Selected Properties of Etravirine

Other names	Intelence, TMC-125
Manufacturer	Janssen Inc.
Pharmacology/Mechanism of Action	A di-aryl-pyrimidine (DAPY) derivative NNRTI. The inherent molecular flexibility of TMC125 relative to other NNRTIs permits the compound to retain its binding affinity to the reverse transcriptase in spite of the binding site changes induced by the presence of common NNRTI resistance mutations.
Activity	Shows high intrinsic activity against both wild-type HIV-1 and against HIV strains harboring resistance inducing mutations. TMC125 exhibits potent *in vitro* anti-HIV activity with an EC50 against wild-type HIV-1 of 1.4 nM, and little or no loss of activity (<5-fold reduction in susceptibility) against HIV-1 variants having key NNRTI resistance mutations. In extensive testing of more than 1,000 clinical HIV-1 isolates, all exhibiting resistance to at least one currently marketed NNRTI, the EC50 of TMC125 was below 100nM for 95% of the isolates. In addition, it appears that the development of resistance by the virus may be inhibited by TMC125's unique pharmacologic properties.
Resistance - genotypic	• Preliminary analyses of data from the DUET trials have identified 13 mutations associated with decreased virological responses to etravirine • Mutations: V90I, L100I, V106I, Y181C/I/V, A98G, K101E/P, V179D/F, G190A/S At least 3 of these mutations had to be present in combination before the response to etravirine was diminished to levels on par with that of placebo
Resistance - phenotypic	
Cross-Resistance	
Oral Bioavailability	Unknown The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]
Effect of Food	**Give with food. Type of meal not important.** • Fasted State: AUC ↓ 51% compared to a standard breakfast. • Light Breakfast (Croissant): AUC ↓ 20% compared to a standard breakfast. Not clinically relevant • Enhanced Fiber Breakfast: AUC ↓ 25% compared to a standard breakfast. Not clinically relevant • High Fat Breakfast (70g): AUC ↑ 9% compared to a standard breakfast. Not clinically relevant (Scholler-Gyure et al. 2008)

Protein Binding	>99.8%
Vd	
Tmax	2.5 to 4 hours
serum T ½	41 +/- 20 hours
Drug Concentrations	Dose-proportional kinetics observed in healthy volunteer studies. The same daily dose of etravirine results in similar daily exposure whether given in a daily or BID regimen [Sholler-Gyure et al. 2007]. • **Etravirine 100mg BID with food** (n=23): Cmin 215 ± 86ng/ml; Cmax 471 ± 141 ng/ml, AUC12 3925 ± 1251 ng.h/ml • **Etravirine 200mg Daily with food** (n=24): Cmin 163 ± 76 ng/ml; Cmax 659 ± 177 ng/ml, AUC24 8054 ± 2748 ng.h/ml • **Etravirine 200mg BID with food** (n=39): Cmin 469 ± 149ng/ml; Cmax 959 ± 278 ng/ml, AUC12 8195 ± 2428 ng.h/ml • **Etravirine 400mg Daily with food** (n=37): Cmin 364 ± 133 ng/ml; Cmax 1393 ± 386 ng/ml, AUC24 17220 ± 5009 ng.h/ml Population PK data from DUET trials [Kakuda et al. 2008] • Mean AUC12H: 5506 ng.h/ml • Mean Cmax: 393ng/ml • Interpatient Variability: 60% • Intrapatient Variability: 40% • Similar ETR exposure for different races (Blacks, Caucasians, Asians) and between sexes (M/F) • Trend for higher ETR levels with increased age • Higher ETR levels with decreasing weight HBV/HCV coinfected patients had higher ETR exposures (see dosing in hepatic impairment). <u>Cervicovaginal fluid concentrations:</u> In 12 HIV-infected women on etravirine for a median of 142 days in combination with a median of 3 other ARVs and undetectable VL in blood plasma (BP) and cervicovaginal fluid (CVF), etravirine demonstrated good penetration into the genital tract. CVF and BP etravirine concentrations were 857 ng/mL (385-1682) and 592 ng/mL (391-839), determined 13.25 (9.5-14) and 12.4(9-14) hours respectively after the last drug intake. CVF/BP ratio of etravirine concentrations was approximately 1.19 (0.4-4.80). The median etravirine CVF exposure was approximately 350 fold higher than the EC_{50} for wild type HIV-1 (0.3-2.3ng/ml), possibly contributing to virological control in the compartment.[Clavel et al. 2011] <u>Seminal concentrations:</u> Semen (SP) and blood plasma (BP) concentrations of etravirine were assessed in 10 HIV-positive, treatment experienced males on therapy for a median of 52 weeks (12-124). Median (range)

