National PBM Drug Monograph

Telbivudine (Tyzeka™)

May 2007

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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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:[1-3]

- Telbivudine is a synthetic thymidine nucleoside analogue that inhibits hepatitis B virus (HBV) DNA synthesis through DNA chain termination. It is currently approved for the treatment of chronic hepatitis B in adult patients.
- In the pivotal, Phase III, randomized, double-blind clinical trial, telbivudine 600mg once daily was compared to lamivudine 100mg once daily in nucleoside-naïve, compensated, chronic hepatitis B adults who are hepatitis B envelope antigen (HBeAg)-positive or HBeAg-negative. Telbivudine was noninferior to lamivudine in achievement of the Therapeutic and Histological Response in both HBeAg subpopulations.
- Telbivudine displayed a similar safety profile to lamivudine with the exception of higher rate of elevated creatine kinase (9% vs 3%, respectively). Three telbivudine-treated patients were diagnosed with myopathy with muscular weakness, which resolved following discontinuation of telbivudine.
- Lamivudine was associated with higher rates of genotypic resistance than telbivudine. Resistance to telbivudine after 1 and 2 years therapy was 4.4% and 21.6% in HBeAg-positive and 2.7% and 8.6% in HBeAg-negative patients, respectively.
- Telbivudine-resistant HBV demonstrated in vitro cross resistance with lamivudine.
- Place in therapy: Telbivudine offers an alternative to adefovir dipivoxil, entecavir, or peginterferon alfa-2a for first-line therapy in nucleoside-naïve patients. However, telbivudine demonstrated a higher incidence of resistance than other recommended first-line oral nucleos(t)ide options (i.e. adefovir, entecavir). Due to clinical failures associated with resistance, clinicians are selecting first-line agents that minimize the development or selection of resistance. Thus, adefovir and entecavir are preferred oral agents compared to telbivudine for the treatment of chronic hepatitis B in nucleos(t)ide-naïve patients. Telbivudine as with lamivudine may have a role in certain clinical scenarios such as short-term or combination therapy.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating telbivudine 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[1]

Telbivudine is a synthetic thymidine nucleoside analogue. It undergoes intracellular phosphorylation to an active triphosphate form, telbivudine 5'-triphosphate. Through competition with the natural substrate, the active form becomes incorporated into HBV DNA, which leads to DNA chain termination and subsequent, inhibition of HBV DNA synthesis.

Pharmacokinetics[1-2]

In dose ranging studies, the pharmacokinetics of telbivudine was similar in healthy subjects and in patients with chronic hepatitis B. Pharmacokinetic studies were not specifically conducted at the 600mg dose in patients with chronic HBV; therefore, the predicted pharmacokinetic values were derived from population pharmacokinetic analysis from healthy volunteers and HBV infected patients (Refer to Table 1). Steady-state concentrations were achieved at 5 – 7 days.

The pharmacokinetics of telbivudine is dependent on renal clearance. A single-dose study conducted in subjects (non-HBV infected) with varying degree of renal dysfunction including hemodialysis demonstrated that higher plasma exposure was seen in subjects with moderate or severe renal dysfunction. Dose interval adjustments are recommended for patients with CrCL < 50 mL/min (Refer to Dose and Administration). In comparison, gender, race, and hepatic impairment did not affect the pharmacokinetic profile of telbivudine; therefore, dosing adjustment based on these variables is not needed.

Table 1. Pharmacokinetics of Telbivudine

Parameter	Telbivudine
$Cmax_{ss}$	3251 ng/mL
$Tmax_{ss}$	2.1 hours
AUC_{ss}	31679 ng/mL·hr
$T_{1/2}$	51.4 hours
Volume of distribution	8.2 L/kg
Protein Binding	3.3% to human plasma proteins
Bioavailability	≥40%.
Metabolism	Does not undergo metabolism. Not a substrate or inhibitor of CYP 450 isoenzymes.
Elimination	Primarily eliminated by urinary excretion of unchanged drug. 42% of dose eliminated renally and 50% eliminated in feces.

Microbiology[1]

Telbivudine acts as an inhibitor of HBV first and second strand synthesis (EC_{50} value = 1.3 ± 1.6µM and 0.2 ± 0.2µM, respectively). No inhibition occurred at the HBV priming reaction. Telbivudine does not display activity against HIV-1 (EC_{50} valve > 100µM). In cell-based combination studies, telbivudine did not antagonize the anti-HIV activity of nucleos(t)ide agents (i.e. abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine).

