Generic (Trade Name): Adefovir dipivoxil (Hepsera™)

Manufacturer: Gilead Sciences, Inc.

Indication: For the treatment of adults showing evidence of active hepatitis B viral replication and either persistent elevations in serum aminotransferases (alanine aminotransferase (ALT) or aspartate aminotransferase) or histologically active disease.¹

Current Regulatory Status: Adefovir dipivoxil received marketing approval from the Food and Drug Administration (FDA) for the above indication in September 2002.² In March 2003, all 15 member states of the European Union approved its use in adults with compensated liver disease, evidence of active viral replication, persistently elevated serum ALT levels and histological evidence of active liver inflammation fibrosis or decompensated liver disease. Regulatory filings have also been made in Australia, Switzerland, Turkey and Canada.³

Description: It is thought that adefovir dipivoxil reduces viral load by inhibiting an enzyme responsible for viral replication—nucleotide reverse transcriptase. Adefovir dipivoxil is metabolized to adefovir, which by itself has limited oral bioavailability. After oral administration, adefovir peak levels are achieved in 30 minutes to four hours, while its mean terminal elimination half-life is approximately 7.5 hours. Its approved dosage is 10 mg daily. The optimal treatment duration is unknown. Adefovir is mainly renally excreted via glomerular filtration and active tubular secretion, so dosage adjustments are required in the presence of renal impairment. Adefovir is not a known inhibitor or a substrate of common cytochrome p450 enzymes; its ability to induce enzymes has not been elucidated.¹

Current Treatment: Interferon alfa (Intron® A, Schering; Roferon®-A, Roche) and lamivudine (Heptovir®, - GSK) have been used to decrease viral levels and abnormal liver enzymes in individuals with active chronic hepatitis B infection.⁶ These responses are seldom sustained after treatment is ended. There is evidence to suggest that interferon can reduce the incidence of hepatocellular carcinoma.⁷ Monotherapy is generally recommended, although the effects of polytherapy are being investigated. Other unapproved drugs or strategies under investigation include famciclovir, entecavir, emtricitabine and pretreatment with glucocorticosteroids.⁸ Guidance papers can assist in the selection and optimization of therapy.⁹¹²
Emerging Drug List
ADEFOVIR DIPIVOXIL FOR HEPATITIS B VIRUS INFECTION

**Cost:**
In the US, a month of therapy with Hepsera™ costs US$440 (wholesaler acquisition cost for 30 tablets).²

**Evidence:**

**Adefovir dipivoxil in addition to or versus standard therapy:** In a 48-week study, individuals with evidence of active lamivudine-resistant hepatitis B viral replication (HbeAg positive), compensated liver disease and adequate renal function (n=59) were randomized to receive adefovir 10 mg, adefovir 10 mg with lamivudine, or continued lamivudine therapy as a control. The effect of treatment on liver histology or fibrosis was not reported. The mean decrease in serum hepatitis B virus (HBV) DNA (±standard deviation) at 16 weeks was 3.11±0.94, 2.95±0.64 and 0.00±0.28 log₁₀ copies/mL in the adefovir, combination and lamivudine groups respectively.¹

Adefovir 10 mg daily for 48 weeks was added to existing anti-HIV therapy, including lamivudine 150 mg twice daily, in a cohort of 35 hepatitis B (HbsAg) positive individuals (five with cirrhosis) infected with HIV. Reductions in histology-fibrosis scores were observed in a subset of 14 patients who underwent liver biopsies. Further reductions in HBV DNA concentrations were detectable in 31 assessable patients, with two patients exhibiting HbeAg seroconversion. The markers for HIV disease were not significantly changed.¹³

**Adefovir dipivoxil versus placebo:** The descriptions of two randomized trials focusing on individuals with compensated liver disease and adequate renal function have been published.¹⁴,¹⁵ Hadziyannis *et al.* randomized individuals with detectable chronic HBV infection and without evidence of hepatitis B viral replication (HbeAg negative) to either adefovir 10 mg daily (n=123) or placebo (n=67). At 48 weeks, an improved histologic response was more frequently reported in the adefovir arms (absolute difference 30.3%, 95% CI: 15.4 to 45.2).

Marcellin *et al.* randomized patients with detectable HbeAg and chronic HBV infection to receive placebo (n=170), adefovir 10 mg (n=172) or adefovir 30 mg (n=173). Histologic improvement was noted in 53%, 59% and 25% of patients who received adefovir 10 mg, 30 mg and placebo respectively (P<0.001 active versus placebo). Viral resistance was not detected during these trials.

Limited data are available on the off-label use of adefovir by patients with decompensated liver disease.¹⁶,¹⁷ The results of phase I and II trials, open-label trials and resistance surveillance have also been published.¹³,¹⁶-²²
**Emerging Drug List**

**ADEFOVIR DIPIVOXIL FOR HEPATITIS B VIRUS INFECTION**

**Adverse Effects:**
Adefovir seems to have a negligible effect on 48-week mortality and serious morbidity, as indicated by the occurrence of death and serious or severe adverse events in placebo-controlled trials. Adefovir can cause laboratory abnormalities that require medical attention.

Nephrotoxicity, as seen in dose-dependent increases in serum creatinine and decreases in serum phosphorous, is a recognized limitation of adefovir. In individuals who entered randomized placebo-controlled trials with adequate renal function, the incidence of treatment-emergent nephrotoxicity was 4% after 48 weeks. With a longer duration of treatment, the cumulative risk reached 10% by 96 weeks in a Kaplan-Meier analysis. In a cohort of patients awaiting liver transplantation and who had varying degrees of renal function, treatment-emergent nephrotoxicity occurred at a higher frequency. During earlier investigations of adefovir 60 mg to 120 mg, nephrotoxicity also occurred in individuals with HIV. As a result, the manufacturer suggests that renal function be assessed during adefovir treatment, particularly in those patients at risk for or with kidney disease.

Acute exacerbations of hepatitis, as shown by an increase in enzyme markers of liver damage after drug discontinuation, occurred in a significant proportion (>50%) of participants in placebo-controlled trials. As a result, it is recommended that hepatic function be monitored after the cessation of treatment.

The pooled placebo-controlled studies indicate that asthenia, headache, abdominal pain, nausea, flatulence, diarrhea and dyspepsia were reported in 3% or more of patients, paralleling the rate reported in the placebo group.

**Commentary:**
There are no long-term trials comparing adefovir with current therapies from which to make a decision regarding its use. Short-term comparative trials describing surrogate endpoint responses and treatment-emergent morbidity in treatment-naive patients are also lacking. The evidence on surrogate endpoint responses in patients with documented lamivudine resistance is noteworthy. A lack of detected viral resistance is also worth mention, although this resistance may become inevitable. Differences in treatment-emergent morbidity between lamivudine and adefovir recipients have not been described. They would help define the role of adefovir. In particular, its potential nephrotoxicity during treatment and hepatotoxicity upon cessation need to be weighed against any therapeutic advantages.

**References:**
Emerging Drug List

**ADEFOVIR DIPIVOXIL FOR HEPATITIS B VIRUS INFECTION**


