

**National PBM Drug Monograph Addendum
Adefovir Dipivoxil (Hepsera®)
May 2007**

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

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<http://vaww.pbm.va.gov/drugmonograph/adefovirmonographs.pdf>

Introduction¹⁻²

High rates of resistance to lamivudine coupled with recent FDA-approval of several anti-HBV agents have led to changes in treatment recommendations for chronic hepatitis B. Currently, adefovir dipivoxil, entecavir, or peginterferon alfa-2a is recommended as first-line therapy for the treatment of chronic hepatitis B in nucleos(t)ide naïve patients. Furthermore, the management of antiviral resistant HBV particularly lamivudine resistant isolates is becoming more frequently encountered in clinical practice.

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 (restricted to GI and ID) and entecavir (restricted to GI and ID).

Efficacy and Safety associated with Long-term Adefovir Therapy

HBeAg-negative chronic hepatitis B³⁻⁵

This is an extension of the pivotal, Phase III trial (Study 438) utilized to receive the FDA-approved indication for treatment of chronic hepatitis B in HBeAg-negative adults. Refer to original monograph for study design and patient demographics. Briefly, patients with HBeAg-negative chronic hepatitis were randomized to receive adefovir dipivoxil 10mg daily or placebo for 48 weeks (primary efficacy analysis occurred at week 48 for study 438). At week 49, the adefovir dipivoxil treatment arm underwent another randomization to receive either adefovir dipivoxil or placebo for another 47 weeks while the original placebo treatment arm was switched to adefovir dipivoxil. At week 96, 125 of the 139 patients assigned to receive adefovir dipivoxil from weeks 49 to 95 continued in the open-label extension study to evaluate long-term safety and efficacy up to study week 240. In comparison, patients receiving placebo from weeks 49 – 95 were entered in another study although data regarding resistance and hepatocellular carcinoma from these patients were included in these results.

Efficacy endpoints:

- HBV DNA <1000 copies/mL
- Normalization of ALT levels
- HBsAg seroconversion
- Histologic improvement

Of the 125 patients enrolled in the open-label extension trial, 70 patients received adefovir dipivoxil for up to 240 weeks while the remaining 55 patients received study drug up to 192 weeks (these patients received placebo up to week 48). The percent of patients with HBV DNA <1000 copies/mL and normalization of ALT levels decreased over 48 – 240 weeks (Refer to Table 1). However, the authors state that the proportion of patients is similar across the study period when the analysis accounted for patients who dropped out for reasons other than resistance or hepatocellular carcinoma. Five patients underwent HBsAg seroconversion during the study. Long-term adefovir dipivoxil therapy was associated

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with histological improvement (Refer to Table 2). Genotypic resistance (A181V, N236T) was detected in 29% of the patients by 240 weeks (Table 3).

Table 1. Efficacy Results (ITT Population)

	48 weeks	96 weeks	144 weeks	192 weeks	240 weeks
HBV DNA <1000 copies/mL	71%	71%	73%	62%	53%
Normalization of ALT levels	75%	65%	68%	63%	59%

Table 2. Histologic Improvement by Ranked Assessment

Response	Patients randomized to adefovir up to 48 weeks (liver biopsy at 48 Weeks; n=112)	Patients in placebo treatment arm, then randomized to adefovir with subsequent open-label adefovir (liver biopsy at 192 weeks; n=22)	Patients in adefovir arm, then randomized to continue adefovir with subsequent open-label adefovir (liver biopsy at 240 weeks; n=24)
Improvement in necroinflammation	80%	86%	83%
Improvement in fibrosis	48%	73%	75%

Table 3. Resistance throughout 240 weeks

	48 weeks	96 weeks	144 weeks	192 weeks	240 weeks
Mutation ^a	0%	3%	11%	18%	29%

^a Presence of N236T or A181V

Among the 125 patients participating in the open-label extension trial, none of the serious adverse events were considered to be related to study drug. Two patients discontinued adefovir dipivoxil due to adverse events; one patient experienced rise in serum creatinine while the other had an elevation in ALT. Four patients experienced a rise in serum creatinine ≥ 0.5 mg/dL from baseline (maximum value = 1.5mg/dL; maximum increase = 0.8mg/dL). There were 6 of the 183 adefovir dipivoxil-treated patients that developed hepatocellular carcinoma during the study period.

In conclusion, this study provides long-term efficacy and safety of adefovir dipivoxil in small cohort of patients with HBeAg-negative chronic hepatitis B. At 5 years, a high percent of patients maintained virologic, biochemical, and histological efficacy; however, adefovir mutations were seen in 29% of patients at year 5. In addition, adefovir dipivoxil was generally well-tolerated during long-term therapy with only two discontinuations related to study drug.

