in the placebo arm) (see table below).

The majority of the ADRs reported during treatment with INTELENCE were grade 1 to 2 in severity. Grade 3 or 4 ADRs were reported in 22.2% and 17.2% of the INTELENCE and placebo treated patients, respectively. The most commonly reported grade 3 or 4 ADRs were hypertriglyceridaemia (4.2% in the INTELENCE arm and 2.3% in the placebo arm) and hypercholesterolaemia (2.2% in the INTELENCE arm and 2.3% in the placebo arm), renal failure (2.0% in the INTELENCE arm and 1.2% in the placebo arm) and anaemia (1.7% in the INTELENCE arm and 1.3% in the placebo arm). For treatment emergent clinical laboratory abnormalities (grade 3 or 4) reported in greater than or equal to 2% of INTELENCE treated patients (see **Table 8: Treatment Emergent Laboratory Abnormalities**). All other grade 3 and/or 4 ADRs were reported in less than 1.5% of the INTELENCE treated patients. 5.2% of patients in the INTELENCE arm discontinued treatment due to ADRs compared to 2.6% of patients in the placebo arm. The most common ADRs leading to discontinuation was rash (2.2% in the INTELENCE arm versus 0% in the placebo arm).

Rash was most frequently mild to moderate, generally macular to maculopapular or erythematous, mostly occurred in the second week of therapy and was infrequent after week 4. Rash was mostly self-limiting and generally resolved within 1-2 weeks on continued therapy (see **PRECAUTIONS**). The incidence of rash was higher in women compared to men in the INTELENCE arm in the DUET trials. In the larger Phase IIb/III database (N = 1223), no gender difference was seen. There was no gender difference in severity or treatment discontinuation due to rash. In patients with a history of NNRTI-related rash, there was no apparent increased risk for the development of INTELENCE-related rash compared to patients without a history of NNRTI-related rash.

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

<b>Table 7: Treatment-Emergent Adverse Reactions of at least Moderate Intensity (Grades 2-4) in <math>\geq</math> 1% of Adult Patients in the INTELENCE Treatment Groups</b>		
<b>System Organ Class, Preferred Term, %</b>	<b>DUET-1 and DUET-2 Trials</b>	
	<b>INTELENCE + BR N=599</b>	<b>Placebo + BR N=604</b>
<b><i>Cardiac Disorders</i></b>		
Myocardial infarction	1.3%	0.3%
<b><i>Blood and Lymphatic System Disorders</i></b>		
Anaemia	4.0%	3.8%
Thrombocytopenia	1.3%	1.5%
<b><i>Gastrointestinal Disorders</i></b>		
Diarrhoea	7.0%	11.3%
Nausea	5.2%	4.8%
Abdominal pain	3.5%	3.1%
Vomiting	2.8%	2.8%
Gastroesophageal reflux disease	1.8%	1.0%
Flatulence	1.5%	1.0%
Gastritis	1.5%	1.0%
<b><i>General Disorders and Administration Site Conditions</i></b>		
Fatigue	3.5%	4.6%
<b><i>Metabolism and Nutrition Disorders</i></b>		
Hypertriglyceridemia	6.3%	4.3%
Hypercholesterolemia	4.3%	3.6%
Hyperlipidemia	2.5%	1.3%
Hyperglycaemia	1.5%	0.7%
Diabetes mellitus	1.3%	0.2%
<b><i>Nervous System Disorders</i></b>		
Peripheral neuropathy	3.8%	2.0%
Headache	3.0%	4.5%
<b><i>Psychiatric Disorders</i></b>		
Insomnia,	2.7%	2.8%
Anxiety	1.7%	2.6%
<b><i>Renal and Urinary Disorders</i></b>		
Renal failure	2.7%	2.0%
<b><i>Skin and Subcutaneous Tissue Disorders</i></b>		

Rash	10.0%	3.5%
Lipohypertrophy	1.0%	0.3%
Night sweats	1.0%	1.0%
<b>Vascular Disorders</b>		
Hypertension	3.2%	2.5%
N=total number of patients per treatment group BR = Background Regimen		

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

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

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

#### Laboratory Abnormalities in Treatment-Experienced Patients:

Treatment-emergent Grade 3 to Grade 4 laboratory abnormalities, considered ADRs, reported in  $\geq$  2% of adult patients treated with INTELENCE are presented in Table 8.

