National PBM Drug Monograph

Entecavir (Baraclude®)

November 2006

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Entecavir is a guanosine nucleoside analogue that inhibits all three steps of viral replication. It is currently approved for treatment of chronic HBV in treatment naïve patients, and also those co-infected with HIV.
- The pharmacokinetics of entecavir appears to be dose proportional. It is renally eliminated so dosage must be adjusted in renal impairment. Absorption is affected by food; entecavir should be given on an empty stomach.
- In two Phase III multicenter, double-blinded, randomized clinical trials involving HBeAg positive and negative chronic hepatitis B patients, entecavir 0.5 mg daily significantly improved histologic, virologic, and biochemical response rates compared to lamivudine 100 mg daily.
- In lamivudine-refractory HBeAg-positive chronic hepatitis B patients, entecavir 1 mg daily significantly improved virologic, biochemical, and serological response rates compared to lamivudine 100 mg daily.
- To date, there has not been evidence of entecavir resistance mutations with up to 96 weeks of treatment in patients that were not resistant to lamivudine.
- The most commonly reported adverse events in clinical trials of entecavir were headache, fatigue, dizziness and nausea during clinical trials.
- The use of entecavir is associated with durability of HBeAg seroconversion of 82% after 6 months of follow up evaluation. This is in comparison to rates of 50-80% with lamivudine, 91% with adefovir and 80-90% with interferon alfa-2b.
- It appears that entecavir may be the treatment of choice for patients who require therapy for periods of longer than a year, in patients who have developed lamivudine resistance, HBeAg-negative patients with HBV DNA $\geq$2000 IU/ml ($\geq 10^4$ copies/mL) and elevated aminotransferase levels or histological disease, compensated cirrhotic patients or as first line therapy for patients who are co-infected with HIV and receiving effective treatment for HIV..

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating entecavir (Baraclude®) for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,2]

Entecavir is a guanosine nucleoside analogue. It undergoes intracellular phosphorylation to an active triphosphate form that inhibits hepatitis B virus (HBV) polymerase. The active form results in the inhibition of base priming reverse transcription and positive stranded DNA synthesis that HBV polymerase is responsible for.

Both the single and multiple dose pharmacokinetics of entecavir have been evaluated in healthy subjects and in patients with HBV. Entecavir displays dose proportional pharmacokinetics with either single or multiple dose administration. Entecavir is not a substrate or inducer of hepatic metabolism. It is predominately eliminated renally by glomerular filtration and tubular secretion.

Following oral administration, entecavir reaches peak plasma concentrations within 1.5 hours. Steady state is achieved following six to ten days of once daily dosing. The bioavailability of the oral tablet is equal to the oral solution. Food does impact the absorption characteristics of entecavir, resulting in a decrease of 44-46% in peak plasma concentrations.

The pharmacokinetics of entecavir in various stages of renal dysfunction has been evaluated. Dosage adjustment is required in patients with creatinine clearances <50 mL/min and those patients on dialysis, both continuous ambulatory peritoneal and hemodialysis. Additionally, changes in exposure to entecavir that has been demonstrated in an elderly population (increased area under the curve) are likely related to renal function. There appears to be no effect on entecavir pharmacokinetics by moderate or severe liver failure.

FDA Approved Indication(s) and Off-label Uses

Entecavir is indicated for the treatment of chronic HBV infection in adults that have evidence of active viral replication and either persistent elevations in serum aminotransferases (ALT or AST) or histologically proven active disease. This indication extends to both treatment naïve and patients who are co-infected with HBV and HIV. Additionally, entecavir has been studied in a lamivudine resistant population with favorable results.

Current VA National Formulary Alternatives[1]

Several agents can be utilized in the treatment of HBV. Current formulary alternatives include lamivudine, pegylated interferon and emtricitabine/tenofovir. Nonformulary alternatives include adefovir.

Dosage and Administration[1]

The recommended dosage in treatment naïve patients >16 years of age is 0.5 mg daily. In patients who are receiving lamivudine or are lamivudine resistant the dosage is 1.0 mg daily. Entecavir should be administered on an empty stomach.