HBeAg-positive chronic hepatitis B⁶⁻⁸

This is an extension of the pivotal, Phase III trial (Study 437) utilized to receive the FDA-approved indication for treatment of chronic hepatitis B in HBeAg-positive adults. Limited data are available as only published in abstract. Refer to original monograph for study design and patient demographics. Patients assigned to the adefovir dipivoxil 10mg once daily treatment arm for first 48 weeks were eligible to participate in this open-label extension study to assess long-term safety and efficacy up to 240 weeks if he/she did not seroconvert in years 1 and 2. After completing 48 weeks, the adefovir dipivoxil 10mg once daily arm was randomized to receive adefovir dipivoxil 10mg once daily (n=85) or placebo (n=71). However, there was a “misallocation” of study medication; 91% of patients received at least one incorrect dose of placebo or adefovir dipivoxil in the beginning year 2. At 96 weeks, enrollment for open-label adefovir dipivoxil was available for patients who did not undergo HBeAg seroconversion.

Efficacy endpoints:

- HBeAg seroconversion
- Histologic improvement

Sixty-five patients were included in the extension study. Demographics include median age of 34 years old, 83% male, race (74% Asian, 23% Caucasian), median HBV DNA of 8.45 log₁₀ copies/mL, and median ALT of 2 X ULN. Adefovir dipivoxil therapy was associated with increasing rates of HBeAg seroconversion from 14% to 48% at 48 and 240 weeks, respectively (Refer to Table 4). Improvement in necroinflammation and fibrosis occurred in 67% and 60% of adefovir dipivoxil-treated patients, respectively (Table 5).

Table 4. HBeAg Seroconversion

	48 weeks	96 weeks	144 weeks	240 weeks
HBeAg seroconversion	14%	33%	46%	48%

Table 5. Histologic Improvement by Ranked Assessment

Response	Patients receiving adefovir with liver biopsy at baseline and week 48 (n=150)	Patients receiving adefovir with liver biopsy at baseline and week 240 (n=15)
Improvement in necroinflammation	71%	67%
Improvement in fibrosis	41%	60%

Of the 65 patients enrolled in the extension study, 59% experienced a rebound in HBV DNA or did not achieve suppression of HBV DNA levels by 240 weeks. Genotypic resistance (A181V, N236T) was detected in 20% of patients by 240 weeks.

In respect to safety, adefovir dipivoxil was well-tolerated with no serious adverse events reported. Six patients receiving long-term adefovir dipivoxil had a serum creatinine increase of ≥ 0.5 mg/dL from baseline, which led to the discontinuation of adefovir dipivoxil in 2 of these patients.

In conclusion, this extension study provides efficacy and safety data in a small number of patients receiving adefovir dipivoxil therapy for up to five years; however, the misallocation of study medication from year 1 to 2 limits the internal validity of this study. By year 5, 48% of patients underwent HBeAg seroconversion; however, adefovir resistance was detected in 20% of patients.

Effectiveness of Adefovir dipivoxil in Lamivudine-Refractory Patients

*Wait-listed and post-liver transplantation patients*⁹⁻¹⁰

This is an open-label, compassionate use study for the treatment of adefovir dipivoxil in lamivudine-resistant chronic hepatitis B in wait-listed and post-liver transplantation patients. The efficacy and safety of administering adefovir dipivoxil was evaluated in this population. Inclusion criteria included 1) detectable serum HBV DNA while receiving lamivudine therapy 2) pre- or post- liver transplantation 3) ALT ≥ 1.2 X ULN 4) PT ≤ 3 seconds above normal range 5) serum creatinine < 1.5 mg/dL 6) serum phosphorus ≥ 2.0 mg/dL 7) no history of variceal bleeding or hepatic encephalopathy. Patients were able to receive concurrent administration of hepatitis B immune globulin and/or lamivudine.