FDA Approved Indication[1]

Telbivudine is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Current VA National Formulary Alternatives

Current FDA-approved formulary alternatives for treatment of chronic hepatitis B include lamivudine, peginterferon alfa-2a, interferon alfa-2b, adefovir dipivoxil and entecavir **(**restricted to GI and ID).

Dosage and Administration[1]

The recommended dose in adults and adolescents (≥ 16 years old) for the treatment of chronic hepatitis B is 600mg orally once daily. Telbivudine may be administered without regard to food.

Hepatic Impairment: No dosage adjustments needed for patients with hepatic impairment.

Renal Impairment: Adjustments of dose interval are recommended in patients with CrCl < 50 mL/min including End-stage renal disease (ESRD) patients receiving hemodialysis. (Refer to Table 2).

Table 2. Dosage Recommendations in Renal Impairment Provided in the Package Insert

Creatinine Clearance (mL/min)	Dose of Telbivudine
≥50	600mg orally once daily
30 – 49	600mg orally every 48 hours
< 30 (excluding patients receiving dialysis)	600mg orally every 72 hours
ESRD receiving hemodialysis[a]	600mg orally every 96 hours; administer after hemodialysis

[a]Recommendations for dosage adjustment in ESRD patients receiving CAPD are not available.

Efficacy

Use for treatment of chronic hepatitis B in nucleoside-naïve patients (Week 52)[1-2,4]

The GLOBE Study (NV-02B-007) was the pivotal, Phase III trial utilized to receive the FDA-approved indication for treatment of chronic hepatitis B. The study was powered to have separate analysis for each HBeAg subpopulations. The trial has only been published as an abstract.

In this randomized, double-blind clinical trial, telbivudine 600mg once daily was compared to lamivudine 100mg once daily in nucleoside-naïve, compensated chronic hepatitis B adults who are HBeAg-positive or HBeAg-negative. Prior to randomization, subjects were stratified by HBeAg status (positive or negative) and ALT level (ALT <2.5 x ULN versus ALT ≥ 2.5 x ULN). Inclusion criteria included 1) 16-70 years old, 2) ALT ≥ (1.3 – 10) x ULN 3) Liver biopsy within 12 months prior to randomization with histology compatible with chronic hepatitis B 4) Compensated liver disease 5) Serum HBV DNA level ≥ 6 $\log_{10}$ copies/mL.

Efficacy was evaluated at 52 weeks and 104 weeks; however, data for the FDA-indication was based upon analysis done at 52 weeks (Refer to Table 3). Subjects that achieved virologic response were allowed to be discontinued from treatment (without study discontinuation).

Endpoints

- Primary efficacy endpoint:
  - Therapeutic Response: defined as loss of detectable serum HBeAg or ALT normalization AND serum HBV DNA < 10^5 copies/mL by PCR.
- Principal secondary efficacy
  - Histologic improvement on liver biopsy at 52 weeks, which was defined as at least 2-point reduction in Knodell necroinflammatory score and no worsening of fibrosis.
- Other secondary endpoints include changes in serum HBV DNA, HBeAg status, HBeAb status, ALT normalization and virologic breakthrough.

Table 3. Efficacy Results at 52 weeks (ITT Population)

	Telbivudine (n=680)	**Lamivudine** (n=687)	**p-value**

Therapeutic Response			
HBeAg-positive (n=921)	345/458 (75%)	310/463 (67%)	0.0047
HBeAg-negative (n=446)	167/222 (75%)	173/224 (77%)	0.6187
Histological Response (mITT population)			
HBeAg-positive	69%	60%	0.0105
HBeAg-negative	69%	68%	0.8994
Mean HBV DNA reduction from baseline (log_{10} copies/mL)			
HBeAg-positive	-6.4	-5.5	<0.0001
HBeAg-negative	-5.2	-4.4	<0.0001
% Subjects HBV DNA non-detectable by PCR			
HBeAg-positive	60%	40%	<0.0001
HBeAg-negative	88%	71%	<0.0001
ALT Normalization			
HBeAg-positive	77%	75%	>0.05
HBeAg-negative	74%	79%	>0.05
HBeAg Seroconversion			
HBeAg-positive	22%	21%	>0.05
HBeAg Loss			
HBeAg-positive	26%	23%	>0.05

