



Therapeutic Class ReviewSM

Antiviral Therapy in HIV Infection: AtriplaTM

December 2006

New Product for Review:

efavirenz/emtricitabine/tenofovir

(AtriplaTM) [Bristol-Myers Squibb and Gilead]

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

- Atripla is a combination of three antiretroviral agents: efavirenz (Sustiva), a non-nucleoside reverse transcriptase inhibitor (NNRTI), and two nucleoside reverse transcriptase inhibitors (NRTIs), emtricitabine (Emtriva) and tenofovir (Viread).
- The components in Atripla are considered first-line in the treatment of HIV-1 infection in treatment-naïve patients.
- The manufacturer promotes this product as a convenient, single tablet, once-daily regimen.
- The U.S. FDA encourages the development of HIV therapies that improve adherence to therapy because high rates of adherence are associated with virologic success.
- Improved adherence in HIV therapy is related to decreased pill burden, decreased frequency of administration, and improved tolerability of the regimen. These practical considerations are included in determining the overall value of the medication.
- A single dose of Atripla is bioequivalent with its individual components given together at the same time.
- The cost of Atripla is similar to the individual components that make up this combination product.

Evidence

- There is no useful evidence (open-label study design) supporting the efficacy of the combination of antiretroviral agents found in Atripla in treatment-naïve HIV-infected adults.
- There is no useful evidence (open-label study design) available to assess the safety and tolerability of Atripla relative to alternative antiretroviral regimens.
- There are currently no studies demonstrating improved adherence with Atripla over the individual components taken separately, or over other NRTI-based regimens.

Decision

Atripla is preferred/formulary because:

- The individual components of Atripla are established as first-line agents in treatment-naïve HIV patients.
- There is no additional cost for Atripla over the cost of its individual components.

Products

Table 1: Antiretroviral Medications Used in the Treatment of HIV Infection:

Drug Product	Date of FDA Approval	FDA Approved Indication	Dose/Route	Potential Off-Label Uses
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs):				
delavirdine (Rescriptor [®]) ^{1, 29}	4/1997	Treatment of HIV-1 infection in combination with at least two other active antiretroviral agents.	400 mg p.o. t.i.d	occupational HIV post-exposure prophylaxis
efavirenz (Sustiva [®]) ^{2, 29}	9/1998	Treatment of HIV-1 infection in combination with other antiretroviral medications (combine with a PI +/-or NRTI).	600 mg p.o. q.d. [empty stomach]	occupational HIV post-exposure prophylaxis
nevirapine (Viramune [®]) ^{3, 29}	6/1996	Treatment of HIV-1 infection in combination with other antiretroviral medications.	200 mg p.o. q.d. x 14 days, then b.i.d.	perinatal and postnatal trans-mission of HIV
Nucleoside Reverse Transcriptase Inhibitors (NRTIs):				
abacavir (Ziagen [®]) ^{4, 29}	12/1998	Treatment of HIV-1 infection in combination with other antiretroviral medications.	300 mg p.o. b.i.d. or 600 mg p.o. q.d.	occupational HIV post-exposure prophylaxis
abacavir/lamivudine (Epzicom [®]) ^{5, 29} [600 mg/300 mg]	8/2004	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1 tablet p.o. q.d.	occupational HIV post-exposure prophylaxis
abacavir/lamivudine/zidovudine (Trizivir [®]) ^{6, 29} [300 mg/150 mg/300 mg]	11/2000	Treatment of HIV-1 infection alone or in combination with other antiretroviral medications.	1 tablet p.o. b.i.d.	occupational HIV post-exposure prophylaxis
didanosine (Videx [®]) ^{7, 29}	10/1991	Treatment of HIV-1 infection in combination with other antiretroviral medications.	≥ 60 kg: 200 mg b.i.d. < 60 kg: 125 mg b.i.d. [empty stomach]	occupational HIV post-exposure prophylaxis
didanosine [generic] (Videx EC [®]) ^{8, 29}	10/2000	Treatment of HIV-1 infection in combination with other antiretroviral medications.	≥ 60 kg: 400 mg q.d. < 60 kg: 250 mg q.d. [empty stomach]	occupational HIV post-exposure prophylaxis

Table 1 (continued):

Drug Product	Date of FDA Approval	FDA Approved Indication	Dose/Route	Potential Off-Label Uses
Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Continued):				
emtricitabine (Emtriva®) ^{9, 29}	7/2003	Treatment of HIV-1 infection in combination with other antiretroviral medications.	200 mg p.o. q.d.	Hepatitis B infection
emtricitabine/tenofovir (Truvada®) ^{10, 29} [200 mg/300 mg]	8/2004	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1 tablet p.o. q.d.	Hepatitis B infection
lamivudine (EpiVir®) ^{11, 29}	11/1995	1) Treatment of HIV-1 infection in combination with other antiretroviral medications. 2) Hepatitis B (EpiVir HBV)	150 mg p.o. b.i.d. or 300 mg p.o. q.d.	occupational HIV post-exposure prophylaxis; Perinatal and postnatal transmission of HIV
lamivudine/zidovudine (Combivir®) ^{12, 29} [150 mg/300 mg]	9/1997	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1 tablet p.o. b.i.d.	perinatal HIV transmission prevention
stavudine (Zerit®) ^{13, 29}	6/1994	Treatment of HIV-1 infection in combination with other antiretroviral medications.	≥ 60 kg: 40 mg b.i.d. < 60 kg: 30 mg b.i.d. (every 12 hours)	occupational HIV post-exposure prophylaxis
tenofovir (Viread®) ^{14, 29}	10/2001	Treatment of HIV-1 infection in combination with other antiretroviral medications.	300 mg p.o. q.d.	Hepatitis B
zalcitabine (Hivid®) ^{15, 29}	6/1992	Treatment of HIV-1 infection in combination with other antiretroviral medications.	0.75 mg p.o. q. 8 hrs	
zidovudine [generic] (Retrovir®) ^{16, 29}	3/1987	Treatment of HIV-1 infection in combination with other antiretroviral medications.	300 mg p.o. b.i.d. or 200 mg p.o. t.i.d.	occupational HIV post-exposure prophylaxis; Hepatitis B; perinatal HIV transmission prevention
Protease Inhibitors (PIs):				
amprenavir (Agenerase®) ^{17, 29}	4/1999	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1200 mg p.o. b.i.d. (decrease by 50% if given with ritonavir)	occupational HIV post-exposure prophylaxis
atazanavir (Reyataz®) ^{18, 29}	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. (with ritonavir) [take with food]	
darunavir (Prezista™) ^{19, 29}	6/2006	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. [take with food]	
fosamprenavir (Lexiva®) ^{20, 28}	10/2003	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1400 mg p.o. b.i.d. (decrease by 50% if given with ritonavir)	
indinavir (Crixivan®) ^{21, 29}	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