Efficacy endpoints:

- Primary:
 - Time-weighted average change in serum HBV DNA (log₁₀ copies/mL) from baseline up to week 24.
- Secondary (Weeks 24, 48, 96, and 144):
 - Change in serum HBV DNA from baseline

- Serum HBV DNA (<1,000 copies/mL)
- HBeAg loss or seroconversion
- Change in ALT from baseline
- Normalization of ALT levels
- Changes in Child-Pugh-Turcotte score compared to baseline
- Normalization of albumin, bilirubin, and prothrombin time

A total of 467 patients were enrolled in the study. All patients were assessed for safety (226 wait-listed and 241 post-transplantation). In comparison, 384 patients (176 wait-listed and 208 post-transplantation) were evaluated for efficacy due to the requirement of baseline and subsequent on-therapy HBV DNA viral load. The wait-listed patients were further sub-grouped to “on-study transplantation” for evaluation of safety (n=61) and efficacy (n=57); these patients were previously part of the wait-listed group and then underwent liver transplantation. Efficacy endpoints for the on-study transplantation were included with the wait-listed patients up to the time the patient underwent liver transplantation. Demographics were reported for wait-listed, post-transplantation, and on-study transplantation. In general, demographics were similar among groups with the following exceptions 1) on-study transplant group had lower serum baseline HBV DNA and serum ALT levels 2) post-transplantation had more patients with lower Child-Turcotte-Pugh scores. Almost all of the patients (462/467) received lamivudine along with adefovir dipivoxil; however, the specific details (e.g., duration of lamivudine therapy) are unknown. The investigators documented lamivudine start date on all patients with stop dates recorded on an unspecified subset.

Efficacy endpoints were evaluated for up to 96 weeks in wait-listed and for up to 144 weeks in post-liver transplantation patients (Refer to Table 6). In the both cohorts, patients experienced improvement in virologic, biochemical and histological response rates. The wait-listed patients experienced an average change in HBV DNA of $-3.5 \log_{10}$ copies/mL at 96 weeks, while the post-liver transplantation patients had a larger reduction in HBV DNA of $-4.5 \log_{10}$ copies/mL at 96 weeks. Both groups had 65% of patients with undetectable HBV DNA levels (<1000 copies/mL) at 96 weeks; this percent increased to 78% in the post-liver transplantation patients at 144 weeks. Normalization of ALT levels was seen in 77% of wait-listed patients at 96 weeks and 58% of post-liver transplantation patients at 144 weeks. Although the number of patients with liver biopsies at baseline and post-therapy were low, improvements in the median Child-Pugh-Turcotte scores were documented in these patients. For the patients that underwent “on-study transplantation”, no recurrences of HBsAg or serum HBV DNA have been confirmed (defined as two consecutive positive tests). In addition to adefovir dipivoxil and lamivudine therapy, 34 of the 57 patients received concomitant administration of hepatitis B immune globulin. Longer follow-up is needed in this subpopulation as the median time post-transplant was only 36 months.

Table 6. Efficacy Results

	Wait-Listed ^a			Post-liver transplantation			
	Week 24	Week 48	Week 96	Week 24	Week 48	Week 96	Week 144
<i>Primary Endpoint</i> Time-weighted average change in serum HBV DNA (log ₁₀ copies/mL) from baseline [Mean (±SD)]	-2.7 (1.3) n=176 p<0.001	–	–	-2.9 (1.3) n=208 p<0.001	–	–	–
Change in serum HBV DNA from baseline (log ₁₀ copies/mL) [Mean (±SD)]	–	-3.5 (1.6) n=83 p<0.001	-3.5 (1.7) n=22 p<0.001	–	-4.0 (1.6) n=164 p<0.001	-4.5 (1.5) n=96 p<0.001	-4.6 (1.5) n=46 p<0.001
Serum HBV DNA <1,000 copies/mL	–	59% (45/76)	65% (13/20)	–	40% (64/159)	65% (61/94)	78% (35/45)
HBeAg loss	–	48% (15/31)	88% (7/8)	–	31% (30/98)	58% (29/50)	–
HBeAg seroconversion	–	23% (7/31)	38% (3/8)	–	11% (11/98)	34% (17/50)	–
Change in ALT from baseline (IU/L) [Mean (±SD)]	–	-145.2 (227.2) n=75	-103.3 (156.0) N=13	–	-81.1 (156.7) n=137	-72.5 (149.4) n=84	-65.4 (223.4) n=33
Normalization of ALT levels (if >ULN at baseline)	–	77% (49/64)	77% (10/13)	–	51% (56/110)	70% (46/66)	58% (15/26)
Changes in Child-Pugh-Turcotte score from baseline [Median]	–	-2 n=32 p<0.001	-2 n=5 p=0.063	–	-3 n=20 p<0.001	-3 n=11 p=0.001	-3 n=7 p=0.031
Normalization of albumin	–	76% (28/37)	–	–	81% (21/26)	–	–
Normalization of bilirubin	–	60% (28/47)	–	–	76% (29/38)	–	–
Normalization of PT	–	84% (26/31)	–	–	56% (5/9)	–	–

^a Includes wait-listed patients who never underwent and those who underwent a liver transplantation up to the time of transplantation.

