

HIV CareLink

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First Agent in Integrase Inhibitor Class, Raltegravir (ral-TEG-ra-vir) (Isentress™; eye-SEN-tris), Approved for Use in HIV-1 Infected Treatment Experienced Adults

Jeffrey Beal, MD

Clinical Director, Florida/Caribbean AIDS Education and Training Center

Joanne J. Orrick, PharmD, BCPS

Faculty, Florida/Caribbean AIDS Education and Training Center

On October 12, 2007 the FDA approved raltegravir (formerly MK-0518) for use in combination with other antiretroviral agents (ARVs) in treatment experienced HIV-infected patients with evidence of HIV-1 replication despite ongoing ARV therapy. This is the first in the class of integrase inhibitors to be approved and was developed by Merck & Company, Inc. Prescribing and other information is available at www.isentress.com

EDITORS

Jeffrey Beal, M.D.
(239) 839-4645
aetbeal@embarqmail.com

Joanne Orrick, Pharm.D., B.C.P.S.
(352) 273-6365
orricj@ufl.edu

MANAGING EDITOR

Kimberly Alfonso, M.Acc.
(813) 974-4430
alfonso@fmhi.usf.edu

ABOUT US

The Florida/Caribbean AIDS Education and Training Center provides HIV education, consultation, and resource materials to health care providers in Florida, Puerto Rico and the US Virgin Islands.

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Mechanism of action:

- Integrase is one of three enzymes required for HIV replication, and catalyzes the stepwise process that results in the integration of the HIV-1 deoxyribonucleic acid (DNA) into the genome of the host cell.
- Raltegravir blocks the strand transfer step of integration which blocks viral replication.

Clinical Trial Results (Phase II and III):

Phase	Protocol Number	Dose(s) of Raltegravir Studied	Number of Patients Receiving Raltegravir [†]	Population	Key Purpose	Major Findings Regarding Raltegravir
Phase II	004	100 mg b.i.d.	39 [‡]	Treatment-Naïve	Part 1: Dose Finding and Proof of Concept (Monotherapy) Part 2: Dose Finding In the Setting of Combination Therapy	<ul style="list-style-type: none"> • Comparable Efficacy Across All Doses • Efficacy Comparable to Standard of Care • Generally well tolerated at all doses as monotherapy for 10 days • Generally well tolerated at all doses as compared to efavirenz when both are given in combination with tenofovir and lamivudine.
		200 mg b.i.d.	40 [‡]			
		400 mg b.i.d.	41 [‡]			
		600 mg b.i.d.	40 [‡]			
	005	200 mg b.i.d.	43	Treatment-Experienced	Dose Finding In the Setting of Combination Therapy	<ul style="list-style-type: none"> • Comparable Efficacy Across All Doses • Efficacy Superior to Placebo • Generally well tolerated at all doses as compared to placebo, both given in combination with OBT across all doses.
		400 mg b.i.d.	45			
		600 mg b.i.d.	45			
Phase III	018	400 mg b.i.d.	232	Treatment-Experienced	Demonstration of Efficacy	<ul style="list-style-type: none"> • Efficacy Superior to Placebo • Generally well tolerated as compared to placebo, both given in combination with OBT
	019	400 mg b.i.d.	230	Treatment-Experienced	Demonstration of Efficacy	<ul style="list-style-type: none"> • Efficacy Superior to Placebo • Generally well tolerated as compared to placebo, both given in combination with OBT

[†] Includes only patients who received at least one dose of raltegravir.

[‡] Numbers are from Part II and include both Part I and Part II patients.

<http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4314b1-01-Merck.pdf>

OBT = Optimized background therapy.

Resistance Data:

- Virus isolated from raltegravir failures displayed mutation at either amino acid residue 148 or 155.
- Primary Mutations (N148H/Q/R or N155H)
- ↓ susceptibility 13 to 46-fold
- One or more secondary mutations occurred in the majority of raltegravir failures
 - L74M, E92Q, T97A, E138K, G140S
 - When combined with either primary mutation susceptibility ↓ 64 to 521-fold
- Resistance conferred by ≥ 2 integrase mutations

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Metabolism:

- Glucuronidation primarily by uridine diphosphate (UDP) glucuronyltransferase 1A1 (UGT1A1)
- Majority of the dose (50-74%) is excreted in feces with remainder appearing in urine
- Neither a substrate nor an inhibitor of the cytochrome P450 enzymes; does not inhibit P-glycoprotein-mediated transport

Drug-Drug Interactions:

- Rifampin causes a modest ↓ in raltegravir levels. Phenobarbital and phenytoin may have a similar effect; caution should be used when co-administering raltegravir with these drugs.
- TPV/r reduces plasma concentration of raltegravir, but based on clinical trial data, no dosage adjustment is recommended.
- ATV ↑ raltegravir levels, however no dosage adjustments recommended.
- Other potent inducers or inhibitors of UGT1A1 studied to date have not caused any clinically significant raltegravir level change.

Safety:

- Appears to be well tolerated irrespective of gender or race
- In studies to date, not associated with lipodystrophy or lipoatrophy
- Well tolerated in patients with active Hepatitis B and/or C
- Diarrhea, nausea, headache and pyrexia were the most frequently reported adverse effects of moderate or severe intensity
- ↑ ALT, AST, triglyceride or CPK were the most frequent laboratory adverse effects.
- Myopathy & rhabdomyolysis have been reported, but relationship of these events to raltegravir is not known. Caution recommended with increased monitoring when used with drugs known to cause these conditions.
- Immune reconstitution syndrome
- Raltegravir + TDF + 3TC (Merck 004, phase II) revealed no increase in fasting cholesterol, LDL, or triglyceride levels.

Dose/Dosage Form:

- 400 mg bid without regard to food in combination with an optimized background regimen
- 400 mg tablets (pink oval-shaped)
- Storage: controlled room temperature (20-25° C; 68-77° F), excursions permitted to 15-30° C; 59-86° F
- Pregnancy Category C

Availability/Pricing:

- Raltegravir is expected to be available in pharmacies within the next 2 weeks
- Cost: \$810 for 30 day supply (wholesale acquisition cost, WAC)
- The drug has not yet been approved for use in patients on the Florida ADAP or Medicaid programs

References:

1. Product Information. Isentress (raltegravir). Merck & Company, 2007.
2. <http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-431b1-01-Merck.pdf>

FDA Approves Additional Fosamprenavir (Lexiva®) Dose For PI Naïve Patients

On October 12, 2007, the Food Drug Administration approved fosamprenavir 1400 mg with 100 mg of ritonavir in adult patients who had not previously taken a protease inhibitor (PI). The approval was based on pharmacokinetic data demonstrating comparable blood plasma levels in healthy volunteers when fosamprenavir was administered with the lower 100 mg dose of ritonavir and the previously approved 200 mg dose of ritonavir. This information has been added to the fosamprenavir product label.

The 2007 HIV Update: Changing Times - New Challenges

Presented by

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