National PBM Drug Monograph

Adefovir Dipivoxil, Hepsera™

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

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Introduction

Chronic hepatitis B is one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma. The diagnosis of chronic hepatitis B virus (HBV) infection is based on serologic findings; specifically, the continued presence of HBV surface antigen (HBsAg), high levels of HBV DNA, and usually the presence of hepatitis B envelope antigen (HBeAg). HBeAg negative chronic hepatitis B, referred to as presumed precore mutant chronic hepatitis B, is common in Southern Europe and Asia.[1-3]

Treatment goals of chronic hepatitis B include sustained suppression of viral replication (characterized by a suppression of HBV DNA levels, the loss of HBeAg, and the development of antibody to HBeAg [anti-HBe]), improvement in liver histology, and preventing progression of liver disease. Long-term treatment is necessary in patients who have not lost HBeAg or seroconverted to anti-HBe. Approved chronic HBV treatments include interferon-alpha, lamivudine, and adefovir dipivoxil. However, interferon-alpha is poorly tolerated and has limited efficacy in many subpopulations. Although lamivudine has improved efficacy compared to interferon-alpha in patients with chronic HBV, lamivudine has developed emerging resistance.[4-9] Adefovir dipivoxil respresents a new therapeutic agent that appears be well tolerated with little evidence of resistance to date.

Pharmacology/Pharmacokinetics[10-12]

Adefovir dipivoxil is an oral prodrug of adefovir, an acyclic nucleotide analogue with activity against hepadnaviruses, retroviruses, and herpes viruses. The active intracellular metabolite of adefovir, adefovir diphosphate, selectively inhibits HBV DNA polymerases (reverse transcriptases) through competitive inhibition and chain-termination of HBV replication.

Orally administered adefovir dipivoxil undergoes rapid enzymatic hydrolysis, yielding adefovir during the absorption process in the gastrointestinal tract. The oral bioavailability of a 10 mg dose of adefovir dipivoxil is 59%; plasma concentrations are unaffected when taken with food. The pharmacokinetics of adefovir dipivoxil after single and multiple oral administrations are similar in patients with chronic hepatitis B and healthy subjects.

Adefovir is primarily eliminated as unchanged drug by tubular secretion and glomerular filtration. The elimination half-life of adefovir is 6 to 7 hours and 12 to 36 hours for adefovir diphosphate, which allows for once daily dosing. The elimination half-life is significantly reduced in patients with moderate and severe renal impairment (CLcr <50 mL/min or patients with end stage renal disease (ESRD) requiring hemodialysis), and dose interval modifications are necessary in these populations. Dose adjustments are not necessary in patients with hepatic impairment.

There appears to be no substantial differences in the pharmacokinetics of adefovir with regards to age, body weight, sex, or race. However, pharmacokinetic data is not available or limited in the pediatric population, pregnant women or geriatric patients.

FDA Approved Indication(s)

Adefovir dipivoxil has been approved for the treatment of chronic hepatitis B in adults who have compensated liver function with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease. In addition, adefovir dipivoxil is approved for use

in adults who have clinical evidence of lamivudine-resistant hepatitis B with or without compensated liver function.

Current VA National Formulary Status

Currently available and approved products for chronic hepatitis B treatment include interferon-alpha and lamivudine.

Dosage and Administration[11, 12]

The optimal dose of adefovir dipivoxil is 10 mg daily. The dosing interval of adefovir dipivoxil should be adjusted to once every 48 hours in patients with moderate renal impairment (CLcr <50 mL/min) and once every 72 hours in severe renal impairment (CLcr <20 mL/min). In patients with ESRD (CLcr <10 mL/min), adefovir dipivoxil should be administered once weekly following completion of hemodialysis.

Renal functions should be monitored routinely for all patients while on treatment, especially in patients with pre-existing or other risks of renal impairment. The dose of the agent should be adjusted accordingly for renal function.

The optimal duration of treatment is still unknown, and is currently being evaluated in clinical studies.

Adverse Effects (Safety Data)[11, 12]

Pooled adverse effects between adefovir dipivoxil 10 mg are similar to placebo for up to 96 weeks of treatment. The most common adverse events with the use of adefovir dipivoxil include headache, pharyngitis, asthenia, abdominal pain, and flu-like symptoms; these effects occurred in up to 13% of patients. None of these events led to treatment discontinuation.