Telbivudine was found to be noninferior to lamivudine in both HBeAg subpopulations for primary (Therapeutic Response) and main secondary (Histologic Response) endpoints. Telbivudine demonstrated significantly greater reductions in mean HBV DNA viral load at 12 weeks in HBeAg-positive and 8 weeks in HBeAg-negative patients. There was still a statistically significant greater reduction in mean HBV DNA viral load at 52 weeks in both HBeAg subpopulations. Resistance (defined as treatment emergent viral breakthrough with confirmed resistance mutations) was seen 3% in HBeAg-positive and 2% of HBeAg-negative telbivudine-treated patients while resistance occurred in 8% and 9% of lamivudine-treated patients, respectively ($p<0.05$ for both HBeAg subpopulations).

According to the FDA product review, an identified strength of the study was the large sample size, which enabled separate analyses performed for the HBeAg-positive and -negative groups. Several limitations were also identified. First, there were a low number of African/African-Americans (1.2%) enrolled in this study compared to Asians (76%) and Caucasians (15%). Thus, the FDA has requested an additional safety and efficacy study conducted in African-American and Hispanics. Secondly, patients with decompensated liver disease were excluded; therefore, the efficacy of telbivudine can not be extrapolated to patients with decompensated liver disease. A study is on-going to evaluate telbivudine in patients with decompensated liver disease. Lastly, the efficacy of telbivudine was only compared to lamivudine. Head-to-head trials comparing telbivudine to the newer agents such as adefovir and entecavir are needed. Preliminary results of a trial comparing telbivudine to adefovir are summarized below.

In conclusion, telbivudine was found to be noninferior to lamivudine in the primary and secondary endpoints. Telbivudine displayed potent and rapid antiviral activity. Genotypic resistance was seen after one year of telbivudine therapy. Lastly, the ethnicity of this study was predominately Asian; the results of this study may not be generalizable to the VA population.

Use for treatment of chronic hepatitis B in nucleoside-naïve patients (Week 104)[5]

This study is a continuation of the GLOBE study to evaluate clinical and virologic endpoints at week 104 (Refer to Table 4). Refer to the study design of the GLOBE study. Liver biopsies were not performed at week 104 (only at baseline and week 52). This trial has only been published as an abstract and data have not been submitted to the FDA for evaluation, yet.

Table 4. Efficacy Results at 104 weeks (ITT Population)

	Telbivudine (n=680)	**Lamivudine** (n=687)	**p-value**
Therapeutic Response			
HBeAg-positive	61%	47%	<0.05
HBeAg-negative	74%	62%	<0.05
Mean HBV DNA reduction (log_{10} copies/mL)			
HBeAg-positive	-5.7	-4.4	<0.05
HBeAg-negative	-5.0	-4.2	<0.05
% Subjects HBV DNA non-detectable by PCR			
HBeAg-positive	54%	38%	<0.05
HBeAg-negative	79%	53%	<0.05
ALT Normalization			
HBeAg-positive	67%	61%	>0.05
HBeAg-negative	75%	67%	>0.05
HBeAg Seroconversion			
HBeAg-positive	29%	24%	>0.05
HBeAg Loss			
HBeAg-positive	34%	29%	>0.05

Telbivudine-treated patients had a statistically significant greater therapeutic response in both HBeAg subpopulations at week 104. Similarly, a greater reduction in HBV DNA reduction viral load and percent non-detectable HBV DNA by PCR was seen in the telbivudine-receipts compared to lamivudine-receipts in both HBeAg subpopulations.

Telbivudine vs. Adefovir in HBeAg-positive Chronic Hepatitis B[6]

This has only been published in abstract form and data have not been submitted to the FDA for evaluation, yet.

