Etravirine (ETR, Intelence)

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Formulations

Tablets: 25 mg, 100 mg, 200 mg

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonate and Infant Dose

- Etravirine (ETR) is not approved for use in neonates or infants.

Child Dose

- ETR is not approved for use in children aged <2 years.

Etravirine Dosing Table for Antiretroviral Therapy-Experienced Children and Adolescents Aged 2 to 18 Years and Weighing ≥10 kg

Body Weight	Twice-Daily Dose
10 kg to <20 kg	100 mg
20 kg to <25 kg	125 mg
25 kg to <30 kg	150 mg
≥30 kg	200 mg

- ETR is approved for use in children and adolescents who are treatment experienced. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends that ETR is used as part of a regimen that includes a ritonavir (RTV)-boosted protease inhibitor (PI) (see Efficacy in Clinical Trials and Drug Interactions below).
- Cobicistat-boosted PIs, non-nucleoside reverse transcriptase inhibitors, bictegravir, and elvitegravir/cobicistat should not be used with ETR. Raltegravir and dolutegravir should only be used with ETR with RTV-boosted atazanavir, darunavir, or lopinavir.

Adult Dose for Antiretroviral Therapy-Experienced Patients

- ETR 200 mg twice daily with food

Selected Adverse Events

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

Special Instructions

- ETR tablets are sensitive to moisture; store the tablets at room temperature in the original container with desiccant.
- Always administer ETR with food. Area under the curve 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.
- Swallowing ETR tablets whole is the preferred means of administration. Although the package insert contains instructions for dispersing ETR tablets in water or other liquids, using this administration method generally results in lower ETR exposures compared with swallowing tablets whole. Children who receive dispersed ETR tablets should switch to swallowing tablets whole as soon as developmentally able.

Metabolism/Elimination

- ETR is an inducer of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate for CYP3A4, CYP2C9, and CYP2C19.
- ETR is involved in multiple interactions with antiretroviral agents and other drugs (see Drug Interactions below).

	Etravirine Dosing in Patients with Hepatic Impairment • No dose adjustment is required when using ETR in patients with mild or moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment. Etravirine Dosing in Patients with Renal Impairment • No dose adjustment is required when using ETR in patients with renal impairment.

Drug Interactions

Additional information about drug interactions is available in Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- Etravirine (ETR) is associated with multiple drug interactions. A patient's medication profile should be carefully reviewed for potential drug interactions before ETR is administered.
- ETR **should not be administered** with tipranavir/ritonavir, fosamprenavir/ritonavir, unboosted protease inhibitors (PIs), or cobicistat-boosted PIs.[1]
- ETR **should not be administered** with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine [NVP], efavirenz [EFV], rilpivirine, doravirine).
- ETR **should not be administered** with bictegravir or elvitegravir/cobicistat. ETR reduces the trough concentration of raltegravir[2] (RAL) and dolutegravir (DTG). RAL and DTG should be used with ETR only when these drugs are coadministered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.

Major Toxicities

- *More common:* Nausea, diarrhea, and mild rash. Rash occurs most commonly during the first 6 weeks of therapy. Rash generally resolves after 1 week to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with ETR. However, patients who have a history of severe rash with prior NNRTI use **should not receive ETR.**
- *Less common (more severe):* Peripheral neuropathy, severe rash, hypersensitivity reactions (HSRs), and erythema multiforme all have been reported. Instances of severe rash have included Stevens-Johnson syndrome, and HSRs have included constitutional symptoms and organ dysfunction, including hepatic failure. Discontinue ETR 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). Clinicians should monitor a patient's clinical status, including levels of liver transaminases, and initiate appropriate therapy when necessary. Continuing to use ETR after the onset of severe rash may result in a life-threatening reaction. People who have a history of severe rash while using NVP or EFV **should not receive ETR.**

Resistance

The International AIDS Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

ETR is approved by the U.S. Food and Drug Administration for use in antiretroviral therapy (ART)-experienced children and adolescents aged 2 to 18 years.

Efficacy in Clinical Trials

In the Paediatric study of Intelence As an NNRTI Option (PIANO) study,[3] ART-experienced children aged 6 years to <18 years received ETR with a ritonavir (RTV)-boosted PI as part of an optimized background regimen. At Week 24, 67% of these participants had plasma HIV RNA concentrations <400 copies/mL, and 52% had HIV RNA <50 copies/mL. At Week 48, 56% of the participants had HIV RNA <50 copies/mL and a mean increase in their CD4 T lymphocyte (CD4) cell counts of 156 cells/mm^3 from baseline. At Week 48, 68% of children aged 6 years to <12 years had plasma HIV RNA <50 copies/mL, whereas only 48% of adolescents aged 12 years to <18 years achieved a plasma viral load of <50 copies/mL.

