



Therapeutic Class ReviewSM

Antivirals – raltegravir (IsentressTM)

February 2008

New Product for Review:
raltegravir (IsentressTM) [Merck]

Dossier Provided by Manufacturer: Yes
Dossier Evaluation: 3

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Executive Summary

HIV infection in the United States:^[1]

- Approximately 1.2 million people in the US are infected with HIV.^[1]
 - 492,000/1.2 million (41%) of those infected with HIV are on antiretroviral therapy.
 - Of those on therapy, 77,911/492,000 (16%) are on third-line (salvage) agents.
- According to the HIV Cost and Services Utilization Study (HCSUS), phenotypic resistance to at least one drug was observed in approximately 80% of individuals with viral loads > 500 copies/ml.
 - Resistance to two or more classes of antiretrovirals (ARVs) was observed in 51% of individuals.
 - Up to 14% had triple class resistance.

Raltegravir (Isentress):

- Raltegravir (Isentress) is an HIV-1 integrase strand transfer inhibitor (INSTI).
 - It is the first agent in this new class of ARV medications.
 - It stops replication of HIV-1 by preventing insertion of linear HIV-1 DNA into the host cell genome.
- Raltegravir (Isentress) is indicated for use in treatment-experienced HIV-infected patients.
- Raltegravir (Isentress) is administered orally twice per day in combination with other ARV medications.
 - Boosting with ritonavir (Norvir) is not required.

Evidence

- There is possibly useful evidence from two RCTs supporting the efficacy of raltegravir (Isentress) in treatment-experienced HIV-infected adults.
 - Addition of raltegravir (Isentress) to an optimized background ARV regimen resulted in reduction of HIV viral load below 400 copies/ml in a statistically significant proportion of patients versus background therapy alone.
 - For every three patients treated, one patient had a viral load that dropped below 400 copies/ml over 16 weeks (NNT = 3).
- The evidence from a single trial in treatment-naïve HIV-infected individuals is also not reliable.
 - Only 41 patients received the FDA-approved dose of raltegravir (Isentress).
 - The trial was not powered to show either similarity or superiority to a first-line ARV regimen.
- None of the raltegravir (Isentress) trials was designed to detect specific harms.
- The most common adverse events reported in trials in treatment-experienced patients included diarrhea and headache.

Decision

Raltegravir (Isentress) as preferred/formulary because:

- It addresses an unmet need in HIV-infected patients who have few or no remaining treatment options.
- There is a low probability of inappropriate use.

Products

Table 1: Antiretroviral medications for treatment-experienced patients

Drug Products	FDA approval ^a	Patent Expiration(s) ^b	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
Fusion inhibitors:					
enfuvirtide (Fuzeon [®]) [2]	3/2003	6/2013	Treatment of HIV-1 infection in combination with other antiretroviral medications in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.	90 mg (1 ml) subcutaneously b.i.d.	
Protease inhibitors (PIs) for treatment-experienced patients:					
darunavir (Prezista [™]) [3]	6/2006	12/2015	Treatment of HIV-1 infection in combination with ritonavir and other antiretroviral agents in antiretroviral treatment-experienced patients.	600 mg p.o. b.i.d. plus ritonavir 100 mg b.i.d. [with food]	
tipranavir (Aptivus [®]) [4]	6/2005	12/2015	Treatment of HIV-1 infection, in combination with ritonavir, in patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor.	500 mg p.o. b.i.d. co-administered with ritonavir 200 mg b.i.d. [with food]	
CCR5 co-receptor antagonists					
maraviroc (Selzentry [™]) [5]	8/2007	5/2021	Used in combination with other antiretroviral agents in treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable disease, showing resistance to multiple agents with evidence of HIV-1 replication despite treatment.	150 to 600mg p.o. b.i.d.	Treatment-naïve patients infected with HIV
Integrase strand transfer inhibitors (INSTIs)					
raltegravir (Isentress [™]) [6]	10/2007	10/2012	Treatment of HIV-1 infection in combination with other antiretroviral medications in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.	400mg p.o. b.i.d.	Treatment-naïve patients infected with HIV

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Based on patents listed in Orange Book as of 11/20/07.

^c As listed in © 1974 - 2007 Thomson MICROMEDEX database or as referenced.

Table 2: Pregnancy and Pediatric information

Drug Product	Approval in pediatric patients	Minimum age of approval [#]	Pregnancy category
Protease inhibitors (PIs) for treatment-experienced patients:			
tipranavir (Aptivus [®]) ^[4]		≥ 18 years	Category C
darunavir (Prezista [™]) ^[3]		≥ 18 years	Category B
Fusion inhibitors:			
enfuvirtide (Fuzeon [®]) ^[2]	X	≥ 6 years	Category B
CCR5 co-receptor antagonists:			
maraviroc (Selzentry [™]) ^[5]		≥ 16 years	Category B
Integrase strand transfer inhibitors (INSTIs):			
raltegravir (Isentress [™]) ^[6]		≥ 16 years	Category C

See prescribing information for pediatric dosing of individual products.

References:

1. Product Dossier: Isentress[™] (raltegravir), Merck; Whitehouse Station, NJ; November 2007.
2. Fuzeon[®] (enfuvirtide) Product Information. Roche Laboratories, Inc.: Nutley, NJ; January 2007.
3. Prezista[™] (darunavir) Product Information. Tibotec Therapeutics: Raritan, NJ, October 2006.
4. Aptivus[®] (tipranavir) Product Information. Boehringer Ingelheim Pharmaceuticals, Inc: Ridgefield, CN; October 2007.
5. Selzentry[™] (maraviroc) Product Information. Pfizer: NY, NY; August 2007.
6. Isentress[™] (raltegravir) Product Information. Merck: Whitehouse Station, NJ; October 2007.
7. Department of Health and Human Services (DHHS) Panel on Clinical Practices for the Treatment of HIV Infection: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, October 16, 2006. Available at: <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed on October 16, 2007.
8. Personal communication; Corklin Steinhart, MD, Senior Medical Director, Merck & Co., Inc.; December 4, 2007.
9. Grinsztejn B, Nguyen BY, Katlama C, Gatell JM, Lazzarin A, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug resistant virus: a phase II randomised controlled trial. *Lancet*. 2007;369:1261-9.
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13. International AIDS Society – USA Panel. Treatment for Adult HIV infection: 2006 recommendations of the International AIDS Society – USA Panel. *JAMA*. 2006;296(7):827-843.
14. Josephson F, Albert J, Flamholz L, Gisslén M, Karlström O, et al. Antiretroviral treatment of HIV infection: Swedish recommendations 2007. *Scand J Infect Dis*. 2007;39:486-507.
15. The South African Ministry of Health and Department of Health. National antiretroviral treatment guideline, 2004. Available at: <http://www.hst.org.za/publications/624>. Accessed on October 16, 2007.