In chronic hepatitis B patients with adequate renal function, 4% of patients treated with adefovir dipivoxil 10 mg daily had an increase of ≥0.3 mg/dL in serum creatinine from baseline compared to 2% in the placebo group during 48 weeks of treatment. In follow-up of up to 96 weeks, 10% and 2% of patients treated with adefovir dipivoxil had an increase of ≥0.3 mg/dL and ≥0.5 mg/dL from baseline, respectively. Resolution occurred despite continuation of the agent in 69% of cases, 28% remained unchanged, and 5% required discontinuation of the agent. The incidence of nephrotoxicity increases with higher doses, underlying renal dysfunction at baseline, or when there are other risk factors for renal dysfunction during treatment.

Table 1. Adverse Events Reported in Clinical Trials of Adefovir Dipivoxil Compared to Placebo

Adverse Events	Adefovir dipivoxil 10 mg (n = 294)	Placebo (n = 228)
Asthenia	13%	14%
Headache	9%	10%
Abdominal pain	9%	11%
Nausea	5%	8%
Flatulence	4%	4%
Diarrhea	3%	4%
Dyspepsia	3%	2%

Precautions/Contraindications[11]

Although adefovir dipivoxil has limited activity against HIV, administration of the agent in chronic hepatitis B patients with unrecognized or untreated HIV infection may result in emergence of HIV resistance. Thus, patients should be offered HIV antibody testing prior to initiating adefovir dipivoxil.

In patients who do not achieve HBeAg seroconversion, hepatitis may be exacerbated after discontinuation of adefovir dipivoxil. In clinical trials, this occurred in up to 25% of patients resulting in serum alanine aminotransaminase (ALT) elevations (≥10 times the upper limits of normal) and increases in HBV DNA levels but was not associated with hepatic decompensation. Therefore, hepatic functions should be monitored closely after stopping treatment.

Severe lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals. Most cases have occurred in women and in some cases, have resulted in fatalities. Obesity and prolonged nucleoside analog exposure may be risk factors. Adefovir dipivoxil should be discontinued immediately in any patient that develops clinical signs or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

The risk of nephrotoxicity may be increased in patients with underlying renal dysfunction and in patients taking concomitant nephrotoxic agents (i.e. cyclosporine, tacrolimus, aminoglycosides, vancomycin, and non-steroidal anti-inflammatory agents). Renal function should be monitored while on treatment and the dose of the adefovir dipivoxil should be adjusted accordingly.

The agent is contraindicated in patients with hypersensitivity to any product component. Adefovir dipivoxil is a pregnancy category C agent and should be used only if benefits outweigh the risks.

Drug Interactions

Adefovir is not a substrate or inhibitor of human cytochrome P450 enzymes. There appears to be no significant drug-drug interactions between concomitant adefovir dipivoxil administration with lamivudine, acetaminophen, or trimethoprim/sulfamethoxazole in healthy volunteers; coadministration with ibuprofen (800 mg three times daily) resulted in 33% higher plasma concentrations of adefovir, which appears related to increased oral bioavailability of adefovir.[11, 13]

There appears to be no drug-drug interactions with concomitant administration of adefovir dipivoxil with ritonavir or nelfinavir. However, adefovir dipivoxil may decrease serum concentrations of delaviridine and saquinavir. Increased plasma concentrations of didanosine occurred with concurrent adefovir dipivoxil administration; this did not correlate with an increased risk of didanosine-related adverse events at adefovir dipivoxil doses of 60 mg or 120 mg daily.[data on file, Gilead Sciences]

Clinical Trials[11, 14-16]

<table>
<tr><td>Citation</td><td>Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):808-16.</td></tr>
<tr><td>Study Goals</td><td>To determine the efficacy and safety of adefovir dipivoxil compared to placebo</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Phase III multicenter, multinational clinical trial
➢ Randomized (1:1:1)
➢ Double-blinded
➢ Placebo-controlled
➢ Treatment with either adefovir dipivoxil 30 mg daily, adefovir dipivoxil 10 mg daily, or placebo
➢ Primary efficacy endpoint was histological improvement at week 48 of treatment compared to baseline using the Knodell Histologic Activity Index (HAI) score
➢ Secondary efficacy endpoints at week 48 included suppression of HBV replication, biochemical response, HBeAg seroconversion, and safety data
➢ 96 week treatment duration
• Data Analysis
➢ Intention to treat (ITT)
➢ Cochran-Mantel-Haenszel
➢ Two sided significance at alpha=0.05 for pair wise comparisons</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Documented HBsAg positive ≥6 months
➢ HBeAg positive
➢ HBV DNA levels ≥10^6 copies/mL
➢ Elevated ALT (≥1.2 to 10 times the upper limits of normal)
➢ Compensated liver disease
➢ Adequate renal function (serum creatinine ≤1.5 mg/dL)
➢ HIV, HCV, and HDV seronegative
➢ Liver biopsy at baseline

