



Therapeutic Class ReviewSM

Antivirals (HIV) – etravirine (IntelenceTM)

April 2008

New Product for Review:

etravirine (IntelenceTM) [Tibotec]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: 3 (high quality)

- 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.
- Treatment-experienced patients have failed multiple antiretroviral (ARV) regimens and have resistance to multiple ARV classes, which limits their treatment options.
- 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.
- The goal of therapy for treatment-experienced HIV-infected patients is maximal viral suppression.
- National guidelines recommend that when switching regimens after treatment failure, at least two (preferably three) fully active ARV agents, as determined by resistance test results and prior treatment history, should be initiated.

Etravirine (Intelence):

- Etravirine (Intelence), a non-nucleoside reverse transcriptase inhibitor (NNRTI):
 - Has shown *in vitro* activity against HIV-1 strains that are resistant to conventional NNRTIs.
 - Is indicated for use in treatment-experienced HIV-infected patients who have continued viral replication with HIV-1 strains resistant to an NNRTI and other ARV agents.
 - Should be administered concomitantly with other active ARV agents.

- The virologic activity of etravirine (Intelence) in treatment-experienced HIV-infected patients may be limited by the degree of resistance to other NNRTIs.
- Etravirine (Intelence) is administered orally as two tablets (200 mg) twice per day in combination with other ARV medications (pill burden = 4 tablets per day). It should be taken after meals to improve absorption.

Evidence

- There is possibly useful evidence from two RCTs supporting the efficacy of etravirine (Intelence) in treatment-experienced HIV-infected adults.
 - Addition of etravirine (Intelence) to ritonavir-boosted darunavir (Prezista) plus a background ARV regimen resulted in an undetectable viral load (< 50 copies/ml HIV RNA) in a statistically significant proportion of patients versus ritonavir-boosted darunavir (Prezista) plus a background ARV regimen.
 - For every six patients treated, one patient achieved an undetectable viral load over 24 weeks (NNT = 6).
- There is currently no evidence comparing the efficacy of etravirine (Intelence) to other medications approved for treatment-experienced HIV-infected patients.
- Interpretation of harms information from etravirine (Intelence) clinical trials is complicated by the concomitant administration of other ARV medications because it makes it difficult to determine which adverse effects are due to etravirine (Intelence) versus the background therapies.
- The most common adverse events (AEs) reported in trials in treatment-experienced patients included rash and diarrhea. Similar AEs are also reported with other medications in the NNRTI class.
- Severe skin and hypersensitivity reactions have been reported with etravirine (Intelence) in post-marketing surveillance reports.

Decision

Etravirine (Intelence) is preferred/formulary because:

- There is reliable evidence that it helps to decrease viral load in patients with resistant strains of HIV-1 when used with other ARV agents (NNT = 6).
- There is a low risk of overuse or inappropriate use.

Products

Table 1: Antiretrovirals for treatment-experienced patients

Drug Products	FDA approval ^a	Patent Expiration(s) ^b	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
Non-nucleoside reverse transcriptase inhibitor (NNRTI) for treatment-experienced patients:					
etravirine (Intence™) [2]	1/2008	not available	Treatment-experienced HIV patients (in combination with other ARV agents) with evidence of viral replication and HIV-1 strains resistant to an NNRTI and other ARV agents.	200 mg (2 tabs) p.o. b.i.d. [with food]	
Fusion inhibitors:					
enfuvirtide (Fuzeon®) [3]	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™) [4]	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®) [5]	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. plus ritonavir 200 mg b.i.d. [with food]	
CCR5 co-receptor antagonists					
maraviroc (Selzentry™) [6]	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™) [7]	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 2/12/08.

^c As listed in © 1974 – 2008 Thomson MICROMEDEX database or as referenced.

Table 2: Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Drug Products	FDA approval ^a	Patent Expiration(s) ^b	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
delavirdine (Rescriptor®) ^[18]	4/1997	10/2013 6/2019	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®) ^[19]	9/1998	9/2014 4/2019	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®) ^[20]	6/1996	5/2012	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

^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 2/12/08.

^c As listed in © 1974 – 2008 Thomson MICROMEDEX database or as referenced.

Table 3: Pregnancy and Pediatric information

Drug Product	Approval in pediatric patients	Minimum age of approval [#]	Pregnancy category
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) for treatment-experienced patients:			
etravirine (Intelence™) ^[2]		≥ 18 years	Category B
Protease inhibitors (PIs) for treatment-experienced patients:			
tipranavir (Aptivus®) ^[5]		≥ 18 years	Category C
darunavir (Prezista™) ^[4]		≥ 18 years	Category B
Fusion inhibitors:			
enfuvirtide (Fuzeon®) ^[3]	X	≥ 6 years	Category B
CCR5 co-receptor antagonists:			
maraviroc (Selzentry™) ^[6]		≥ 16 years	Category B
Integrase strand transfer inhibitors (INSTIs):			
raltegravir (Isentress™) ^[7]		≥ 16 years	Category C

[#] see prescribing information for pediatric dosing of individual products.

References

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