	SP etravirine concentration was 62.9 ng/mL (31.2-166), and values were above the protein-free IC50 range (0.39-2.4 ng/mL) in all cases. Median (range) etravirine SP:BP ratio was 0.16 (0.07_0.26). SP VL was<40 copies/mL in all patients, whereas BP VL was detectable in one patient with poor adherence. Total etravirine concentrations in male genital secretion are modest, reaching only 16% of the BP concentration, but nevertheless, more than 10 times above the wild type IC50 range.[Tiraboschi et al. 2012] Bioequivalence has been demonstrated between the 200 mg etravirine non-coated tablet and two of the 100 mg etravirine non-coated tablets in healthy volunteers.[Kakuda et al. 2011] <u>CYP2C9 and 2C19 metabolizer status:</u> Based on a meta-analysis of phase I trials, CYP2C9 metabolizer status had no apparent effect on etravirine pharmacokinetics. In contrast, subjects with a CYP2C19 allele associated with decreased activity (i.e., *2, *3, *4, *5, *6, *8, *9) exhibited 21-41% higher etravirine pharmacokinetics. In Phase III trials, there was no observed association between PK and safety suggesting this increase is not clinically relevant.[Kakuda et al. 2013]
Minimum target trough concentrations (for wildtype virus)	
CSF (% of serum)	2010 CNS Penetration Effectiveness (CPE) Score: 2 [Letendre S et al. 2010]
Metabolism	Etravirine is a substrate of CYP3A4, CYP2C9, and CYP2C19. Etravirine is a weak inducer of CYP3A4, weak inhibitor of CYP2C9 and a moderate inhibitor of CYP2C19. Etravirine also inhibits p-glycoprotein. Etravirine has no clinically relevant effect on CYP1A2 or CYP2D6.[Scholler-Gyure, 2008]
Excretion	
Dosing – Adult	200 mg po BID following a meal. Patients who are unable to swallow etravirine tablets whole may disperse the tablets in a glass of water. Once 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. If one is switching to etravirine from efavirenz therapy, the switch may be made without adjustment to etravirine dosage.[Boffito M et al. 2009].

<table>
<tr><td>Dosing – Pediatric</td><td>Children 6 to less than 18 years old and weighing at least 16 kg:
<table><tr><th>Weight (kg)</th><th>Dose</th></tr><tr><td>16 to <20 kg</td><td>100 mg BID</td></tr><tr><td>20 to <25 kg</td><td>125 mg BID</td></tr><tr><td>25 to <30 kg</td><td>150 mg BID</td></tr><tr><td>≥30 kg</td><td>200 mg BID</td></tr></table>A population pharmacokinetic model indicates that etravirine 5.2mg/kg BID in children and adolescents (6-17 years) provides comparable exposure to adults receiving 200mg BID.[Kakuda et al. 2011].</td></tr>
<tr><td>Special instructions for pediatric patients</td><td>Patients should be instructed to swallow etravirine tablets whole with a liquid such as water. Patients who are unable to swallow the tablets whole may disperse the tablets 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 medication,
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 grapefruit juice or warm (greater than 40°C) or carbonated beverages should be avoided.</td></tr>
</table>