Genotypic analysis was performed on samples with HBV DNA >1000 copies/mL at weeks 48, 96, and 144 to detect adefovir mutations. Adefovir mutation, rtN236T, was only detected in two patients at 96 weeks. (Refer to Table 7). Similarly, resistance mutation (rtN236T) was detected in 2 of 8 patients at week 90 and 128 that experienced virologic rebound (defined as HBV DNA > 1 log₁₀ copies/mL from nadir measurement). All four of the patients harboring the rtN236T mutation experienced ALT elevations and virologic rebound.

Table 7. Resistance throughout 144 weeks

	48 weeks (n=96)	96 weeks (n=114)	144 weeks (n=47)
Adefovir resistance	0%	2%	2%

Safety of adefovir dipivoxil was assessed in three populations: on-study transplantation (n=61), wait-listed (n=226), and post-transplantation (n=241). As expected, all post-transplantation patients were receiving nephrotoxic immunosuppressants. High rate of treatment-related adverse events were noted in the post-transplantation (46%) compared to on-study transplantation (15%) and wait-listed (19%). Overall, discontinuation of adefovir dipivoxil secondary to adverse events occurred in 4% of patients, which all appeared to be related to renal adverse events. Approximately half (10/19) of the discontinuations secondary to renal adverse events experienced hepatorenal syndrome or multiorgan failure. Overall, an increase in serum creatinine (≥ 0.5 mg/dL) was detected in 27 (47%) of on-study transplantation, 11 (6%) of wait-listed, and 43 (21%) of post-liver transplant patients. There were 67 deaths reported during the study period; most of the deaths were secondary to complications seen in end-stage liver disease or post liver transplantation. The investigators deemed 3 deaths possibly related to study medication.

In conclusion, adefovir dipivoxil (\pm lamivudine and/or hepatitis B immune globulin) was shown to be effective and safe in wait-listed or post-transplantation patients with lamivudine-resistant HBV.

Adefovir dipivoxil (\pm lamivudine) for treatment of lamivudine-resistant chronic hepatitis B¹¹

This international, multi-center study randomized patients with lamivudine-resistant chronic hepatitis B to one of the following treatment arms for 48 weeks: 1) adefovir dipivoxil 10mg and placebo once daily 2) lamivudine 100mg and placebo once daily 3) adefovir dipivoxil 10mg and lamivudine 100mg once daily. Inclusion criteria included the following: 1) 16 – 65 years old 2) compensated chronic hepatitis B 3) ALT level = 1.2 - 10 X ULN 4) currently receiving lamivudine therapy for minimum of 6 months 5) YMDD mutant HBV 6) serum HBV DNA level ≥ 6 log₁₀ copies/mL.

Efficacy endpoints:

- Primary:
 - Time-weighted average change in serum HBV DNA (log₁₀ copies/mL) from baseline up to week 16.
- Secondary:
 - Time-weighted average change in serum HBV DNA (log₁₀ copies/mL) from baseline up to week 48.
 - Change in serum HBV DNA from baseline
 - Normalization of ALT levels
 - HBeAg loss
 - HBeAg seroconversion
 - Loss of HBsAg

A total of 59 patients were enrolled in the study. Patient demographics include median age of 45 years old, 79% males, race (60% Caucasian, Asian 36%), 97% HBeAg positive, median HBV DNA of 8.12 log₁₀ copies/mL, and median serum ALT of 79 IU/L.

Compared to the group that received lamivudine monotherapy, the adefovir dipivoxil containing regimens (monotherapy or in combination with lamivudine) demonstrated statistically significant improvement in HBV DNA from baseline to week 16 and week 48 as well as improvement in the secondary virologic and biochemical endpoints (Refer to Table 8).