• Exclusion criteria
➢ Previous treatment with interferon or >12 weeks of lamivudine, <6 months prior to enrollment
➢ Treatment with hepatotoxic drugs and nephrotoxic drugs or competitors of renal excretion within 2 month prior to enrollment</td></tr>
<tr><td>Results</td><td>Primary Efficacy Analysis at Week 48
<table>
<tr><th></th><th>N</th><th>Improvement in HAI score[1]</th><th>No Improvement</th><th>Missing/ Unassessable Data</th></tr>
<tr><td>Adefovir dipivoxil 30 mg/day</td><td>165</td><td>59%*</td><td>NA</td><td>NA</td></tr>
<tr><td>Adefovir dipivoxil 10 mg/day</td><td>168</td><td>53%*</td><td>37%</td><td>10%</td></tr>
<tr><td>Placebo</td><td>161</td><td>25%</td><td>67%</td><td>7%</td></tr>
</table>
[1] Defined as ≥2 point decrease in the Knodell necroinflammatory score without concurrent worsening in the Knodell fibrosis score
NA – Not available
*p <0.001 compared to placebo</td></tr>
</table>

Secondary Efficacy Analysis at Week 48

	N	Virologic Response[1]	Biochemical Response[2]	HBeAg Seroconversion[3]
Adefovir dipivoxil 30 mg/day	173	39%[#]	55% (93/169)[#]	14%*
Adefovir dipivoxil 10 mg/day	171	21%[#]	48% (81/168)[#]	12%**
Placebo	167	0%	16% (26/164)	6%

[1] Undetectable serum levels of HBV DNA (<400 copies/mL, Roche Amplicor™ PCR assay)
[2] Normalization of ALT levels
[3] Defined as loss of HBeAg and appearance of anti-HBe

*p<0.05 compared to placebo, **p<0.01 compared to placebo,
[#]p<0.001 compared to placebo

Safety
Adefovir dipivoxil 30 mg daily was associated with the emergence of mild nephrotoxicity in 9% of patients; this did not occur in patients receiving adefovir dipivoxil 10 mg daily or in the placebo group.

Conclusions

Chronic hepatitis B patients treated with adefovir dipivoxil had greater histological improvement and higher virologic, biochemical, and serological response rates compared to placebo. Adefovir dipivoxil 10 mg daily had similar efficacy to 30 mg daily but with less adverse effects and was not associated with nephrotoxicity. There was no evidence of adefovir resistance mutations with up to 48 weeks of treatment.

Critique

Strengths
- Well designed, comprehensive multinational study including Asian, European, and North American sites
- Defined primary and secondary endpoints
- Biopsies were blinded and reviewed by the same histopathologist
- Tested for HBV mutations associated with adefovir resistance

Limitations
- Funded by Gilead Sciences, Inc.
- Enrolled relatively low numbers of African-Americans
- Data on longer term efficacy and safety are pending

Citation

Hadziyannis S, Tassopoulos N, Heathcote J, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):800-7.

Study Goals

To determine the efficacy and safety of adefovir dipivoxil compared to placebo

Methods

- **Study Design**
  - Phase III multicenter, multinational clinical trial
  - Randomized
  - Double-blinded
  - Placebo-controlled
  - Treatment with adefovir dipivoxil 10 mg daily or placebo
  - Primary efficacy endpoint was histological improvement at week 48 of treatment compared to baseline using the Knodell Histologic Activity Index (HAI) score

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Secondary efficacy endpoints at week 48 included suppression of HBV replication, biochemical response, and safety data
96 week treatment duration

• Data Analysis

Intention to treat (ITT)
Cochran-Mantel-Haenszel
Two sided significance at alpha=0.05 for pair wise comparisons

</td></tr>
<tr><td>Criteria</td><td>
• Inclusion criteria

Documented HBsAg positive ≥6 months
HBeAg negative
Anti-HBe positive
HBV DNA levels $\geq 10^5$ copies/mL
Elevated ALT (≥1.5 to 15 times the upper limits of normal)
Compensated liver disease
Adequate renal function (serum creatinine ≤1.5 mg/dL)
HIV, HCV, and HDV seronegative
Liver biopsy at baseline