This was a multi-center, open-label, randomized phase IIIb trial that evaluated the efficacy and safety telbivudine compared to adefovir for 52 weeks. Patients were randomized (1:2) to receive telbivudine 600mg daily or adefovir 10mg daily for 24 weeks. The adefovir group underwent another randomization (1:1) to either continue treatment with adefovir 10mg daily or switch to telbivudine 600mg daily for the remaining 28 weeks of the study. The primary efficacy endpoint was serum HBV DNA reduction at week 24. Secondary endpoints (non-detectable HBV DNA viral load, ALT normalization, and HBeAg loss) were evaluated at weeks 24 and 52. Based upon the study design, primary efficacy endpoint compared the efficacy of telbivudine 600mg daily to adefovir 10mg daily at 24 weeks (Refer to Table 5). In contrast, the final analysis compared telbivudine 600mg daily for 52 weeks, adefovir 10mg daily for 52 weeks, and adefovir dipivoxil 10mg/day for 24 weeks then telbivudine 600mg for 28 weeks (Refer to Table 6).

Table 5. Efficacy Results at Week 24 (ITT Population)

	HBV DNA reduction (log_{10})	HBV DNA PCR non-detectable (copies/mL)	ALT Normalization	HBeAg loss
Telbivudine (n=45)	-6.3[a]	38%[a]	59%	16%
Adefovir (n=90)	-4.9	12%	60%	11%

[a] $p<0.01$, telbivudine vs. adefovir

Table 6. Efficacy Results at Week 52 (ITT Population)

	HBV DNA reduction (log_{10})	HBV DNA PCR non-detectable (copies/mL)	ALT Normalization	HBeAg loss	HBeAg seroconversion
Telbivudine (n=45)	-6.55	58%	77%	31%	27%
Adefovir (n=44)	-5.72	39%	81%	20%	18%
Adefovir to telbivudine (n=46)	-6.44	54%	85%	26%	24%

Telbivudine treatment was associated with statistically significant greater reduction in HBV DNA and percent non-detectable HBV DNA viral load compared to adefovir at 24 weeks. The trend in results is continued at 52 weeks; these endpoints did not maintain statistical significance possibly secondary to reduced sample size and power at this study timepoint. At week 52, viral breakthrough occurred in 3 patients (2 in telbivudine arm and 1 in adefovir arm). Genotypic analysis is pending.

Combination Therapy with lamivudine and telbivudine[7]

Only trial that is currently published in peer-review literature.

This was a multi-center, double-blind, randomized phase 2b trial that evaluated the efficacy and safety of five anti-HBV regimens for 52 weeks in adults with HBeAg-positive chronic hepatitis B and compensated liver disease. Patients were randomized to one of the following daily oral regimens: telbivudine 400 mg, telbivudine 600 mg, telbivudine 400 mg plus lamivudine 100mg, telbivudine 600 mg plus lamivudine 100mg OR lamivudine 100mg. Primary efficacy endpoint was reduction in serum HBV DNA levels from baseline. Several secondary efficacy endpoints were also analyzed. Consistent with the GLOBE study, telbivudine (data combined for 600mg and 400mg treatment arms) demonstrated a statistically significant greater reduction in HBV DNA viral load compared to lamivudine (-6.01 vs -4.57 log_{10} copies/mL; $p<0.05$). However, the combination telbivudine and lamivudine do not display more potent virologic activity compared to telbivudine alone (-5.99 vs -6.01 log_{10} copies/mL; $p>0.05$). No statistical differences were noted in viral breakthrough among groups of treatment types.

Resistance[2]

In the phase III study (GLOBE), virologic failure (≥1,000 copies/mL at week 52) and virologic rebound (≥ 1 log_{10} increase of serum HBV DNA from nadir during therapy at week 52) occurred more frequently in the lamivudine- compared to telbivudine-treated patients (Table 7).

Table 7. Rates of Virologic Failure and Rebound at Week 52

	Virologic Failure	Virologic Rebound
Telbivudine		
HBeAg-positive	33.7% (145/430)	7.9% (34/430)
HBeAg-negative	8.4% (19/227)	4.9% (11/227)
Lamivudine		
HBeAg-positive	53.2% (233/438)	23.5% (233/455)
HBeAg-negative	21.5% (48/223)	16.6% (37/223)

Genotypic analysis (samples from baseline versus on-treatment) was available for 115 of the 164 telbivudine-treated patients that demonstrated virologic failure. Eighty-seven of these 115 patients were found to have amino acid substitutions in the HBV reverse transcriptase. There was an average of 3.4 ± 4.7 substitutions per person. The three most common mutations were ones that have already been associated with genotypic resistance to lamivudine (codon 80 and 204) and adefovir (codon 181). Of the 46 patients with HBV amino acid substitutions at codon 204 (encoding for rtM204), approximately 75% of these patients experienced virologic rebound.