Table 8. Efficacy Results

	Lamivudine (n=19)		Adefovir ^a (n=19)		Adefovir + lamivudine ^a (n=20)	
	Week 16	Week 48	Week 16	Week 48	Week 16	Week 48
<i>Primary Endpoint</i> Time-weighted avg. change in serum HBV DNA (log ₁₀ copies/mL) from baseline [Mean (±SD)]	-0.00 (0.34)	-0.10 (0.39)	-2.66 (0.80) p<0.001	-3.38 (1.05) p<0.001	-2.50 (0.54) p<0.001	-3.09 (0.67) p<0.001
Change in serum HBV DNA from baseline (log ₁₀ copies/mL) [Mean (±SD)]	0.00 (0.28)	-0.31 (0.93)	-3.11 (0.94) p<0.001	-4.00 (1.41) p<0.001	-2.95 (0.64) p<0.001	-3.46 (1.10) P<0.001
Serum HBV DNA <1,000 copies/mL	NR	0%	NR	26% p=0.018	NR	35% p=0.005
HBeAg loss	NR	0%	NR	16% p=0.075	NR	17% p=0.067
HBeAg seroconversion	NR	0%	NR	11% p=0.152	NR	6% p=0.304
Change in ALT from baseline (IU/L) [Mean (±SD)]	NR	0.0 (30.8) 95% CI: -4.2, 14.2	NR	-87.7 (121.7) 95% CI: -143.9,-31.5	NR	-48.6 (82) 95% CI: -84.5, -12.6
Normalization of ALT levels (if >ULN at baseline)	NR	5%	NR	47% p=0.004	NR	53% p=0.001

^ap-values are compared to lamivudine monotherapy.
NR=not reported

Adverse events were described as “all grades at any time during the study”, which led to high percentage of patients experiencing any adverse event (100% in lamivudine arm vs 95% in adefovir dipivoxil vs 90% in adefovir dipivoxil + lamivudine). However, none of the adverse events led to discontinuation of study treatment. Of the 5 serious adverse events reported, the investigators did not consider these related to study medications. Seven patients in the adefovir dipivoxil arm experienced Grade 3 ALT elevations (Table 9), which occurred within 12 weeks of adefovir dipivoxil therapy with the exception of one patient. Five patients had resolution of ALT elevations at week 48 while the remaining two patients experienced reductions in the Grade severity. Of the 3 lamivudine-treated patients with Grade 4 ALT elevations, a reduction occurred to Grade 2 at week 48.

Table 9. Laboratory Abnormalities (maximum postbaseline measurement)

	Lamivudine (n=19)	Adefovir dipivoxil (n=19)	Adefovir dipivoxil + lamivudine (n=20)
ALT elevation			
Grade 3	0 (0%)	7 (37%)	1 (5%)
Grade 4	3 (16%)	0 (0%)	1 (5%)
AST elevation			
Grade 3	1 (5%)	1 (5%)	0 (0%)
Grade 4	2 (11%)	0 (0%)	0 (0%)
Amylase			
Grade 3	3 (16%)	0 (0%)	2 (10%)
Grade 4	0 (0%)	0 (0%)	0 (0%)
Increase in Scr \geq 0.5mg/dL above baseline	0 (0%)	0 (0%)	0 (0%)
Serum phosphorus level <1.5mg/dL	0 (0%)	0 (0%)	0 (0%)

In conclusion, adefovir dipivoxil monotherapy or in combination with lamivudine demonstrated virologic and biochemical effectiveness in patients with lamivudine-resistant, compensated chronic hepatitis B. The authors noted that more patients in the adefovir dipivoxil monotherapy arm experienced an ALT elevation compared to the combination of adefovir dipivoxil and lamivudine or lamivudine monotherapy arm. These ALT elevations (5-10 times ULN) were not associated with elevations in HBV DNA level or hepatic decompensation. It is hypothesized that adefovir dipivoxil monotherapy may cause a re-emergence of wild-type HBV while adding adefovir dipivoxil to on-going lamivudine therapy may provide protection against this transformation. Due to the potential of ALT flares leading to more severe consequences in patients with advanced stage liver disease (i.e., cirrhosis, decompensated liver disease), combination therapy may be more appropriate for this population.

Adefovir and lamivudine combination therapy compared to adefovir monotherapy in lamivudine resistant patients with HBeAg-negative chronic hepatitis B¹²

This multicenter study conducted in Italy evaluated the long-term efficacy and safety of adefovir and lamivudine combination therapy compared to adefovir monotherapy in lamivudine resistant patients with HBeAg-negative chronic hepatitis B. Limited data are available as only published in abstract. Study design included both retrospective and prospective evaluation of a cohort of 588 patients enrolled in an expanded access program. The efficacy endpoints were the following: 1) HBV-DNA undetectable ($<3 \log_{10}$ copies/mL) 2) virologic breakthrough ($>1 \log_{10}$ HBV DNA) 3) adefovir resistance (presence of mutations and virologic breakthrough) 4) ALT normalization. Safety endpoint was serum creatinine increase >0.5 mg/mL from baseline. No statistical significant differences were noted in virological and biochemical responses in the combination versus the monotherapy treatment groups. However, virologic breakthrough [67/273 (24%) vs 13/264 (5%); $p<0.001$] and adefovir resistance [29/273 (11%) vs 0/264 (0%); $p<0.001$] occurred more frequently in adefovir monotherapy compared to combination therapy. As a result, the combination group maintained higher rate of virological response over 3 years compared to adefovir monotherapy (74% vs 59%, $p<0.001$). Overall, serum creatinine elevations were noted in 8% of patients; no differences were noted between treatment groups. The authors conclude that adding adefovir to on-going lamivudine therapy rather than switching to adefovir monotherapy may reduce emergence of adefovir mutations.