Table 1 (continued):

Drug Product	Date of FDA Approval	FDA Approved Indication	Dose/Route	Potential Off-Label Uses
Protease Inhibitors (PIs) (Continued):				
lopinavir/ritonavir (Kaletra®) ^{22, 29} [133.3 mg/33.3 mg]	9/2000	Treatment of HIV-1 infection in combination with other antiretroviral medications.	3 caps p.o. b.i.d. or 6 caps p.o. q.d. [with food]	occupational HIV post-exposure prophylaxis
nelfinavir (Viracept®) ^{23, 29}	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®) ^{24, 29}	3/1996	Treatment of HIV-1 infection in combination with other antiretroviral medications.	600 mg p.o. b.i.d. [\$10.72 per 100 mg cap]	occupational HIV post-exposure prophylaxis
saquinavir (Invirase®) ^{26, 29}	12/1995	Treatment of HIV-1 infection in combination with other antiretroviral medications.	1000 mg p.o. b.i.d. + ritonavir 100 mg b.i.d. [with food]	occupational HIV post-exposure prophylaxis
tipranavir (Aptivus®) ^{27, 29}	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. co-administered with ritonavir 200 mg b.i.d. [with food]	
Fusion Inhibitors:				
enfuvirtide (Fuzeon®) ^{27, 29}	3/2003	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.	
Combination NNRTIs plus NRTIs:				
efavirenz/emtricitabine/tenofovir (Atripla™) ^{28, 29} [600 mg/ 200 mg/ 300 mg]	7/2006	Treatment of HIV-1 infection alone as a complete regimen, or in combination with other antiretroviral agents in adult patients.	1 tablet p.o. daily [empty stomach]	

Table 2: Characteristics of Antiretroviral Medications in Specific Subpopulations

Drug Product	Approval in pediatric patients	Minimum age of approval [#]	Pregnancy category
NNRTIs:			
delavirdine (Rescriptor [®]) ¹			Category C
efavirenz (Sustiva [®]) ²	X	≥ 3 years	Category D
nevirapine (Viramune [®]) ³	X	≥ 2 months	Category C
NRTIs:			
abacavir (Ziagen [®]) ⁴	X	≥ 3 months	Category C
abacavir/lamivudine (Epzicom [®]) ⁵			Category C
abacavir/lamivudine/zidovudine (Trizivir [®]) ⁶			Category C
didanosine (Videx [®]) ⁷	X	≥ 2 weeks	Category B
didanosine enteric coated (Videx [®] EC) ⁸			Category B
emtricitabine (Emtriva [®]) ⁹			Category B
emtricitabine/tenofovir (Truvada [®]) ¹⁰			Category B
lamivudine (EpiVir [®]) ¹¹	X	≥ 3 months	Category C
lamivudine/zidovudine (Combivir [®]) ¹²			Category C
stavudine (Zerit [®]) ¹³	X	from birth	Category C
tenofovir (Viread [®]) ¹⁴			Category B
zalcitabine (Hivid [®]) ¹⁵	X	≥ 13 years	Category C
zidovudine (Retrovir [®]) ¹⁶	X	from birth (intravenous)	Category C
Protease Inhibitors (PIs):			
amprenavir (Agenerase [®]) ¹⁷	X	≥ 4 years	Category C
atazanavir (Reyataz [®]) ¹⁸			Category B
darunavir (Prezista [™]) ¹⁹			Category B
fosamprenavir (Lexiva [®]) ²⁰			Category C
indinavir (Crixivan [®]) ²¹			Category C
lopinavir/ritonavir (Kaletra [®]) ²²	X	≥ 6 months	Category C
nelfinavir (Viracept [®]) ²³	X	≥ 2 years	Category B
ritonavir (Norvir [®]) ²⁴	X	≥ 2 years	Category B
saquinavir (Invirase [®]) ²⁵			Category B
tipranavir (Aptivus [®]) ²⁶			Category C
Fusion Inhibitors:			
enfuvirtide (Fuzeon [®]) ²⁷	X	≥ 6 years	Category B
Combination NNRTIs plus NRTIs:			
efavirenz/emtricitabine/tenofovir (Atripla [™]) ²⁸			Category D

See prescribing information for pediatric dosing of individual products.

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