Cross-Resistance[2]

In cell-based studies, telbivudine demonstrated cross-resistance with lamivudine or adefovir. Specifically, telbivudine lacks activity against lamivudine-resistant HBV strains harboring rtM204I mutation or rtL180M/rtM204V double mutation. In contrast, telbivudine displayed activity against lamivudine-resistant HBV strains containing the rtM204V single mutation. Telbivudine also showed reduced activity against adefovir-resistant strains containing the rtA181V mutation; however, susceptibility to telbivudine was seen with adefovir-resistant strains harboring the rtN236T.

Adverse Events (Safety Data)[1,2]

Incidence of adverse events was primarily assessed in the Globe Study. This was the Phase III, double-blind study that randomized patients with chronic hepatitis B to telbivudine 600mg once daily (n=680) or lamivudine 100mg once daily (n=687). The median duration of treatment was 60 weeks.

Deaths

There were no deaths attributed to telbivudine in the clinical trials.

Common Adverse Events

The incidence of treatment-related clinical adverse events was similar between telbivudine and lamivudine (Refer to Table 8). In respect to treatment-emergent laboratory abnormalities (Grade 3 - 4), creatine kinase (CK) elevations were more frequent in telbivudine-treated patients compared those on lamivudine (9% vs. 3%). Refer to Table 9. Overall, CK elevations (Grade 1 - 4) occurred in 72% of telbivudine-treated patients versus 42% lamivudine-treated patients ($p<0.001$). Eight percent of the telbivudine-treated patients experienced CK-related adverse event, which lead to discontinuation or interruption in 9% of these patients and eventual recovery. There were 3 telbivudine-subjects that were diagnosed with myopathy with muscular weakness, which recovered after discontinuation of the study drug. No cases of rhabdomyolysis with or without renal failure have been reported in the clinical trials. Another notable difference in treatment-emergent laboratory abnormalities is that lamivudine-treated patients experienced ALT elevations more frequently than telbivudine-treated patients. The on-treatment ALT flares were 5% in lamivudine-treated subjects compared to 3% telbivudine-treated subjects. The ALT flares occurred more common in HBeAg-positive than in HBeAg-negative patients. Overall, rates of

discontinuation due to adverse events were 0.6% (4/680) for telbivudine- and 1.0% (7/687) for lamivudine- receipts.

Table 8. Selected Treatment-Emergent Adverse Events (Grade 2 -4) Reported in the GLOBE Study

	Telbivudine 600mg (n=680)	**Lamivudine100mg (n=687)**
All subjects with any Grade 2-4 adverse events	22%	22%
General		
Fatigue/malaise	1%	1%
Pyrexia	1%	<1%
Musculoskeletal & Connective Tissue		
Arthralgia	<1%	1%
Muscle-related symptoms	2%	2%
Gastrointestinal		
Abdominal Pain	<1%	<1%
Diarrhea/loose stools	<1%	<1%
Gastritis	<1%	0
Respiratory, thoracic & mediastinal		
Cough	<1%	<1%
Nervous System		
Headache	1%	2%

Table 9. Selected Treatment-Emergent Laboratory Abnormalities (Grade 3 -4) Reported in the GLOBE Study

	Telbivudine 600mg (n=680)	**Lamivudine100mg (n=687)**
Creatine Kinase (CK) ≥ 7 x ULN	9%	3%
ALT > 10 x ULN and 2 x baseline	3%	5%
ALT > 3 x baseline	4%	8%
AST > 3 x baseline	3%	6%
Lipase > 2.5 x ULN	2%	4%
Amylase > 3 x ULN	<1%	<1%
Total bilirubin > 5 x ULN	<1%	<1%
Neutropenia (ANC ≤ 749/mm^3)	2%	2%
Thrombocytopenia (platelets ≤ 49,999/mm^3)	<1%	<1%

Contraindications/precautions[1]

Contraindications

- Known hypersensitivity to any component of the product.

Box warnings

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have 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 telbivudine.
- Severe acute exacerbations of hepatitis B have occurred in patients who discontinue therapy for HBV including telbivudine.

Warnings
- Cases of myopathy have been reported in patients receiving telbivudine.

