



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Etravirine (ETR, Intelence, TMC 125) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

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

Adult Dose (Antiretroviral-Experienced Patients):

- 200 mg twice daily following a meal

Selected Adverse Events

- Nausea
- Diarrhea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity with rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

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

- In the PIANO study⁴, ARV-experienced children aged 6 to <18 years received etravirine with a ritonavir-boosted HIV-1 PI as part of an optimized background regimen. 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, and a mean increase in CD4 cell count from baseline of 156 cells/mm³. 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%).
- In a retrospective study of 23 adolescents and young adults conducted by Briz et al., 78% achieved an HIV-1 RNA <50 copies/mL at a median of 48.4 weeks of follow-up.²

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 AUC_{12h} and minimum plasma concentration (C_{min}) were below preset statistical targets based on prior studies involving adults.³ 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.⁴

Pharmacokinetics of Etravirine

	Mean AUC _{0-12h} (ng*h/mL)	Mean C _{0h} (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: AUC_{0-12h} = Area under the curve for 12 hours post-dose; C_{0h} = pre-dose concentration during chronic administration

Etravirine is often combined with darunavir/ritonavir for treatment of adults with HIV infection with prior virologic failure. Cressey et al. examined PK data from 36 adolescents and young adults receiving etravirine 200 mg bid in combination with darunavir/ritonavir 600 mg/100 mg twice daily. The pharmacokinetic exposures of both agents were similar to those seen in adults, although with high inter-individual variability.⁵ The pharmacokinetics of both drugs were also studied in adolescents and young adults receiving darunavir/ritonavir 800 mg/100 mg once daily with either etravirine 200 mg twice daily or etravirine 400 mg once daily.⁶ Darunavir concentrations were higher when coadministered with etravirine, particularly when the latter was given 200 mg twice daily. Etravirine exposures were lower, particularly when given twice daily, although the authors commented on the limited sample size involved in these studies. While the combination of etravirine and darunavir/ritonavir has been effective in a small cohort of adolescents with HIV infection,⁷ and in 51% of participants in the PIANO study,⁴ 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 (Grade 2 or higher) 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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