



Therapeutic Class ReviewSM

HIV antiviral therapy; protease inhibitors: darunavir (PrezistaTM)

December 2006

New Product for Review:

darunavir (PrezistaTM) [Tibotec]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: 3

- 1- dossier w/missing components
- 2- all components present, except pharmacoeconomic model
- 3- all components present (comprehensive)

Executive Summary

- Darunavir (Prezista):
 - Received FDA approval in June 2006.
 - Is used in combination with other antiretroviral (ARV) medications.
 - Must be co-administered with ritonavir (Norvir[®]) to boost serum drug levels to concentrations that will inhibit HIV replication.
 - Is the 10th PI approved in the U.S., and the 2nd PI indicated for use in treatment-experienced populations.
- Treatment-experienced patients are those patients with extensive prior antiretroviral experience and drug resistance who are experiencing treatment failure (virologic failure, immunologic failure, and/or clinical progression).
- HIV resistant to other PIs (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir) remains susceptible to darunavir (Prezista) based on analysis of clinical isolates.

Evidence

- There is no useful evidence to show that darunavir (Prezista) is superior to existing ritonavir- (Norvir) boosted PI regimens based on its ability to suppress HIV-1 replication.
- Interpretation of efficacy and safety information for new PIs is difficult, as they are always given in combination with other ARV medications which vary from patient to patient (confounders).
- There is no useful evidence to show that darunavir (Prezista) is better tolerated than other PIs.

Decision

Darunavir (Prezista) is preferred/formulary because:

- Currently, there are no other preferred/formulary protease inhibitors available for treatment-experienced HIV-1 patients.
- HIV specialists indicate there is a need for a treatment option for this population.

Products

Drug Product	Date of FDA Approval	FDA Approved Indication	Dose/Route	Potential Off-Label Uses ^a
amprenavir (Agenerase [®]) ² [50 mg, and 150 mg cap]	4/1999	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1200 mg p.o. b.i.d. 1200 mg p.o. q.d. plus ritonavir 200 mg q.d.	occupational HIV post-exposure prophylaxis
atazanavir (Reyataz [®]) ³ [100 mg, 150 mg, and 200 mg cap]	6/2003	Treatment of HIV-1 infection in combination with other antiretroviral medications.	400 mg p.o. q.d. 300 mg p.o. q.d. plus ritonavir 100 mg q.d. [with food]	
fosamprenavir (Lexiva [®]) ⁴ [700 mg tab]	10/2003	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1400 mg p.o. b.i.d. 1400 mg p.o. q.d. plus ritonavir 200 mg q.d.	
indinavir (Crixivan [®]) ⁵ [100 mg, 200 mg, 333 mg, and 400 mg cap]	3/1996	Treatment of HIV-1 infection in combination with other antiretroviral medications.	800 mg p.o. q. 8 hrs [empty stomach]	occupational HIV post-exposure prophylaxis
lopinavir/ritonavir (Kaletra [®]) ⁶ [200 mg/50 mg tab]	9/2000	Treatment of HIV-1 infection in combination with other antiretroviral medications.	2 tabs p.o. b.i.d. or 4 tabs p.o. q.d. [with food]	occupational HIV post-exposure prophylaxis
nelfinavir (Viracept [®]) ⁷ [250 mg and 625 mg tab]	3/1997	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1250 mg p.o. b.i.d. or 750 mg t.i.d. [with food]	occupational HIV post-exposure prophylaxis
ritonavir (Norvir [®]) ⁸ [100 mg cap]	3/1996	Treatment of HIV-1 infection in combination with other antiretroviral medications.	600 mg p.o. b.i.d.	occupational HIV post-exposure prophylaxis
saquinavir (Invirase [®]) ¹⁰ 200 mg cap and 500 mg tab]	12/1995	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1000 mg p.o. b.i.d. plus ritonavir 100 mg b.i.d. [with food]	occupational HIV post-exposure prophylaxis
tipranavir (Aptivus [®]) ¹¹ [250 mg cap]	6/2005	Treatment of HIV-1 infection in combination with ritonavir in patients with evidence of viral replication that are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.	500 mg p.o. b.i.d. plus ritonavir 200 mg b.i.d. [with food]	
darunavir (Prezista [®]) [300 mg tab]	6/2006	Treatment of HIV-1 infection in combination with ritonavir and other antiretroviral agents in antiretroviral treatment-experienced adults.	600 mg p.o. b.i.d. plus ritonavir 100 mg b.i.d. [with food]	

^a As listed in © 1974 - 2006 Thomson MICROMEDEX database^[12] or as referenced.

Black Box Warnings associated with protease inhibitor therapy:

	Intracranial hemorrhage*	Inhibition of hepatic enzymes*	Severe hepatotoxicity*	Other
Protease Inhibitors:				
amprenavir (Agenerase [®]) ¹				X^a
atazanavir (Reyataz [®]) ²				
darunavir (Prezista [™]) ³				
fosamprenavir (Lexiva [®]) ⁴				
indinavir (Crixivan [®]) ⁵				
lopinavir/ritonavir (Kaletra [®]) ⁶				
nelfinavir (Viracept [®]) ⁷				
ritonavir (Norvir [®]) ⁸		X		
saquinavir (Invirase [®]) ⁹				X^b
tipranavir (Aptivus [®]) ¹⁰	X		X	

* may be life-threatening and in some cases fatal

^a Agenerase oral solution contains propylene glycol and is contraindicated in infants & children < 4 years of age.

^b Saquinavir capsules and tablets are not bioequivalent and cannot be interchanged.

References

1. Agenerase[®] (amprenavir) Product Information. Research Triangle Park, NC: GlaxoSmithKline, 2005.
2. Reyataz[®] (atazanavir) Product Information. Princeton, NJ: Bristol-Myers Squibb, 2005.
3. Prezista[®] (darunavir) Product Information. Raritan, NJ: Tibotec, 2006.
4. Lexiva[®] (fosamprenavir) Product Information. Research Triangle Park, NC: GlaxoSmithKline, 2005.
5. Crixivan[®] (indinavir) Product Information. Whitehouse Station, NJ: Merck & Co. Inc., 2005.
6. Kaletra[®] (lopinavir/ritonavir) Product Information. North Chicago, IL: Abbott Laboratories, 2005.
7. Viracept[®] (nelfinavir) Product Information. La Jolla, CA: Pfizer, 2004.
8. Norvir[®] (ritonavir) Product Information. North Chicago, IL: Abbott Laboratories, 2005.
9. Invirase[®] (saquinavir) Product Information. Nutley, NJ: Roche Laboratories, Inc., 2004.
10. Aptivus[®] (tipranavir) Product Information. Ridgefield, CN: Boehringer Ingelheim Pharmaceuticals, Inc., 2005.
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12. 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 10, 2006. Available at: <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed on October 10, 2006.
13. World Health Organization (WHO) HIV/AIDS Programme. Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access. Recommendations for a public health approach, 2006 revision. Available at: <http://www.who.int/hiv/pub/guidelines/WHO%20Adult%20ART%20Guidelines.pdf>. Accessed on October 13, 2006.
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17. Center for Drug Evaluation and Research. Approval package for application number NDA 21-976; Medical Review. Available at: http://www.fda.gov/cder/foi/nda/2006/021976s000_Sprycel_MedR.pdf. Accessed on 9/8/2006.