Precautions
- Dosage adjustment is recommended in patients with renal insufficiency including patients receiving hemodialysis and CAPD.
- The use of telbivudine for the treatment of lamivudine- and/or adefovir- resistant HBV infection has not been evaluated in well-controlled studies.
- The safety and efficacy of telbivudine has not been evaluated in liver transplant recipients. Because telbivudine is primarily eliminated by renal excretion, renal function should be closely monitored in liver transplant recipients that are receiving an immunosuppressant that can affect renal function such as cyclosporine or tacrolimus.

Pregnancy/Nursing Mothers
- Pregnancy category B.
- It is not known if telbivudine is excreted in human breast milk, but it has been transferred to nursing rats.

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 trade name Tyzeka

Tarceva 100mg tablet, Tarka 1mg tablet, Taztia XT 120mg capsule, Tyzine nasal solution, Tygacil 50mg intravenous, Sustiva 600mg tablet, Teczem 180mg tablet, Tiazac 120mg capsule, Zyprexa 10mg tablet

LA/SA for generic name telbivudine

Lamivudine 150mg tablet, Zidovudine 300mg tablet, Stavudine 15, 20, 30, 40mg capsule or oral solution, Terbinafine 250mg tablet, Terbutaline 2.5mg tablet, Delavirdine 100/200mg tablet, Ticlopidine 250mg tablet, Tizanidine 2mg tablet, Tolterodine 1mg tablet, Teveten 600mg tablet, Lodine XL 600mg tablet, Ribavirin 600mg tablet

Drug-Drug Interactions[1-2]

No meaningful drug-drug interactions have been identified.
- The pharmacokinetics of telbivudine was not altered by the co-administration of lamivudine, adefovir dipivoxil, cyclosporine, or pegylated interferon-alfa 2a. Similarly, the pharmacokinetics of lamivudine, adefovir dipivoxil, or cyclosporine was not impacted by co-administration of telbivudine; the effect of telbivudine on pegylated interferon-alfa 2a could not be evaluated.

- In vitro studies have shown that telbivudine is not an inhibitor or substrate of cytochrome P450 isoenzymes (1A2, 2C9, 2C19, 2D26, 2E1, and 3A4). Telbivudine is not a substrate for P-gp and the ability to inhibit P-gp was not studied.

Acquisition Costs

The VA cost of telbivudine (one bottle of 30 tablets) is $339.90.

Table 10. Cost for anti-HBV agents

Drug	Dose	Cost Dose ($)	Cost/Year/patient ($)
Telbivudine	600mg orally once daily	$11.33	$4135.45
Lamivudine	100mg orally once daily	$4.07	$1485.55
Adefovir	10mg orally once daily	$11.09	$4047.85
Entecavir	0.5mg orally once daily	$14.45	$5274.25
Peginterferon alfa-2a	180mcg subcutaneous once weekly	$126.16	$6560.32
Interferon alfa-2a	10 million IU SQ or IM three times a week	$34.00	$5304.00

Conclusions

In the phase III trial, telbivudine was noninferior to lamivudine in achievement of Therapeutic and Histological Response in both HBeAg subpopulations. Telbivudine displayed more rapid and potent virologic activity than lamivudine. Lamivudine, at the time of study initiation, was the appropriate comparative agent; however, it is no longer considered as a first-line agent due to high rates of resistance associated with long-term therapy. The safety profile of telbivudine was similar to lamivudine with the exception of elevations of CK. Genotypic resistance was seen with lamivudine and telbivudine at one year; resistances rates continued to increase at year two. Longer follow-up studies are needed to assess the durability of telbivudine beyond two years. Although not compared in head to head trials, resistance rates seen with telbivudine are likely higher than with adefovir and entecavir. The VA cost of telbivudine is comparable to adefovir.

Recommendations

Although telbivudine displayed potent virologic activity, the data appear to suggest a higher incidence of resistance to telbivudine than other recommended first-line oral nucleos(t)ide options (i.e. adefovir, entecavir). Due to clinical failures associated with resistance, clinicians are selecting first-line agents that minimize the development or selection of resistance. Thus, adefovir and entecavir are preferred oral agents for treatment of chronic hepatitis B in nucleos(t)ide-naïve patients while telbivudine should be considered second-line oral therapy. However, telbivudine as with lamivudine may have a role in certain clinical scenarios such as short-term or combination therapy. Further studies are needed to define the role of telbivudine in combination with nucleotides or peginterferon for the treatment of chronic hepatitis B.

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