*Adefovir dipivoxil and lamivudine for treatment of lamivudine-resistant chronic hepatitis B in patients with compensated or decompensated liver disease*¹³

This study evaluated the efficacy and safety of adding adefovir dipivoxil to on-going lamivudine therapy in patients with chronic hepatitis B harboring the YMDD mutation. Patients were divided into two groups. Group A consisted of patients with compensated, HBeAg-positive hepatitis B; these patients were randomized to receive adefovir dipivoxil 10mg once daily or placebo for 52 weeks along with on-going lamivudine. In comparison, Group B had decompensated or recurrent hepatitis B after liver transplantation; these patients were enrolled in open-label adefovir dipivoxil 10mg once daily for 52 weeks along with on-going lamivudine. Other inclusion criteria included the following: 1) ≥ 18 years old 2) ALT level $>1.2 \times \text{ULN}$ 3) currently receiving lamivudine therapy for minimum of 6 months 4) YMDD mutant HBV 5) serum HBV DNA level $\geq 10^6$ copies/mL.

Efficacy endpoints:

- Primary:
 - HBV DNA response (defined as percent of patients with HBV DNA $\leq 10^5$ copies/mL or $\geq 2 \log_{10}$ reduction from baseline at week 48 or 52 if baseline HBV DNA $> 10^5$ copies/mL).
- Secondary:
 - Assessed for Group A and B
 - Change in serum HBV DNA from baseline
 - Serum HBV DNA (<200 copies/mL)
 - HBeAg loss
 - Normalization of ALT levels
 - Patients with YMDD mutant HBV DNA
 - Assessed only for Group B
 - Histological changes
 - Disease progression (defined as spontaneous bacterial peritonitis, bleeding gastric/esophageal varices or hepatocellular carcinoma during treatment)

A total of 40 patients were enrolled in the study. Patient demographics include median age of 53 years old, 88% males, 68% HBeAg positive, median HBV DNA level of $8.61 \log_{10}$ copies/mL and mean serum ALT of 127 IU/L.

In Group A, patients who received adefovir dipivoxil with lamivudine had significantly higher HBV DNA response compared to patients that received lamivudine monotherapy. Secondary virologic and biochemical endpoints were also significantly better in the group that received adefovir dipivoxil (Refer to Table 10). In Group B, these non-randomized patients experienced high HBV DNA response rates as well (Table 10). Group B patients who did not receive a liver transplant prior to study entry also experienced an improvement in the median Child-Pugh-Turcotte score of -1.0; however, disease progression occurred in one patient in Group B (variceal hemorrhage).

Table 10. Efficacy Results at week 48 and 52

	Group A ^a		Group B
	Lamivudine + Placebo (n=48)	Lamivudine + Adefovir dipivoxil (n=46)	Lamivudine + Adefovir dipivoxil (n=40)
Primary Endpoint HBV DNA response	5/46 (11%)	39/46 (85%) p≤0.01	36/39 (92%)
Change in serum HBV DNA from baseline (log ₁₀ copies/mL) [Median]	+0.3	-4.6 p≤0.01	-4.6
Serum HBV DNA <1,000 copies/mL	0/48 (0%)	9/46 (20%) p≤0.01	NR
HBsAg loss	1/42 (2%)	6/40 (15%)	8/27 (30%)
Normalization of ALT levels (if >ULN at baseline)	3/47 (6%)	14/46 (30%) p=0.002	20/38 (53%)
Presence of mutation	44/46 (96%)	26/42 (62%)	21/37 (57%)

^ap-values are compared to lamivudine monotherapy.

Adverse events (defined as at least one adverse event) were high among patients enrolled in this study. In Group A, adverse events were similar between patients enrolled in lamivudine-placebo arm compared to those in lamivudine-adefovur dipivoxil arm (83% vs 82%). In comparison, Group B patients experienced a higher rate of adverse events (95%). One patient in Group B died secondary to respiratory failure. No serious adverse events were considered to be related to study medications. No elevations of serum creatinine were reported in this study.