In a retrospective study of 23 adolescents and young adults in Spain receiving ETR-based therapy, 78% of participants achieved HIV RNA <50 copies/mL at a median of 48.4 weeks of follow-up.[4]

In the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1090 trial,[5] ART-experienced children aged ≥2 years to <6 years received ETR with an RTV-boosted PI as part of an optimized background regimen. Participants received ETR at a dose of 100 mg twice daily (10 kg to <20 kg) or 125 mg twice daily (20 kg to <25 kg). At Week 48, 75% had an HIV-1 RNA <400 copies/mL or a >2-log reduction in HIV-1 RNA from baseline. The mean increase in CD4 count and CD4 percentage over 48 weeks was 298.5 cells/mm^3 and 5.2%, respectively. Due to the PIANO and IMPAACT P1090 study findings, if ETR is utilized to treat an ART-experienced child or adolescent, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends that ETR is part of a regimen that includes a RTV-boosted PI plus an optimized background regimen.

Pharmacokinetics

In a Phase 1 dose-finding study that involved children aged 6 to 17 years, 17 children were given ETR 4 mg/kg twice daily. The study reported that two pharmacokinetic (PK) parameters—area under the curve for 12 hours post-dose ($AUC_{0–12h}$) and minimum plasma concentration (C_{min})—were lower than the corresponding parameters observed in adults during previous studies.[6] However, a higher dose (ETR 5.2 mg/kg twice daily; maximum 200 mg per dose) yielded acceptable parameters and was chosen for evaluation in the Phase 2 PIANO study. Exposures (mean $AUC_{0–12h}$) remained lower in older adolescents than in adults and younger children, and exposures were lower in Asian participants than in either White or Black participants. In the PIANO study, children and adolescents with ETR concentrations in the lowest quartile (<2,704 ng·h/mL or pre-dose concentration [C_{0h}] <145 ng/mL) were less likely to achieve sustained virologic responses (defined as plasma viral loads

<50 copies/mL) after 48 weeks of treatment than those with ETR concentrations in the upper three quartiles.[7]

Table A. Pharmacokinetic Parameters in Children, Adolescents, and Adults Receiving Etravirine Twice Daily with an Optimized Background Regimen, Including a Ritonavir-Boosted Protease Inhibitor[7]

Population	Mean ETR $AUC_{0–12h}$ (ng·h/mL)	Mean ETR 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 (n = 575)	5,506	393

Key: $AUC_{0–12h}$ = area under the curve for 12 hours post-dose; C_{0h} = pre-dose concentration; ETR = etravirine

IMPAACT P1090 examined the PK and safety of ETR in treatment-experienced children with HIV aged ≥2 years to <6 years.[5] All participants received ETR as part of an optimized background regimen, which included a RTV-boosted PI. The tablets were swallowed whole or dispersed in liquid. ETR was initially given at a dose of 5.2 mg/kg twice daily to a cohort of six children; however, at this dose, the geometric mean ETR $AUC_{0–12h}$ values fell below the target range of 60% of the values seen in adults. Subsequent participants were given twice-daily doses of ETR that were determined by weight band: children weighing 10 kg to <20 kg were given 100 mg twice daily, and children weighing 20 kg to <25 kg were given 125 mg twice daily.

The protocol-specified PK targets for ETR were achieved at these doses; the geometric mean $AUC_{0–12h}$ was 3,823 ng·hr/mL, which was within the target range of 2,713 ng·hr/mL to 6,783 ng·hr/mL (60% to 150% of the $AUC_{0–12h}$ value seen in adults). However, considerable intersubject variability was observed, with 5 (33.3%) of 15 participants having $AUC_{0–12h}$ values that were below the 10th percentile for the adult $AUC_{0–12h}$ range (<2,350 ng·hr/mL). The ETR $AUC_{0–12h}$ values were significantly lower in children who received dispersed tablets than in children who swallowed intact tablets: 2,919 ng·hr/mL (n = 11) versus 10,982 ng·hr/mL (n = 3), respectively (P = 0.0008). The Panel recommends that children swallow tablets whole (rather than dispersed in liquid) as soon as developmentally able.

Six children with HIV aged 1 year to <2 years also were enrolled in IMPAACT P1090. Although the ETR exposures satisfied protocol-defined PK targets ($AUC_{0–12h}$ between 2,713 ng·hr/mL and 6,783 ng·hr/mL), they were lower in these children compared with historical data in adults and adolescents (geometric mean ETR $AUC_{0–12h}$ of 3,328 ng·hr/mL). Virologic failure, which was defined as a confirmed viral load of ≥400 copies/mL or less than a 2-log reduction in HIV-1 RNA from baseline, occurred in four of six children by Week 48. Thus, the Panel does not recommend the use of ETR in those younger than 2 years of age.

Given that both the PIANO and IMPAACT P1090 trials were conducted in children receiving RTV-boosted PIs as part of their optimized background regimens, the Panel recommends using ETR as part of a regimen that includes an RTV-boosted PI.

Toxicity

In the PIANO study, rash and diarrhea were the most common adverse drug reactions that were deemed to be possibly related to the use of ETR. 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 female patients (13 of 64 patients; 20.3%) than in male patients (2 of 37 patients; 5.4%).[7] In IMPAACT P1090, adverse drug reactions that were reported for children aged ≥2 years to <6 years were comparable in frequency, type, and severity to those reported for adults. Twelve participants (46.2%) developed Grade 1 or 2 rashes within the first 48 weeks of ETR, but no subject discontinued the study prematurely due to rash. Diarrhea occurred in 8 (30.8%) of 26 patients.[5]

References

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