

# Etravirine (TMC125)

**Brand Name: Intelence**

**Drug Class: Non-nucleoside Reverse Transcriptase Inhibitors**

## Drug Description

Etravirine, also known as Intelence or TMC125, is a diarylpyrimidine (DAPY) derivative with potent *in vitro* activity against HIV. [1]

*In vitro*, etravirine has equipotent activity against wild-type HIV and NNRTI-resistant variants that encode L100I, K103N, Y181C, Y188L, and G190A/S mutations. [2]

## HIV/AIDS-Related Uses

Etravirine, also known as Intelence or TMC125, was approved by the FDA on January 18, 2008 for use in combination with at least two other antiretroviral agents for the treatment of adults with HIV-1 infection. This medication does not cure HIV infection or AIDS and does not reduce the risk of passing the virus to other people.[3]

## Pharmacology

TMC125 was designed by Belgian scientists to reduce drug resistance, partly by making a flexible molecule that can fit in the active pocket of HIV's reverse transcriptase in different ways, even when the shape of that pocket changes because of viral mutations that would defeat other drugs.[4] TMC125 is a highly flexible compound with low *in vitro* toxicity.[5] TMC125 has garnered attention because of its activity against NNRTI-resistant HIV strains.[6]

A substantial improvement in the relative oral bioavailability of TMC125 was achieved with new tablet formulation, compared with tablet formulations used in initial studies. In the TMC125-C170 trial, all 45 HIV uninfected participants received 1 reference dose of 400 mg TMC125. After a 2-week washout period, participants received 1 of 4 test formulations of TMC125. Pharmacokinetics of TMC125 were assessed for 96 hours postdose. Results indicated marked increases in the area under the concentration-time curve (AUC) and the maximum serum concentration (C<sub>max</sub>) for all test formulations compared with the reference dose. The time to maximum concentration (T<sub>max</sub>) and

the elimination half-life were similar for all treatments. Less intersubject variability was observed for the test formulations compared with the reference dose. Treatment with TMC125 was generally safe and well tolerated. The new tablet formulation also reduces pill burden.[7]

Several studies of TMC125 in HIV infected people have been promising. In the TMC125-C207 study conducted in London, England, TMC125's effectiveness in HIV infected men with documented efavirenz resistance taking an NNRTI-containing regimen was evaluated. In this open-label, Phase IIa study of 16 HIV infected men with 10- to 500-fold resistance to efavirenz, treatment with TMC125 for 7 days resulted in a median decrease in viral load of slightly less than 10-fold. Seven patients (44%) had a viral load decrease greater than 10-fold. There was no relationship between response to the drug and patient genotype or phenotype.[8] [9]

In the TMC125-C208 trial conducted in the Russian Federation in 2001, a 7-day monotherapy course of TMC125 at a dosage of 900 mg twice daily was given to 12 HIV infected, antiretroviral therapy (ART)-naive patients. The treatment duration was limited to 7 days to prevent the selection of NNRTI-resistant mutants, because a rapid emergence of resistance has been observed for first-generation NNRTIs when given as monotherapy. TMC125-C208's results were compared to the Dutch ERA study that took place between 1997 and 2000, which evaluated the effect of a 5-drug, triple-class ART regimen in ART-naive individuals with either primary or chronic HIV-1 infection. Analysis indicated that 1 week of TMC125 monotherapy resulted in a similar decline in viral load compared with 1 week of therapy with a 5-drug regimen. The apparent ability of TMC125 to substantially reduce HIV viral load in only 7 days of monotherapy suggests that starting treatment with a TMC125-containing regimen could provide better long-term suppression of HIV replication.[10]

In the TMC125-C223 trial, 199 HIV infected patients with NNRTI- and PI-resistant HIV were randomly assigned to receive an

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## Pharmacology (cont.)

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investigator-selected background therapy of TMC125 at either 400 mg or 800 mg twice daily or a standard-of-care regimen. At Week 24, viral load was reduced by more than 90% in the 2 TMC125 treatment arms compared with less than 50% in the control arm. These reductions in each treatment arm were statistically significant when compared individually with the control arm.[11] [12] Week 48 analysis indicated mean HIV viral load log<sub>10</sub> reductions of -0.88, 1.01, and -0.14 for the 400-mg, 800-mg, and standard-of-care groups, respectively. At Week 48, TMC125 showed high rates of sustained efficacy in these heavily pretreated patients. Analysis of response compared with baseline resistance suggests that TMC125 retains activity in the presence of multiple NNRTI mutations, a situation in which current NNRTIs are not expected to be effective.[13]

Highly treatment-experienced HIV infected patients with drug-resistant HIV may benefit from using TMC125 together with darunavir, a protease inhibitor (PI) approved by the FDA in 2006. Five men started taking twice-daily darunavir 600 mg with ritonavir 100 mg, and twice-daily 20-mg TMC125, with a combination of nucleoside reverse transcriptase inhibitors and/or enfuvirtide. Viral load, CD4 count, and safety parameters were followed from baseline to Week 24; genotypic resistance was assessed at baseline and on the most recent blood sample with detectable viral load. About a month after initiating study treatment, TMC125 coadministered with ritonavir-boosted darunavir were well tolerated. Interim results at Week 4 for the first four study participants indicate that viral load decreased and CD4 count increased, with no PI-associated mutations observed by Week 4.[14]

