



Therapeutic Class ReviewSM

GI: Chronic Hepatitis B – telbivudine (TyzekaTM)

April 2007
Confidential

New Product for Review:
telbivudine (TyzekaTM) [Idenix Pharmaceuticals]

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)

Available Therapeutic Alternatives:

Preferred/Formulary	Non-Preferred/Non-Formulary
adefovir (Hepsera [®]) [Gilead]	entecavir (Baraclude [®]) [Bristol-Myers Squibb]
lamivudine (Epivir HBV [®]) [GlaxoSmithKline]	telbivudine (Tyzeka TM) [Idenix Pharmaceuticals]
interferon alfa-2b (IntronA [®]) [Schering]	
peginterferon alfa-2a (Pegasys [®])* [Roche]	

* Covered with prior authorization

Executive Summary

- CHB is a major contributor in global rates of cirrhosis, hepatocellular carcinoma (HCC), and mortality.
- The aims of treatment are suppression of HBV replication and remission of liver disease.
- Current therapy strategies include interferon alfa and antiviral medications such as adefovir (Hepsera), entecavir (Baraclude), lamivudine (Epivir HBV), and telbivudine (Tyzeka).
- The manufacturer promotes telbivudine (Tyzeka) as:
 - An important new first-line therapy.
 - Having earlier and more profound viral suppression than lamivudine.
 - Superior to lamivudine (early viral suppression correlates with greater antiviral and clinical efficacy).
- Resistance to the antiviral medications used to treat CHB is a growing concern.
 - Hepatitis B resistance has been reported with all antivirals used to treat CHB.
 - Resistance to lamivudine (Epivir HBV) develops at a rate of approximately 20% for each year that a patient is treated.
 - Lamivudine-resistant HBV strains have a high level of cross resistance to telbivudine (Tyzeka) as well as reduced susceptibility to entecavir (Baraclude).
 - Resistance patterns vary by geographical area.

- The usefulness of telbivudine (Tyzeka) is limited by its overlapping resistance profile with other agents.
 - FDA Medical Review: the niche for telbivudine (Tyzeka) remains unclear.
- Current treatment guidelines do not recommend lamivudine (Epivir HBV) or telbivudine (Tyzeka) as first-line options because of concerns with resistance.
- Adherence to therapy is an important consideration in the treatment of CHB.
 - Up to 30% of cases of viral rebound are due to non-compliance with antiviral therapy.
- Although not yet supported by reliable clinical evidence, practice guidelines are moving toward combination therapy as a strategy for treating resistant populations.

Evidence

- Telbivudine (Tyzeka) in an HBeAg-positive population:
 - Telbivudine (Tyzeka) was superior to lamivudine (Epivir HBV) based on composite endpoint of decreased viral load and seroconversion to HBeAg-negative over the 52-week study period.
- Telbivudine (Tyzeka) in an HBeAg-negative population:
 - Telbivudine (Tyzeka) was similar to lamivudine (Epivir HBV) based on composite endpoint of decreased viral load and normalization of liver function tests over the 52-week study period.
- There is currently no evidence for telbivudine (Tyzeka) in lamivudine-resistant populations.
- There is no new evidence (since the July 2005 review) for adefovir (Hepsera) or entecavir (Baraclude) that is appraised as useful or possibly useful.
- Elevations in CK and myopathy occurred at a higher rate with telbivudine (Tyzeka) than with lamivudine (Epivir) in Phase II and Phase III trials up to 52 weeks in duration.

Considerations in subpopulations:

- *Pediatrics:* Safety and effectiveness of telbivudine in pediatric patients have not been established.
- *Geriatrics:* There were not sufficient numbers of patients 65 years of age and older enrolled in clinical trials to determine whether they respond differently than younger subjects. Because there is a greater frequency of decreased renal function in the elderly, special consideration should be taken when dosing telbivudine (Tyzeka) in this population.
- Race, ethnicity, or gender: No information provided.

Conclusions

- Telbivudine (Tyzeka) is non-preferred/non-formulary because:
 - There is no useful evidence demonstrating its superiority over Epivir HBV.
 - It is a poor choice for treatment of resistant HBV.
- Lamivudine (Epivir HBV) and adefovir (Hepsera) are preferred/formulary.
- Entecavir (Baraclude) is non-preferred/non-formulary.

Products

Drug Products	FDA approval ^a	Patent Expiration(s) ^d	FDA approved indications	Usual Dose/Route	Cost ^b	Potential Off-label Uses ^c
adefovir (Hepsera) ¹	9/2002	9/2014	Adult chronic hepatitis B with evidence of vial replication and either evidence of persistent elevations in ALT or histologically active disease (including HBeAg+, HBeAg-, lamivudine resistant strains).	10 mg orally once daily	\$669	In combination with other hepatitis B therapies.
entecavir (Baraclude) ²	3/2005	10/2010	Adult chronic hepatitis B with evidence of vial replication and either evidence of persistent elevations in ALT or histologically active disease (including HBeAg+, HBeAg-, and some limited data on lamivudine resistant strains).	0.5 mg orally once daily 1 mg orally daily in patients who do not respond to lamivudine	\$747	In combination with other hepatitis B therapies.
interferon alfa-2b (Intron A) ³	3/1997	No information available	Adult and pediatric patients who are serum HBsAg positive for at least 6 months and have evidence of HBV replication (serum HBeAg positive) with elevated serum ALT.	30 to 35 million IU per week, administered subcutaneously or intramuscularly, either as 5 million IU daily (QD) or as 10 million IU three times a week (TIW) for 16 weeks	\$2,036	In combination with other hepatitis B therapies.
lamivudine (EpiVir HBV) ⁴	12/1998	1/2014	Adult and pediatric chronic hepatitis B with evidence of vial replication and active liver inflammation.	100 mg orally once daily (children 3 mg/kg/daily)	\$267	In combination with other hepatitis B therapies.
peginterferon alfa-2a [†] (Pegasys) ⁵	10/2002	No information available	<ul style="list-style-type: none"> • Adult chronic hepatitis C. • Adult HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease and evidence of viral replication and liver inflammation. 	180 mcg subcutaneous injection once weekly x 48 weeks	\$1,988	In combination with other hepatitis B therapies.
telbivudine (Tyzeka [™]) ⁶	10/2006	10/2011	<ul style="list-style-type: none"> • Adult HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease and evidence of viral replication and liver inflammation. 	600 mg orally once daily	\$569	In combination with other hepatitis B therapies.

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

^b Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of January 2007 for 28 days of therapy.

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

^d Based on patents listed in the Orange Book as of March 2007

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