Efficacy

In two Phase III multicenter, double-blinded, randomized clinical trials involving HBeAg positive and negative chronic hepatitis B patients, entecavir 0.5 mg daily significantly improved histologic, virologic, and biochemical response rates compared to lamivudine 100 mg daily. In HBeAg-positive chronic hepatitis B patients, serological response was similar in both treatment arms. Treatment results at week 48 are summarized in Tables 1 and 2. [4,5] In patients who achieved virologic response (HBV DNA <0.7 mEq/mL) by week 48 of treatment, continued treatment for up to 96 weeks showed greater continued virologic response with entecavir compared to lamivudine.[6,7]

Table 1. Results in Treatment Naïve, HBeAg-positive Chronic Hepatitis B Patients at Week 48[4]

Endpoints	Entecavir 0.5 mg/day (N=354)	Lamivudine 100 mg/day (N=355)	P Value
Histologic Improvement[a]	72%	62%	0.009
Virologic Response			
Undetectable HBV DNA[b]	67%	36%	<0.001
Mean HBV DNA change from baseline (log copies/mL)*	-6.9±2.0	-5.4 ±2.6	<0.001
Biochemical Response[c]	68%	60%	0.02
HBeAg Seroconversion[d]	21%	18%	0.33

Table 2. Results in Treatment Naïve, HBeAg-negative Chronic Hepatitis B Patients at Week 48[5]

Endpoints	Entecavir 0.5 mg/day (N=325)	Lamivudine 100 mg/day (N=313)	P Value
Histologic Improvement[a]	70%	61%	0.01
Virologic Response			
Undetectable HBV DNA[b]	90%	72%	<0.001
Mean HBV DNA change from baseline (log copies/mL)**	-5.0±1.7	-4.5±1.9	<0.001

Biochemical Response[c]	78%	71%	0.045

[a] Defined as ≥2 point decrease in the Knodell necroinflammatory score without concurrent worsening in the Knodell fibrosis score

[b] Undetectable serum levels of HBV DNA (LLQ <300 copies/mL; Roche COBAS Amplicor™ PCR assay, version 2.0)

[c] Normalization of ALT levels (≤1 x ULN)

[d] Defined as loss of HBeAg and appearance of anti-HBe

*340 patients in the entecavir group and 324 patients in the lamivudine group with paired baseline and week 48 HBV DNA measurements

**314 patients in the entecavir group and 295 patients in the lamivudine group with paired baseline and week 48 HBV DNA measurements

In lamivudine-refractory HBeAg-positive chronic hepatitis B patients, entecavir 1mg daily significantly improved virologic, biochemical, and serological response rates compared to lamivudine 100 mg daily. The results are summarized in Table 3.

Table 3. Results in Lamivudine-Refractory, HBeAg-positive Chronic Hepatitis B Patients at Week 96[8]

Endpoints	**Entecavir 1 mg/day (N=141)**	**Lamivudine 100 mg/day (N=145)**	**P Value**
Virologic Response[a]	30%	<1%	<0.0001
Biochemical Response[b]	85%	29%	<0.0001
HBeAg Seroconversion[c]	16%	4%	0.0011
ALT flare[d]	1%	11%	Not available

[a] Undetectable serum levels of HBV DNA (LLQ <300 copies/mL; Roche COBAS Amplicor™ PCR assay, version 2.0)

[b] Normalization of ALT levels (≤1 x ULN)

[c] Defined as loss of HBeAg and appearance of anti-HBe

[d] Defined as ALT > 2 x baseline and 10 x ULN while on treatment

Resistance

To date, there has not been evidence of entecavir resistance mutations with up to 96 weeks of treatment in patients that were not resistant to lamivudine. In lamivudine-resistant patients, genotypic mutations conferring entecavir resistance occurred in up to 16% by the end of 96 weeks of entecavir treatment. [5,7,9]

Adverse Events (Safety Data)[1]

The adverse effects of entecavir have been described in four double blind trials where patients received entecavir or lamivudine. Table 4 describes the distribution of adverse events in these groups.