Adjust in Liver Dysfunction	No dose adjustment is required in patients with mild or moderate hepatic impairment. The pharmacokinetics of etravirine have not been studied in patients with severe hepatic impairment. The pharmacokinetics of etravirine 200mg BID were assessed in 16 HIV negative subjects with mild to moderate hepatic impairment, and compared to 16 healthy matched controls. No significant effect on etravirine kinetics was observed in patients with mild hepatic impairment (Child Pugh A). Patients with moderate hepatic impairment (Child Pugh B) had similar Cmin and AUC12h levels but significantly lower Cmax levels VS healthy controls (Day 1: 0.63; 95% CI 0.47-0.85. Day 8: 0.72; 95% CI 0.54-0.96). The authors suggest etravirine dose adjustment is not required in mild – moderate hepatic impairment [Sholler-Gyure et al. 2007]. In a case report where a woman with severe hepatic dysfunction (decompensated liver cirrhosis) received standard doses of tenofovir, etravirine and darunavir/ritonavir, etravirine levels were measured after 8 months of therapy (VL< 50 copies/mL). The etravirine level was 3257 ng/mL (as compared to population PK Cmin from the DUET studies of approximately 300 ng/mL). Etravirine was discontinued, and levels measured 2 and 5 weeks later were 931 ng/mL and 100 ng/mL, respectively. An estimated half-life was calculated to be 237 hours. The patient did not experience any adverse event.[Aboud et al. 2009] HBV/HCV coinfection associated with 1.35 ↑ AUC12h (population PK data from Duet trials) [Kakuda et al. 2008].
Adjust in Renal Failure/Dialysis	No dose adjustment is required in patients with renal impairment. Antiretroviral pharmacokinetics were studied in a 49-year old HIV-positive man virologically suppressed on darunavir/ritonavir 600/100 mg twice daily, etravirine 200 mg twice daily and raltegravir 400 mg twice daily while undergoing hemodialysis three times weekly. The morning dose of the antiretrovirals was taken after completion of the 4-hour morning hemodialysis session. After dialysis, darunavir, etravirine, raltegravir and ritonavir concentrations were decreased by 57%, 29%, 82% and 60%, respectively compared to predialysis levels. A supplemental dose of 600 mg darunavir administered prior to the hemodialysis session was successful in restoring darunavir concentrations approximately equal to expected levels, while administration of a supplemental dose of raltegravir 400 mg was not, likely due to wide intra- and inter-patient variability. Dose supplementation of etravirine was not deemed necessary given the relatively low amount removed during hemodialysis. After 1 year of therapy, the patient maintained viral suppression.[Giguere et al. 2009]
Toxicity	The most frequently reported adverse effects include rash and nausea. In general, in clinical trials, rash was mild to moderate, occurred primarily in the second week of therapy and was infrequent after

	Week 4. Rash generally resolved within 1-2 weeks on continued therapy. The incidence of rash was higher in women compared to men in etravirine arm. Patients with a history of NNRTI-related rash did not appear to be at increased risk for the development of etravirine-related rash compared to patients without a history of NNRTI-related rash. A total of 2% of HIV-1-infected subjects receiving etravirine discontinued from Phase 3 trials due to rash. Rash occurred most commonly during the first 6 weeks of therapy. Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. In Phase 3 clinical trials, Grade 3 and 4 rashes were reported in 1.3% of subjects receiving etravirine compared to 0.2% of placebo subjects. Discontinue etravirine 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, facial edema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction.

Pregnancy & Lactation	*Pregnancy Category B*—Use during pregnancy only if the potential benefit justifies the potential risk. Antiviral Pregnancy Registry available. Register patients by calling 1-800-258-4263. Case series of etravirine use in 5 pregnant women; PK assessments in 3rd trimester showed etravirine concentrations comparable to those seen in non-pregnant adults. Therefore, no dosage adjustment required in pregnancy.[Izureita et al. 2009] Nursing Mothers: Mothers should not breastfeed due to the potential for HIV transmission.
Drug Interactions	Etravirine is metabolized by CYP3A4 & CYP2C. Etravirine induces CYP3A4 and inhibits CYP2C, 2C19 and p-glycoprotein. Effect of etravirine on the kinetics of other agents: • etravirine may ↓ plasma levels of drugs metabolized by CYP 3A4 • etravirine may ↑ plasma levels of drugs metabolized by CYP 2C, 2C19, and p-glycoprotein. Effect of other agents on the kinetics of etravirine: • Drugs that inhibit CYP 3A4 or CYP2C may ↑ etravirine plasma levels • Drugs that induce CYP 3A4 or CYP2C may ↓ etravirine plasma levels. Etravirine should not be co-administered with the following antiretrovirals: • Tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir • Protease inhibitors administered without ritonavir • NNRTIs Co-administration of etravirine with drugs that inhibit or induce CYP3A4, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse reaction profile of etravirine. Co-administration of etravirine with drugs that are substrates of CYP3A4, CYP2C9, CYP2C19 and/or p-glycoprotein may alter the therapeutic effect or adverse reaction profile of the co-administered drugs. Also refer to “Drug interactions with Non-Nucleoside Reverse Transcriptase Inhibitors” table.
Baseline Assessment	
Routine Labs	

Dosage Forms	100 mg oral tablets (F060 formulation), DIN 02306778. 200 mg oral tablets, DIN 02375931. 25 mg tablet for pediatric use (F066 formulation) – available in U.S.. Previous formulations: TF002 50 mg capsule (earliest clinical trials) TF035 200 mg tablet (phase IIb; dosed 800 mg BID)
Storage	Store at room temperature (15-30 C) in original bottle with dessicant. Tablets are hygroscopic and may soften or become harder to swallow if exposed to moisture (personal communications, Tibotec Canada Medical Information, July 2010).