In conclusion, chronic hepatitis B patients with lamivudine resistance demonstrated virologic and biochemical improvement with the addition of adefovir dipivoxil to on-going lamivudine therapy. This was seen in patients with compensated or decompensated liver disease.

Safety and efficacy of adefovir dipivoxil in patients infected with lamivudine-resistant hepatitis B and HIV-1¹⁴⁻¹⁷

This prospective, open-label study evaluated the safety and efficacy of adefovir dipivoxil in patients with lamivudine-resistant hepatitis B and HIV. Adefovir dipivoxil 10mg once daily was added to on-going antiretroviral therapy, which included lamivudine 150mg twice daily. Inclusion criteria included the following: 1) HIV-1 and HBV co-infection 2) currently receiving lamivudine therapy for minimum of 6 months 4) YMDD mutant HBV 5) detectable serum HBV DNA level 6) normal renal function.

Efficacy endpoints:

- Change in serum HBV DNA from baseline
- Change in ALT
- Change in HIV RNA
- Change in CD4⁺

A total of 35 patients were enrolled in the study. Patient demographics include mean age of 41 years old, 97% males, median serum ALT of 81 IU/L, median HBV DNA of 9.76 log₁₀ copies/mL, mean HIV RNA of 2.89 log₁₀ copies/mL, and mean CD4⁺ cell count of 422.8 cells/mm³.

Improvements in virologic and biochemical endpoints for HBV continued throughout the 144 weeks (Table 11). In comparison, HIV RNA levels did not statistically change throughout the 144 weeks while CD4⁺ count trended upwards (Table 11).

Table 11. Efficacy Endpoints

	48 weeks	96 weeks	144 weeks
Change in serum HBV DNA from baseline [Mean (±SD)]	-4.65 (1.43)	-5.63 (1.65)	-6.04 (1.88)
	P<0.001	p<0.001	p<0.001
Change in ALT [Mean (±SD)]	-26.58 (-79.53)	-43.73 (79.34)	-49.00 (89.18)
	95%CI(-55.75, 2.59)	95%CI(-73.36,-14.11)	95%CI(-83.81,-14.19)
Change in HIV RNA [Mean (±SD)]	0.21 (0.62)	0.04 (0.71)	0.05 (0.79)
	p=0.13	p=0.64	p=0.79
Change in CD4 ⁺ [Mean (±SD)]	49.06 (138.06)	58.14 (138.28)	61.00 (155.46)
	P=0.111	p=0.034	p=0.05

Genotypic analysis was performed on samples with HBV DNA > 3 log₁₀ copies/mL at weeks 48, 96, and 144 to detect adefovir mutations. Investigators did not detect adefovir mutations (N236T or A181V) in the analyzed samples. Similarly, genotypic analysis was performed on HIV RNA. Four patients were identified to acquire HIV resistance during concomitant adefovir dipivoxil and antiretroviral therapy; however, none of mutations appear to be associated with HIV resistance seen with adefovir dipivoxil.

The addition of adefovir dipivoxil to antiretroviral therapy in patients with co-infection of HIV and HBV was well-tolerated during the 144 week study. Investigators did not deem any of the serious adverse events related to adefovir dipivoxil therapy. An increase in serum creatinine (≥ 0.5 mg/dL) was detected in two patients. Both patients experienced resolution of elevated creatinine, which occurred after discontinuation of study drug in one patient.

In conclusion, the addition of adefovir dipivoxil to patient's on-going antiretroviral therapy (including lamivudine) resulted in statistically significant change in serum HBV DNA from baseline at 48, 96, and 144 weeks (p<0.001 for each time period). Adefovir mutations were not detected in HBV DNA or HIV RNA. Significant limitations of this study include the open-label, non-randomized study design, short duration and small sample size. Importantly, adefovir dipivoxil should not be used to treat HBV in a HIV-infected patient who is not receiving antiretroviral therapy. Even though adefovir dipivoxil is not reported to display activity against HIV (at the approved dosage of 10mg once daily), the structural similarities between tenofovir and adefovir raise theoretical concerns that adefovir dipivoxil may select out for HIV mutations. Because tenofovir displays potent in vitro activity against HIV and lamivudine-resistant HBV, many consider tenofovir fumarate as the preferred nucleotide analog to administer in co-infected HIV and HBV patients on antiretroviral therapy. Of note, tenofovir fumarate is currently not FDA-approved for treatment of chronic hepatitis B and still undergoing Phase III trials.

