Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Etravirine (ETR, Intelence, TMC 125) (Last updated November 15, 2012; last reviewed November 1, 2012)

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 at least 16 kg):

Weight in kilograms (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.

Special Instructions

- Always administer ETR following a meal. Area under the curve (AUC) of ETR is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to ETR.
- ETR tablets are sensitive to moisture; store at room temperature in original container with desiccant.
- Patients unable to swallow ETR tablets may disperse the tablets in liquid, as follows: 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. 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 ETR 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 ETR in patients with renal impairment: Dose adjustment is not required in

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patients with renal impairment.

Metabolism

- ETR is an inducer of cytochrome P450 3A4 (CYP3A4) and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein (Pgp). It is a substrate for CYP3A4, 2C9, and 2C19.
- Multiple drug interactions (see below).

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- Etravirine is associated with multiple drug interactions. Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions with ETR.
- Etravirine should not be co-administered with the following antiretroviral (ARV) drugs: tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, unboosted protease inhibitors. It should not be administered with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (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.

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, 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://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ETR.html).

Pediatric Use: Etravirine is FDA-approved for use in antiretroviral-experienced children and adolescents aged 6 to 18 years.

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A Phase I dose-finding study involving children aged 6–17 years, with virologic suppression on a stable lopinavir/ritonavir-containing regimen compared doses of 4 mg/kg twice daily and 5.2 mg/kg twice daily using both the investigational 25-mg tablets and the available 100-mg formulation.[2] Etravirine therapy was added for 8 days and pharmacokinetic (PK) sampling and analysis were performed. Among 17 children given 4 mg/kg twice daily, the PK parameters AUC_{12h} and C_{min} were below preset statistical targets compared with these parameters in adults. By comparison, acceptable PK were observed for participants who received 5.2 mg/kg twice daily, including 12 patients aged 6 to <12 years, and 9 study participants ages 12 to 17 years. The higher dose (5.2 mg/kg twice daily; [maximum 200 mg per dose]) was chosen for evaluation in the PIANO study (TMC125-C213), a single-arm, Phase II trial evaluating the PK, safety, tolerability, and efficacy of etravirine in 101 ARV treatment-experienced HIV-1 infected pediatric subjects aged 6 to <18 years and weighing ≥16 kg.[3] Subjects eligible for this trial were on an ARV regimen with confirmed plasma HIV-1 RNA of at least 500 copies/mL and viral susceptibility to etravirine at screening. The median baseline plasma HIV-1 RNA was 3.9 $\log_{10}$ copies/mL, and the median baseline CD4 T lymphocyte (CD4 cell) count was 385 x 10^6 cells per mm^3. At Week 24, 67% of these pediatric subjects had plasma HIV-1 RNA concentrations <400 copies/mL and 52% had <50 copies/mL. The mean CD4 cell count increase from baseline was 112 x 10^6 cells per mm^3. The population 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 table below).

	Mean AUC_{12} (ng*h/mL)	**Mean C_{0h} (ng/mL)**
Children aged 6–11 years (N=41)	5764	381
Adolescents aged 12–17 years (N=60)	4834	323
All Pediatric Participants	5236	347
Adults	5506	393
AUC_{12} = Area under the curve for 12h post dose; C_{0h} = pre-dose concentration during chronic administration.		

The frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adult subjects, except for rash, which was observed more frequently in pediatric subjects. The most common adverse drug reactions (in at least 2% of pediatric subjects) were rash and diarrhea. Rash (≥Grade 2) occurred in 15% of pediatric subjects. In the majority of cases, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was self-limiting and generally resolved within 1 week on continued therapy. The discontinuation rate for rash was 4%. Rash including serious (Grade 3 or 4) events and discontinuations were more frequently observed in female subjects compared with male subjects.

The safety, efficacy, and tolerability of etravirine in treatment-experienced patients was also evaluted 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).[4] The median baseline HIV-1 RNA was 4.5 $\log_{10}$ HIV-1 RNA copies/mL and the median CD4 T-cell count was 445 cells/mm^3. The backbone regimen included at least two 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.

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The efficacy of etravirine-containing regimens in children who have previously been treated with an NNRTI is unclear. However, in a multi-center retrospective study involving genotypic resistance data from 120 children at 8 pediatric centers in Thailand, Puthanakit et al found that 98% of the children had at least one NNRTI resistance mutation, and 48% had etravirine mutation-weighted scores ≥4.[5]

Etravirine is often combined with ritonavir-boosted darunavir for treatment of HIV-infected adults with prior virologic failure. King et al[6] 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,[7] these data suggest a need for continued study of PK interactions involving etravirine and other ARV agents in pediatric patients.

References

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