References:

Aboud M, Castelino S, Back D, Kulasegara R. Etravirine plasma levels in a patient with decompensated liver disease. AIDS 2009;23(10):1293-5.

Boffito M, Jackson A, Lamorde M, Back DJ, Watson V, Taylor J, et al. Pharmacokinetics and safety of etravirine administered once or twice daily after 2 weeks treatment with efavirenz in healthy volunteers J Acquir Immune Defic Syndr 2009;52:222-7.

Clavel C, Peytavin G, Tubiana R, et al. Etravirine penetration in cervicovaginal compartment exceed the median inhibitory concentration in HIV-1 infected women treated with etravirine-containing regimen (DIVA-02 study) [abstract MOPE177]. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, Italy, July 17-20, 2011.

Giguere P, la Porte C, Zhang G, Cameron B. Pharmacokinetics of darunavir, etravirine and raltegravir in an HIV-infected patient on haemodialysis. AIDS 2009;23:740-2.

Izurieta P et al. Safety and pharmacokinetics of etravirine in pregnant HIV-infected women [abstract PE 4.1/6]. 12th European AIDS Conference, Cologne, November 11-14, 2009.

Janssen Inc., Intelence Product Monograph. Toronto, ON. November 16, 2012.

Kakuda TN, Van Solingen-Ristea RM, Onkelinx J, et al. The effect of single- and multiple-dose etravirine on a drug cocktail of representative cytochrome P450 probes and digoxin in healthy subjects. J Clin Pharmacol 2014 Apr;54(4):422-31.

Kakuda T et al. Pharmacokinetics of etravirine according to CYP2C9 and CYP2C19 metabolizer status: a meta-analysis of Phase I Trials [abstract 515]. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, March 3-6, 2013.

Kakuda T et al. Population pharmacokinetics of etravirine in HIV-1-infected treatment-experienced children and adolescents (6-17 years): week 24 primary analysis of the phase II PIANO trial [abstract TULBPE026]. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, Italy, July 17-20, 2011.

Kakuda T et al. Bioavailability of etravirine 200mg administered as a single 200-mg tablet versus two 100-mg tablets in HIV-negative, healthy volunteers [abstract MOPE175]. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, Italy, July 17-20, 2011.

Kakuda T et al. Pharmacokinetics of etravirine are not affected by sex, age, race, use of enfuvirtide or treatment duration in HIV-1 infected patients. 9th Int Workshop on Clin Pharmacol HIV Ther, New Orleans, LA, April 7-9, 2008.

Lazzarin A. Campbell T. Clotet B. Johnson M et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet. 370(9581):39-48, 2007 Jul 7.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Madruga JV. Cahn P. Grinsztejn B et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet. 370(9581):29-38, 2007 Jul 7

Sandkovsky U, Swindells S, Moore R, Acosta EP, Fletcher CV. Acceptable plasma concentrations of raltegravir and etravirine when administered by gastrostomy tube in a patient with advanced multidrug-resistant human immunodeficiency virus infection. Pharmacotherapy 2012: 32(2):142–147.

Scholler-Gyure M, Boffito M, Pozniak A et al. Effects of Different Meal Compositions and Fasted State on the Oral Bioavailability of Etravirine. Pharmacotherapy 2008;28(10):1215–1222.

Scholler-Gyure M, Kakuda TN, De Smedt G, Woodfall B, Lachaert R, Beets G et al. Pharmacokinetics of TMC125 in QD and BID regimens in HIV-1 negative volunteers [abstract A-1427]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2007 Chicago, IL.

Scholler-Gyure M, Kakuda TN, De Smedt G, Woodfall B, Berckmans C, Peeters M, et al. Pharmacokinetics of TMC125 in HIV-1 negative volunteers with mild and moderate hepatic impairment [abstract A-1428]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2007 Chicago, IL.

Tiraboschi J, Niubo J, Ferrer E, Barrera-Castillo G, Rozas N, Maso-Serra M, et al. Etravirine concentrations in seminal plasma in HIV-infected patients [abstract P75]. 11th Congress on Drug Therapy in HIV Infection, Glasgow, November 11-15, 2012.

