



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Etravirine (ETR, Intelence, TMC 125) (Last updated March 1, 2016; last reviewed March 1, 2016)

For additional information see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Tablets: 25 mg, 100 mg, and 200 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

- Not approved for use in children aged <6 years. Studies in infants and children aged 2 months to 6 years are under way.

Antiretroviral-Experienced Children and Adolescents Aged 6–18 Years (and Weighing ≥16 kg)

Body Weight Kilogram (kg)	Dose
16 kg to <20 kg	100 mg twice daily
20 kg to <25 kg	125 mg twice daily
25 kg to <30 kg	150 mg twice daily
≥30 kg	200 mg twice daily

Adult Dose (Antiretroviral-Experienced Patients):

- 200 mg twice daily following a meal

Selected Adverse Events

- Nausea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.
- Diarrhea

Special Instructions

- Always administer etravirine following a meal. Area under the curve of etravirine is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to etravirine.
- Etravirine tablets are sensitive to moisture; store at room temperature in original container with desiccant.
- Patients unable to swallow etravirine tablets may disperse the tablets in liquid, as follows: Place the tablet(s) in 5 mL (1 teaspoon) of water, or enough liquid to cover the medication, and stir well until the water looks milky. If desired, add more water or alternatively orange juice or milk. **Note:** Patients should not place the tablets in orange juice or milk without first adding water. The use of grapefruit juice, warm (>40°C) drinks, or carbonated beverages should be avoided. Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the entire dose is consumed.
- Dosing of etravirine in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

- Dosing of etravirine in patients with renal impairment: Dose adjustment is not required in patients with renal impairment.

Metabolism/Elimination

- Etravirine is an inducer of cytochrome P450 3A4 (CYP3A4) and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate for CYP3A4, 2C9, and 2C19.
- Multiple interactions with antiretroviral agents and other drugs (see text below)

Drug Interactions (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#) and <http://www.hiv-druginteractions.org/>)

- Etravirine is associated with multiple drug interactions. Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions with etravirine.
- Etravirine should not be co-administered with the following antiretroviral (ARV) drugs: tipranavir/ritonavir, fosamprenavir/ritonavir, and unboosted protease inhibitors (PIs). It should not be administered with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine, efavirenz, or rilpivirine). Limited data in adults suggest that etravirine may reduce the trough concentration of raltegravir,¹ but no dose adjustment is currently recommended when etravirine and raltegravir are used together. Etravirine significantly reduces plasma concentrations of dolutegravir; dolutegravir should only be used with etravirine when co-administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.

Major Toxicities

- *More common*: Nausea, diarrhea, and mild rash. Rash occurs most commonly in the first 6 weeks of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with etravirine. However, patients who have a history of severe rash with prior NNRTI use should not receive etravirine.
- *Less common (more severe)*: Peripheral neuropathy, severe rash including Stevens-Johnson syndrome, hypersensitivity reactions (HSRs) (including constitutional findings and sometimes organ dysfunction including hepatic failure), and erythema multiforme have been reported. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or HSRs develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, and 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. It is recommended that patients who have a prior history of severe rash with nevirapine or efavirenz not receive etravirine.

Resistance

The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR/>).

Pediatric Use

Approval

Etravirine is Food and Drug Administration-approved for use in ARV-experienced children and adolescents aged 6 to 18 years.

Efficacy in Clinical Trials

The PIANO study (TMC125-C213) was a single-arm, Phase II trial involving 101 ARV treatment-experienced, HIV-1 infected pediatric participants aged 6 to <18 years and weighing ≥ 16 kg. Participants eligible for this trial were on an ARV regimen with confirmed plasma HIV-1 RNA ≥ 500 copies/mL and viral susceptibility to etravirine at screening. All patients received etravirine with an investigator-selected, optimized background regimen of a ritonavir-boosted PI plus nucleoside/nucleotide analogue reverse transcriptase inhibitors and optional enfuvirtide and/or raltegravir. At Week 24, 67% of these pediatric participants had plasma HIV-1 RNA concentrations <400 copies/mL and 52% had <50 copies/mL. At week 48, 56% of the participants had <50 copies/mL, with a mean CD4 T lymphocyte cell increase of $156 \times 10^6/\text{mm}^3$.² A greater fraction of children aged 6 to <12 years had plasma HIV-1 RNA <50 copies/mL than adolescents aged 12 to <18 years (68% versus 48%), which the investigators attributed to less advanced disease, less prior NNRTI experience at baseline, and better adherence among the children. However, the population pharmacokinetic (PK) data from this Phase II trial (101 treatment-experienced children aged 6–17 years) revealed slightly lower etravirine exposures in adolescents (aged 12–17 years) compared with children aged 6 to 11 years and with adults (see below).