• Exclusion criteria

Previous treatment with interferon or >12 weeks of lamivudine, <6 months prior to enrollment
Treatment with hepatotoxic drugs and nephrotoxic drugs or competitors of renal excretion within 2 month prior to enrollment

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<tr><td>Results</td><td>
Primary Efficacy Analysis at Week 48
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<tr><th></th><th>N</th><th>Improvement in HAI Score[1]</th><th>No Improvement</th><th>Missing/ Unassessable Data</th></tr>
<tr><td>Adefovir dipivoxil 10 mg/day</td><td>121</td><td>64%*</td><td>29%</td><td>7%</td></tr>
<tr><td>Placebo</td><td>57</td><td>35%</td><td>63%</td><td>2%</td></tr>
</table>
[1] Defined as ≥2 point decrease in the Knodell necroinflammatory score without concurrent worsening in the Knodell fibrosis score
*p <0.001

Secondary Efficacy Analysis at Week 48
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<tr><th></th><th>N</th><th>Virologic Response[1]</th><th>Biochemical Response[2]</th></tr>
<tr><td>Adefovir dipivoxil 10 mg/day</td><td>123</td><td>51%*</td><td>72%</td></tr>
<tr><td>Placebo</td><td>61</td><td>0%</td><td>29%</td></tr>
</table>
[1] Undetectable serum levels of HBV DNA (<400 copies/mL, Roche Amplicor™ PCR assay)
[2] Normalization of ALT levels
*p<0.001
</td></tr>
<tr><td>Conclusions</td><td>Adefovir dipivoxil 10 mg daily had greater histological improvement, and higher virologic and biochemical response rates compared to placebo in chronic hepatitis B patients who were HBeAg negative. Adefovir dipivoxil was generally well tolerated and side effects were comparable to placebo. There was no evidence of adefovir resistance mutations with up to</td></tr>
</table>

	48 weeks of treatment.
Critique	**Strengths** • Well designed, comprehensive multinational study including Asian, European, and North American sites • Defined primary and secondary endpoints • Biopsies were blinded and reviewed by the same histopathologist • Tested for HBV mutations associated with adefovir resistance **Limitations** • Funded by Gilead Sciences, Inc. • Enrolled relatively low numbers of African-Americans • Longer term efficacy and safety are pending

Citation	**Peters M, Hann HW, Martin P, et al. Adefovir Dipivoxil Alone and in Combination with Lamivudine Suppresses YMDD Mutant Hepatitis B Virus Replication: 48 Week Preliminary Analysis [abstract]. Annual Meeting of the American Association for the Study of Liver Diseases, November 2002.**
Study Goals	To evaluate the safety and efficacy of adefovir dipivoxil alone and in combination with lamivudine compared to continued lamivudine for the treatment of lamivudine-resistant chronic hepatitis B
Methods	• **Study Design** ➢ Multicenter, multinational clinical trial ➢ Randomized (1:1:1) ➢ Double-blinded ➢ Active-controlled ➢ Treatment with adefovir dipivoxil 10 mg monotherapy or in combination with lamivudine 100 mg daily, or lamivudine 100 mg daily ➢ Primary and secondary efficacy endpoint was decrease in HBV DNA compared to baseline at week 16 and week 48 of treatment, respectively ➢ Additional endpoints at week 48 include biochemical response, HBeAg seroconversion, and safety data ➢ 48 week treatment duration • **Data Analysis** ➢ Wilcoxon Rank Sum Test
Criteria	• **Inclusion criteria** ➢ Chronic hepatitis B ➢ HBsAg positive ➢ HBeAg positive ➢ HBV DNA levels $\geq 10^6$ copies/mL ➢ ALT (≥1.2 times the upper limits of normal) ➢ Compensated liver disease ➢ Confirmed HBV YMDD polymerase mutation • **Exclusion criteria** ➢ Not stated

Results

Primary Efficacy Analysis

	N	16 Week Mean Change in Serum HBV DNA log_{10} copies/ml	48 Week Mean Change in Serum HBV DNA log_{10} copies/ml
Adefovir dipivoxil (10 mg/day)	19	-2.45*	-3.06*
Adefovir dipivoxil (10 mg/day) plus Lamivudine (100 mg/day)	20	-2.45*	-2.93*
Lamivudine (100 mg/day)	19	-0.07	-0.05

p<0.001 compared to lamivudine monotherapy

Secondary Efficacy Analysis

	N	Biochemical Response[2]	HBeAg Seroconversion[3]
Adefovir dipivoxil (10 mg/day)	19	47%*	11%
Adefovir dipivoxil (10 mg/day) plus Lamivudine (100 mg/day)	20	53%*	6%
Lamivudine (100 mg/day)	19	5%	0%

