Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Raltegravir (RAL, Isentress) (Last updated November 5, 2012; last reviewed November 1, 2012)

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

Formulations

Tablets*: 400 mg (film-coated poloxamer tablet)

Chewable Tablets: 100 mg (scored) and 25 mg
* Film-coated tablets and chewable tablets are not interchangeable.

Dosing Recommendations

Neonate/infant dose:

- Not approved for use in neonates/infants.

Pediatric dose:

Children aged 2 to <12 years:

- <25 kg: Chewable tablet twice daily to maximum of 300 mg twice daily (see table)
- ≥25 kg: 400 mg film-coated tablet twice daily OR chewable tablets (see table)

Dosing of chewable tablets in children aged 2 to <12 years of age

Body Weight (kg)	Dose	Number of Chewable Tablets
10 to <14	75 mg twice daily	3 X 25 mg twice daily
14 to <20	100 mg twice daily	1 X 100 mg twice daily
20 to <28	150 mg twice daily	1.5 X 100 mg twice daily
28 to <40	200 mg twice daily	2 X 100 mg twice daily
≥40	300 mg twice daily	3 X 100 mg twice daily

Adolescent (≥12 years of age)/adult dose:

- 400 mg film-coated tablet twice daily

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache
- Fever
- Creatine phosphokinase (CPK) elevation, muscle weakness, and rhabdomyolysis

Special Instructions

- Can be given without regard to food.
- Chewable tablets may be chewed or swallowed whole.
- Film-coated tablets and chewable tablets are not interchangeable. Chewable tablets have better bioavailability than the film-coated tablets. Chewable tablets should be stored in the original package with desiccant to protect from moisture.

Metabolism

- Uridine diphosphate glucotransferase (UGT1A1)-mediated glucuronidation.
- Dosing of RAL 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 RAL in patients with renal impairment: No dosage adjustment necessary.

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

- *Metabolism:* The major route of raltegravir elimination is mediated through glucuronidation by UGT1A1.
- Inducers of UGT1A1 such as rifampin and tipranavir may result in reduced plasma concentrations of raltegravir whereas inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir.
- Efavirenz and etravirine may decrease raltegravir concentrations.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with raltegravir.

Major Toxicities:

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, and itching.
- *Less common:* Abdominal pain, vomiting, insomnia. Patients with chronic active hepatitis B and/or hepatitis C are more likely to experience worsening aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin than are patients who are not coinfected.
- *Rare:* Creatine phosphokinase elevations (Grade 2–4) have been observed in some patients. Myopathy and rhabdomyolysis have been reported. Use raltegravir with caution in patients receiving medications associated with these toxicities. Anxiety, depression, especially in those with prior history. Rash including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis have been reported. Thrombocytopenia.

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/cgi-bin/INIResiNote.cgi).

Pediatric Use: Raltegravir is approved by the Food and Drug Administration (FDA) for use in children aged ≥2 years. Raltegravir has been studied in 126 antiretroviral (ARV) treatment-experienced HIV-1-infected children and adolescents aged 2 to 18 years in combination with an optimized background ARV regimen in IMPAACT P1066. Additional experience from the French expanded access program in treatment-experienced adolescents support the good virologic and immunologic results observed in P1066.[1, 2]

IMPAACT P1066 is a Phase I/II open label multicenter study to evaluate the pharmacokinetic (PK) profile, safety, tolerability, and efficacy of various formulations of raltegravir in HIV-infected children. Subjects received either the 400-mg film-coated tablet formulation twice daily (patients aged 6–18 years and weighing at least 25 kg) or the chewable tablet formulation at a dose of 6 mg/kg twice daily (aged 2 to <12 years). Current pediatric approval and dosing recommendations are based upon these evaluations in 96 patients.[3-7]

In IMPAACT P1066, the initial dose-finding stage includes intensive PK evaluation in various age cohorts: (aged 12 to <19 years, 6 to <12 years, 2 to <6 years). Dose selection was based upon achieving target PK parameters similar to those seen in adults: PK targets are geometric mean (GM) area under the curve of 14-25 µMxh and GM 12 h concentration >33 nM. Additional subjects were then enrolled in each age cohort to evaluate long-term efficacy, tolerability, and safety. Ninety-three (97%) subjects completed 24 weeks of treatment with 54% achieving HIV RNA <50 copies/mL with a mean CD4 T lymphocyte count (percent

[%]) increase of 119 cells/mm^3 (3.8%). The frequency, type, and severity of drug-related adverse reactions through week 24 were comparable to those observed in adult studies. Observed adverse reactions considered drug-related included one patient with grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia; one patient with a grade 2 allergic rash; and one patient with grade 3 ALT and grade 4 AST laboratory elevations.

The investigational raltegravir oral granules for suspension formulation are currently under study in P1066 in children aged 4 weeks to <2 years. Recent data, obtained from 9 children aged 6 months to <2 years, suggest that the oral granules are well tolerated with favorable preliminary efficacy. PK data obtained in 8 of the 9 young children achieved targets similar to those observed in the 2- to 11-year-olds receiving the chewable tablets.[8] A dosage of 6 mg/kg every 12 hours was chosen for continued study in this age group.

The raltegravir chewable tablet has higher oral bioavailability than the film-coated tablet based on a comparative study in healthy adult volunteers.[9] In the PK of raltegravir, interpatient and intrapatient variability is considerable.[10]

References

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