Acquisition Costs

The VA cost of adefovir dipivoxil (one bottle of 30 tablets) is \$332.70

Table 12. 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 dipivoxil	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^{1-3, 6, 15-17}

Adefovir dipivoxil is considered a first-line treatment option for chronic hepatitis B in nucleos(t)ide-naïve and in lamivudine-resistant patients. Long-term studies with adefovir-treated patients have shown sustained virologic, biochemical and histological responses over 4 to 5 years in those who did not develop adefovir-resistance mutations. Although lower than lamivudine, adefovir resistance rates have been reported up to 20-29% at 5 years; clinical failure with adefovir has been associated in patients harboring the rtN236T or A181V mutation. Due to adefovir's activity against lamivudine-resistant HBV, adefovir dipivoxil has a major role in the treatment of lamivudine experienced patients. Adefovir dipivoxil may either be added to on-going lamivudine therapy or switched from lamivudine to adefovir dipivoxil in patients with lamivudine-resistant HBV. Experts suggest that combination of lamivudine and adefovir dipivoxil may be preferred therapy for lamivudine-resistant patients with advanced liver disease to reduce the potential development of adefovir resistance. Similarly, adefovir dipivoxil with or without lamivudine is also recommended for the treatment for entecavir- or telbivudine-resistant HBV. Because tenofovir fumarate displays potent activity against HBV and HIV, tenofovir fumarate rather than adefovir dipivoxil is often utilized in patients co-infected with hepatitis B and HIV on antiretroviral therapy. Tenofovir fumarate is currently not FDA-approved for treatment of chronic hepatitis B; however, Phase III comparative trials of tenofovir fumarate and adefovir dipivoxil are on-going. Treatment recommendations for the chronic hepatitis B will continue to evolve over the next several years with the potential FDA-approval of other anti-HBV agents, completion of head-to-head trials of newer anti-HBV agents and further evaluation of the role of combination therapy.

Recommendations

Adefovir dipivoxil is currently utilized as a first-line agent for the treatment of chronic hepatitis B in nucleos(t)ide-naïve patients as well as management of antiviral resistant HBV. Adefovir dipivoxil does not appear to display cross-resistance to lamivudine-, entecavir-, or telbivudine-resistant HBV. Similar to other oral nucleos(t)ide agents, long-term adefovir dipivoxil therapy was also associated with increasing resistance over time. Future studies are needed to define the role of combination therapy for the treatment of chronic hepatitis B; this may reduce the incidence of resistance seen with the oral agents.

References:

1. Lok AS, McMahon BJ. AASLD Practice Guidelines. Chronic Hepatitis B. *Hepatology*. 2007 Jan 26;45(2):507-539 [Epub ahead of print]
2. 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;4:936-62.
3. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;131:1743-1751.
4. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med*. 2003 Feb 27;348:800-7.
5. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Adefovir Dipivoxil 438 Study Group. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2005 Jun 30;352:2673-81.
6. Marcellin P, Chang TT, Lim SG, et al. Long-term efficacy and safety of adefovir dipivoxil for the treatment of HBeAg-positive chronic hepatitis B (CHB) patients in Study GS-98-437. Poster presented at: 67th Annual Meeting of the American Association for the Study of Liver Disease; October 27-31, 2006, Boston, MA.
7. 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;348:808-16.
8. Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation. *Health Technol Assess*. 2006 Aug;10:1-183.
9. Schiff ER, Lai CL, Hadziyannis S et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. *Hepatology* 2003;38:1419-27.
10. Schiff ER, Lai CL, Hadziyannis S et al. Adefovir dipivoxil for wait-listed and post-liver transplantation patients with lamivudine-resistant hepatitis B: final long-term results. *Liver transpl* 2007;13:349-360.
11. Peters MG, Hann HW, Martin P, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology*. 2004;126:91-101.
12. Lampertico P, Marzono A, Levero M, et al. Adefovir and lamivudine combination therapy is superior to adefovir monotherapy for lamivudine resistant patients with HbeAg-negative chronic hepatitis B. Paper presented at: 56th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); October 27-31, 2006; Boston, MA.
13. Perillo R, Hann HW, Mutimer D, et al. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology*. 2004;126:81-90.

14. Benhamou Y, Thibault V, Vig P. Safety and efficacy of adefovir dipivoxil in patients infected with lamivudine-resistant hepatitis B and HIV-1. *Journal of Hept.* 2006;62-67.
15. Hepsera[®] (Adefovir dipivoxil) package insert, Gilead Sciences, Inc. October 2006
16. Peters MG, Anderson J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology* 2006;44:1110-1116.
17. Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services. October 10, 2006; 1-113. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf>. Accessed (April 2007)

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