Laboratory Parameter Preferred Term, %	DAIDS Toxicity Range	Pooled DUET-1 and DUET-2 Trials	
		INTELENCE + BR N=599	Placebo + BR N=604
<b>GENERAL BIOCHEMISTRY</b>			
<b>Pancreatic Amylase</b>		<b>8.9%</b>	<b>9.4%</b>
Grade 3	> 2-5 x ULN	7.4%	8.4%

Grade 4	> 5 x ULN	1.5%	1.0%
<b>Creatinine</b>		<b>2.0</b>	<b>1.7</b>
Grade 3	> 1.9-3.4 x ULN	2.0	1.5
Grade 4	> 3.4 x ULN	0	0.2
<b>Lipase</b>		<b>3.4%</b>	<b>2.6%</b>
Grade 3	> 3-5 x ULN	2.0%	2.2%
Grade 4	> 5xULN	1.3%	0.5%
<b>GENERAL HAEMATOLOGY</b>			
<b>White blood cell count</b>		<b>2.0</b>	<b>4.3</b>
Grade 3	1,000-1,499/mm <sup>3</sup>	1.0	3.6
Grade 4	<1,000/mm <sup>3</sup>	1.0	0.7
<b>HAEMATOLOGY DIFFERENTIAL COUNTS</b>			
<b>Neutrophils</b>		<b>5.1%</b>	<b>7.5%</b>
Grade 3	500-749/mm <sup>3</sup>	3.5%	4.3%
Grade 4	< 500/mm <sup>3</sup>	1.5%	3.1%
<b>LIPIDS AND GLUCOSE</b>			
<b>Total cholesterol</b>		<b>8.1%</b>	<b>5.3%</b>
Grade 3	> 7.77 mmol/L	8.1%	5.3%
<b>Low density lipoprotein</b>		<b>7.2%</b>	<b>6.6%</b>
Grade 3	> 4.9 mmol/L	7.2%	6.6%
<b>Triglycerides</b>		<b>9.2%</b>	<b>5.8%</b>
Grade 3	8.49-13.56 mmol/L	5.7%	4.0%
Grade 4	> 13.56 mmol/L	3.5%	1.8%
<b>Elevated Glucose Levels</b>		<b>3.5%</b>	<b>2.3%</b>
Grade 3	13.89-27.75 mmol/L	3.5%	2.2%
Grade 4	> 27.75 mmol/L	0%	0.2%
<b>HEPATIC PARAMETERS</b>			
<b>Alanine amino transferase</b>		<b>3.7%</b>	<b>2.0%</b>
Grade 3	5.1-10 x ULN	2.7%	1.7%
Grade 4	> 10 x ULN	1.0%	0.3%
<b>Aspartate amino transferase</b>		<b>3.2%</b>	<b>2.0%</b>
Grade 3	5.1-10 x ULN	2.7%	1.7%
Grade 4	> 10 x ULN	0.5%	0.3%
ULN = Upper Limit of Normal BR = Background Regimen			

#### *Lipodystrophy*

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

#### *Immune Reconstitution Inflammatory Syndrome*

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reconstitution inflammatory syndrome) (see **PRECAUTIONS**).

### **Additional information on special population**

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

Among co-infected patients (n=139) in the pooled analysis for DUET-1 and DUET-2, grade 3 or 4 elevations in AST developed in 9.7% of the 72 patients in the INTELENCE arm and in 6.0% of the 67 patients in the placebo arm; and grade 3 or 4 elevations in ALT developed in 11.1% of patients in the INTELENCE arm and in 7.5% of patients in the placebo arm. Among co-infected patients, 1.4% of those treated with INTELENCE and 2.9% in the placebo arm discontinued because of liver or biliary system disorders. Standard clinical monitoring of patients with chronic hepatitis is considered adequate.

### **Postmarketing experiences**

The following events have been identified during the postmarketing use of INTELENCE. Because these events are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

#### *Immune system disorders*

Fatal cases of toxic epidermal necrolysis have been reported. Severe hypersensitivity reactions including cases of hepatic failure have been reported (see **PRECAUTIONS**).

#### *Musculoskeletal and connective tissue disorders*

rhabdomyolysis

## **DOSAGE AND ADMINISTRATION**

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

*Adults:* The recommended oral dose of INTELENCE is 200 mg (one 200 mg tablet or two 100 mg tablets) taken orally twice daily (b.i.d.), following a meal (see **PHARMACOKINETICS**). Patients should be instructed to swallow the tablet(s) as a whole with a liquid such as water. Patients who are unable to swallow the INTELENCE tablet(s) whole may disperse the tablet(s) in a glass of water. Once the tablet(s) are dispersed, patients should stir the dispersion well, and drink it immediately. The glass should be rinsed with water several times, and each rinse completely swallowed to ensure the entire dose is consumed.

*Hepatic impairment:* no dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). The pharmacokinetics of INTELENCE have not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see **PRECAUTIONS** and **PHARMACOKINETICS**).

*Renal impairment:* No dose adjustment is required in patients with renal impairment (see **PRECAUTIONS** and **PHARMACOKINETICS**).

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

*Elderly:* Limited information is available in this population (see **PRECAUTIONS** and **PHARMACOKINETICS**).

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

## OVERDOSAGE

There is no specific antidote for overdose with INTELENCE. Human experience of overdose with INTELENCE is limited. Treatment of overdose with INTELENCE consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since etravirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance. Contact the Poisons Information Centre (telephone 131126) for advice on management of overdose.

## PRESENTATION AND STORAGE CONDITIONS

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

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

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

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

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

## NAME AND ADDRESS OF SPONSOR

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## POISON SCHEDULE OF THE DRUG

Prescription Only Medicine

Date of TGA approval: 15 August 2011

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