Table 4: **Adverse effects of entecavir versus lamivudine**

	Nucleoside-naive		Lamivudine resistant	
	Entecavir 0.5 mg	Lamivudine 100 mg	Entecavir 1.0 mg	Lamivudine 100 mg
	N=679	N=668	N=183	N=190
Gastrointestinal				
Diarrhea	<1%	0	1%	0
Dyspepsia	<1%	<1%	1%	0
Nausea	<1%	<1%	<1%	2%
Vomiting	<1%	<1%	<1%	0
General				
Fatigue	1%	1%	3%	3%
Nervous system				
Headache	2%	2%	4%	1%
Dizziness	<1%	<1%	0	1%
Somnolence	<1%	<1%	0	0
Psychiatric				
Insomnia	<1%	<1%	0	<1%

Common Adverse Events

Patients most commonly reported headache, fatigue, dizziness and nausea during clinical trials.

Other Adverse Events

Reports of treatment emergent laboratory abnormalities have been described in trials of entecavir versus lamivudine. The most commonly reported include ALT>5.0 ULN, hematuria and lipase >2.0 ULN. In patients who were lamivudine refractory, AST >5.0 ULN were reported. The majority of these abnormalities were accompanied by a $\geq$2 $\log_{10}$/mL reduction in viral load. Additionally, the elevations over baseline for ALT resolved with continued treatment.

Nucleoside naive patients participating in a phase III clinical trials were allowed to discontinue treatment with entecavir at 52 weeks. This discontinuation was accompanied by a disease flare (defined as ALT >10 ULN and >2 X baseline) in 6% of patients who discontinued therapy.

Precautions/Contraindications

Precautions

As previously discussed in the pharmacokinetics section, entecavir dosage must be adjusted in patients with renal impairment.

Creatinine clearance (mL/min)	Usual dose (0.5 mg)	Lamivudine refractory (1 mg)
≥ 50	0.5 mg once daily	1 mg once daily
30 to <50	0.25 mg once daily	0.5 mg once daily
10 to <30	0.15 mg once daily	0.3 mg once daily
<10	0.05 mg once daily	0.1 mg once daily

Patients on hemodialysis should be dosed after dialysis

Lactic acidosis and severe hepatomegaly with steatosis has been reported with the use of nucleoside analogues alone or in combination with antiretrovirals. This is a class effect of reverse transcriptase inhibitors, no specific cases have occurred with entecavir.

Severe acute exacerbations of HBV have been reported in patients who discontinue therapy for HBV including entecavir.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name entecavir

- Severity category major

  Entacapone
- Severity category minor-moderate

  Combivir

  Abacavir

  Epivir

  Amprenavir

LA/SA for trade name Baraclude®

- Severity category minor-moderate

  Baclofen

Drug Interactions[1]

Drug-Drug Interactions

Potential for interaction of entecavir with lamivudine, adefovir and tenofovir has been evaluated in open label multidose trials conducted in healthy volunteers. No significant changes in the parameters of area under the curve or maximum/minimum plasma concentration were seen with any of the combinations.

As tubular secretion is a route for entecavir elimination, drugs which inhibit this (i.e.; probenecid) may prolong the clearance of entecavir.

Acquisition Costs

Table 5: FSS pricing for HBV treatment alternatives (pricing current as of 10-06)

Drug	Dose	Cost/Day/patient ($)	Cost/course/patient ($)
Adefovir dipivoxil*	10 mg QD	10.89	3659.04
Emtricitabine/tenofovir*	200 mg/300 mg QD	14.42	4845.12
Entecavir*	0.5 mg QD	14.11	4740.96
Entecavir*	1 mg QD	14.26	4791.36
Lamivudine#	100 mg QD	3.93	1430.52

* 48 week treatment course, # 52 week treatment course, QD daily

Pharmacoeconomic Analysis

There has been no published economic analysis for entecavir. In an analysis of lamivudine and interferon it was demonstrated that patients with chronic HBV, elevated aminotransferase levels and no cirrhosis that interferon monotherapy was most cost effective in systems with budgetary limits and a population the has a majority of HBeAg- negative patients. If adefovir or lamivudine were used it did increase the cost per QALY however for certain resistant strains it may be cost effective.