[1] Normalization of ALT levels
[2] Defined as loss of HBeAg and appearance of anti-HBe
p<0.005 compared to lamivudine monotherapy

Conclusions

Adefovir dipivoxil 10 mg daily or in combination with lamivudine 100 mg daily resulted in significant reductions in serum HBV DNA, and improved biochemical and serological response rates compared to lamivudine monotherapy in lamivudine-resistant chronic hepatitis B patients. There appears to be no discernable antiviral effect with lamivudine monotherapy in these patients. Patients did not appear to have additional benefit from continued lamivudine use in combination with adefovir dipivoxil.

Critique

Strengths

- Multinational study including European and North American sites
- Used active-control group
- Defined primary and secondary endpoints

Limitations

- Funded by Gilead Sciences, Inc.
- Data in abstract form; preliminary analysis
- Exclusion criteria not specified
- Small sample size
- No African-Americans enrolled
- Longer term efficacy data needed

Acquisition Costs

Generic	trade_name	va_price	valpkg	va_ppu
INTERFERON ALFA-2B,RECOMBINANT 10MILLION UNT/0.2ML INJ,PEN,1.5ML	INTRON A 10MIL UNT/0.2ML INJ PEN 1.5ML	$423.95	1	$423.95
INTERFERON ALFA-2B,RECOMBINANT 10 MILLION UNT/VIL INJ	INTRON A 10 MIL UNT/VIL INJ	$67.48	1	$67.48
INTERFERON ALFA-2B,RECOMBINANT 5MILLION UNT/0.2ML INJ,PEN,1.5ML	INTRON A 5MIL UNT/0.2ML INJ PEN 1.5ML	$220.03	1	$33.74
LAMIVUDINE 100MG TAB	EPIVIR 100MG TAB	$176.82	60	$2.95
ADEFOVIR DIPIVOXIL 10MG TAB	HEPSERA 10MG TAB	$329.35	30	$10.98

Cost Analysis

	Cost per week	Cost per year
Treatment		
Interferon alfa-2b 10 MU, 3 times weekly	$202.44 to $211.98	$10,526.88 to $11,022.70
Interferon alfa-2b 5 MU daily	$236.18	$12,281.36
Lamivudine 100 mg daily	$20.65	$1,078.80
Adefovir dipivoxil 10 mg daily	$76.86	$3,996.72

Conclusions

Adefovir dipivoxil 10 mg daily significantly improved histologic, virologic, biochemical, and serological response rates in HBeAg positive and negative chronic hepatitis B patients compared to placebo. Adefovir dipivoxil appears to have improved efficacy compared to interferon alpha and similar efficacy to lamivudine; however, direct comparative clinical studies are needed. In lamivudine-resistant chronic hepatitis B patients, adefovir dipivoxil reduced viral loads, and improved biochemical and serological response rates compared to lamivudine monotherapy. To date, there appears to be little evidence of adefovir resistance mutations with up to 48 weeks of treatment. Adefovir dipivoxil 10 mg daily appears to be well tolerated, and adverse effects are similar to placebo. The optimal treatment duration still needs to be determined. Long term efficacy and safety data are needed in treatment naïve and lamivudine-resistant patients.

Recommendations

Adefovir dipivoxil has proven efficacy and safety with up to 48 weeks and 96 weeks of treatment in patients with chronic hepatitis B, respectively. Adefovir dipivoxil provides an effective alternative in the treatment of chronic hepatitis B patients who are lamivudine-resistant. Adefovir dipivoxil should have usage criteria developed, which will define specific populations and outcomes for its use.

References:

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13. Kearney B, Knight W, Currie G, et al. Drug-drug interaction study between adefovir dipivoxil and lamivudine, paracetamol, ibuprofen, and trimethoprim/sulfamethoxazole [abstract]. Annual Meeting of The European Association for the Study of the Liver, April 2002.
14. Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):808-16.
15. Hadziyannis S, Tassopoulos N, Heathcote J, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):800-7.
16. Peters M, Hann HW, Martin P, et al. Adefovir dipivoxil alone and in combination with lamivudine suppresses YMDD mutant hepatitis B virus replication: 48 week preliminary analysis [abstract]. Annual Meeting of the American Association for the Study of Liver Diseases, November 2002.

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