The safety, efficacy, and tolerability of etravirine in treatment-experienced patients was also evaluated in a multicenter retrospective study of 23 multidrug-resistant pediatric patients with a median age of 14.2 years (interquartile range 12.5 to 15.8 years).³ The backbone regimen included at least 2 fully active drugs in 91% of patients. During a median of 48.4 weeks of follow-up, 20 patients (87%) achieved HIV-1 RNA <400 copies/mL and 18 of 23 (78%) achieved HIV-1 RNA <50 copies/mL. No patients showed complete resistance to etravirine after follow up but 3 of the 21 patients who interrupted etravirine treatment because of virological or immunological failure had single resistance mutations at baseline.

The efficacy of etravirine-containing regimens in children who have previously been treated with an NNRTI is unclear. However, in a multicenter retrospective study involving genotypic resistance data from 120 children at 8 pediatric centers in Thailand, Puthanakit, et al.⁴ found that 98% of the children had at least one NNRTI resistance mutation, and 48% had etravirine mutation-weighted scores ≥ 4 , which would be predicted to compromise its effectiveness.

Pharmacokinetics

In a Phase I dose-finding study involving children aged 6 to 17 years, 17 children were given 4 mg/kg etravirine twice daily. The PK parameters $\text{AUC}_{12\text{h}}$ and C_{min} were below preset statistical targets based on prior studies involving adults.⁵ Based on acceptable PK parameters, the higher dose (5.2 mg/kg twice daily; maximum 200 mg per dose) was chosen for evaluation in the Phase II PIANO study. Exposures remained lower in older adolescents than in adults and younger children, and Asians compared to either white or black participants.⁶

	Mean $\text{AUC}_{0-12\text{h}}$ (ng*h/mL)	Mean $C_{0\text{h}}$ (ng/mL)
Children Aged 6–11 Years (N = 41)	5,684	377
Adolescents Aged 12–17 Years (N = 60)	4,895	325
Adults	5,506	393

Key to Acronyms: $\text{AUC}_{0-12\text{h}}$ = Area under the curve for 12 hours post-dose; $C_{0\text{h}}$ = pre-dose concentration during chronic administration

Etravirine is often combined with darunavir/ritonavir for treatment of HIV-infected adults with prior virologic failure. King et al.⁷ examined PK data from 37 pediatric patients receiving this combination, all receiving the maximum 200-mg etravirine dose. For both drugs, the estimated 90% confidence intervals for AUC and C_{min} fell below targeted lower limits defined using data from studies in adults. While this combination has been effective in a small cohort of HIV-infected adolescents,⁸ and in 51% of participants in the PIANO study,⁶ these data suggest a need for additional study of PK interactions involving etravirine and other ARV agents in pediatric patients, including regimens that do not include ritonavir-boosted PIs. **Until**

such data become available, panel members recommend using etravirine as part of a regimen that includes a ritonavir-boosted PI.

Toxicity

In the PIANO study, rash and diarrhea were the most common adverse drug reactions deemed possibly related to etravirine. Rash (\geq Grade 2) occurred in 13% of pediatric subjects and emerged at a median of 10 days, lasting a median of 7 days. Rash was observed more frequently in females (17 of 64; 26.6%) than in males (6 of 37; 16.2%). Etravirine was discontinued due to rash in 4 (4%) individuals, all of whom were female. Diarrhea occurred in 3 (3%) and was only reported in adolescents.

References

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