Included in the AMCP dossier for entecavir the manufacturer discusses a cost effectiveness model. This model has not been published nor was the base model available for review. In comments from the manufacturer the model was designed to compare entecavir and lamivudine therapy among HBeAg-positive patients beyond the duration of the clinical trials. The outcome of the model demonstrated that while entecavir has a higher acquisition cost, it yielded longer life expectancy and lower non treatment drug costs than therapy with lamivudine. The sensitivity analysis showed these results to be associated with higher seroconversion, treatment durability and lower resistance rates with entecavir therapy.

Conclusions

Entecavir is highly selective for HBV and inhibits each of the three steps in viral replication. In clinical trials it has demonstrated a significant benefit over lamivudine therapy for HBV. This is most strongly related to the increased development of seroconversion and low occurrence of resistance. Resistance to entecavir has not developed after 2 years of therapy in treatment naïve patients. The adverse event profile is very similar to other agents in this class and does not appear to increase risk for patients receiving therapy. Currently, there are no published trials of entecavir vs. adefovir therapy; these are still in recruitment and follow up phases. The use of entecavir is associated with durability of HBeAg seroconversion of 82% after 6 months of follow up evaluation. This is in comparison to rates of 50-80% with lamivudine, 91% with adefovir and 80-90% with interferon alfa-2b. It appears that entecavir may be the treatment of choice for patients who require therapy for periods of longer than a year, in patients who have developed

lamivudine resistance, HBeAg-negative patients with HBV DNA ≥2000 IU/ml (≥10^4 copies/mL) and elevated aminotransferase levels or histological disease, compensated cirrhotic patients or as first line therapy for patients who are co-infected with HIV.

References:

1. Bristol-Myers Squibb Company. Baraclude™ (entecavir) package insert, Princeton, NJ; March 2005.
2. Matthews SJ. Entecavir for the treatment of Chronic Hepatitis B virus infection. Clin Therapeutics 2006;28(2):184-203.
3. Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update.Clin Gastroenterol Hepatol. 2006 Aug;4(8):936-62. Epub 2006 Jul 14.
4. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et all for the BEHoLD AI463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med. 2006 Mar 9;354(10):1001-10.
5. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. for the BEHoLD AI463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med. 2006 Mar 9;354(10):1011-20. Erratum in: N Engl J Med. 2006 Apr 27;354(17):1863.
6. Gish RG, Chang TT, De Man, et al. Entecavir results in substantial virologic and biochemical improvement and HBeAg seroconversion through 96 weeks of treatment in HbeAg-positive chronic hepatitis B Patients (Study ETV-022). Program and abstracts of the 56th Annual Meeting of the American Association for the Study of Liver Diseases; November 11-15, 2005; San Francisco, California. Abstract 181.
7. Shouval D, Akarca US, Hatzis G, et al. Continued virologic and biochemical improvement through 96 weeks of entecavir treatment in HBeAg(-) chronic hepatitis B patients (study ETV-027). 41st Annual Meeting of the European Association for the Study of the Liver; April 26-30, 2006; Vienna, Austria.
8. Yurdaydin C, Sollano J, Hadziyannis S, et al. Entecavir results in continued virologic and biochemical improvement and HBeAg seroconversion through 96 weeks of treatment in lamivuidne-refractory, HBeAg(+) chronic hepatitis B patients (ETV-026). 41st Annual Meeting of the European Association for the Study of the Liver; April 26-30, 2006; Vienna, Austria.
9. Colonno RJ, Rose RE, Baldick CJ, Klesczewski K, Tenney DJ. Comprehensive resistance monitoring over two years shows no evidence of resistance emergence in entecavir treated nucleoside-naive patients and resistance emergence in lamivudine refractory patients due to the pre-existence of resistance of substitutions caused by lamivudine. 12th International Symposium on Viral Hepatitis and Liver Disease; July 1-5, 2006; Paris, France.
10. Kanwal F, Farid m, Martin P, et al. Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis. Am J Gastroenterol. 2006 Sep;101(9):2076-89.

Prepared October 2006 Contact person: Kathryn Tortorice Pharm D, BCPS, Helen Yee Pharm D, and Alex Monto M.D.