DUET-1 and DUET-2 are two randomized, double-blind, Phase III trials that evaluated the safety and efficacy of etravirine compared with placebo. Both treatment and control arms were administered in combination with background antiretroviral therapy that contains ritonavir-boosted darunavir, nucleoside reverse transcriptase inhibitors, and optional enfuvirtide. All enrolled patients have documented, treatment-resistant HIV. At Week 24 analysis of

591 patients enrolled in DUET-2, TMC125 was statistically superior to the control arm; 75% of patients receiving TMC125 had a viral load less than 400 copies/ml compared with 54% of patients in the control arm.[15] Of the 612 patients enrolled in DUET-1, Week 24 analysis was similar, with a more than 100-fold reduction in viral load seen in the TMC125 arm compared with a 50-fold reduction in the control arm.[16]

In the ongoing Phase III trials of TMC125 combined with ritonavir-boosted darunavir, 13 NNRTI-associated mutations that decreased viral response to TMC125 were observed during interim analyses. V179F, Y181V, Y106I, and V179O appeared in the patients who were considered the worst responders to treatment. The V179F and Y181C mutations always appeared together; this combination has been observed in approved NNRTIs, such as efavirenz and nevirapine, as well. Virologic response, measured by the 50% effective concentration (EC<sub>50</sub>), decreased proportionally with the increasing number of mutations. Complete resistance appears rare, but intermediate resistance to TMC125 may be likely. Only 15% of trial participants displayed 3 or more resistance-associated mutations; these participants displayed the largest decrease in virologic response.[17] [18]

## Adverse Events/Toxicity

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In the TMC125-C206 and TMC125-C216 trials, HCV/HIV and HBV/HIV coinfecting patients experienced worsening of hepatitis-related symptoms when treated with etravirine as compared with non-coinfecting patients treated with etravirine.[19]

Nausea and rash are the most frequently reported adverse events of etravirine.[20]

In the TMC125-C223 trial, approximately 15% of patients receiving etravirine developed rash, and several of these individuals had to discontinue therapy.[21]

Other less common adverse events of etravirine include abdominal pain, fatigue, peripheral neuropathy, headache and hypertension.

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## Adverse Events/Toxicity (cont.)

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Severe rash, including rare cases of Stevens-Johnson syndrome, have been reported in patients receiving etravirine. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, and muscle or joint aches should discontinue etravirine and consult a physician.[22]

## Drug and Food Interactions

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Dose adjustment of etravirine and/or other drugs may be necessary in patients receiving concomitant therapy with drugs that are extensively metabolized by or induce or inhibit CYP3A, CYP2C9 and CYP2C19. Etravirine may inhibit the metabolism of and is predicted to result in clinically important plasma concentration increases of certain anticoagulants (warfarin); antifungals (fluconazole); and benzodiazepines (diazepam).[23]

Because etravirine is an inducer of CYP3A4, coadministration of CYP3A4 substrates with etravirine may result in altered plasma concentrations of the coadministered substrate drug. Etravirine interacts with numerous boosted and unboosted PIs, which results in altered concentrations of etravirine and of the PI. Increased concentrations of amprenavir and nelfinavir, but decreased concentrations of atazanavir and indinavir, have been observed when these PIs were coadministered with etravirine. Concentrations of etravirine may decrease with concomitant administration of ritonavir alone, boosted tipranavir, and boosted darunavir; etravirine concentrations may increase with concomitant boosted atazanavir or lopinavir/ritonavir. Therefore, etravirine should not be administered with any unboosted PI or with the following boosted PIs: tipranavir, fosamprenavir, or atazanavir. Etravirine may be administered at normal dosages with boosted darunavir and saquinavir and may be administered with caution with lopinavir/ritonavir.[24]

Combining etravirine with another NNRTI has not been shown to be beneficial and use of etravirine with efavirenz or nevirapine may cause a significant decrease in the plasma concentration of

etravirine. Combining etravirine with delavirdine may cause a significant increase in the plasma concentration of etravirine. Therefore, etravirine and other NNRTIs should not be coadministered.[25]

## Clinical Trials

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For information on clinical trials that involve Etravirine (TMC125), visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Etravirine (TMC125) AND HIV Infections.

## Dosing Information

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Mode of Delivery: Oral.[26]

Dosage Form: Tablets containing etravirine 100 mg.[27]

## Chemistry

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CAS Name: Benzonitrile, 4-((6-amino-5-bromo-2-((4-cyanophenyl)amino)-4-pyrimidinyl)oxy)-3,5-dimethyl-[28]

CAS Number: 269055-15-4[29]

Molecular formula: C<sub>20</sub>H<sub>15</sub>BrN<sub>6</sub>O[30]

C55.18%, H3.48%, Br18.35%, N19.31%, O3.68%[31]

Molecular weight: 435.31[32]

Physical Description: Odorless white to off-white powder.[33]

## Other Names

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TMC 125[34]

TMC-125[35]

TMC125[36]

ETR[37]

ETV[38]

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## **Further Reading**

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## **Manufacturer Information**

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## **For More Information**

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Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: [http://aidsinfo.nih.gov/live\\_help](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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