

Adefovir Dipivoxil (Hepsera™) Criteria for Use

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

These criteria were developed using the best clinical evidence currently available. The following recommendations are dynamic and will be revised as new clinical information becomes available. These guidelines are intended to assist practitioners in providing consistent, high quality cost-effective care. These guidelines are not intended to interfere with clinical judgment; the clinician should ultimately tailor treatment based on patient specifics.

1. Adefovir dipivoxil was approved in September 2002 for the treatment of chronic hepatitis B in adults with compensated liver function, and in adults who have clinical evidence of lamivudine-resistant hepatitis B with or without compensated liver function.

Criteria for VA Use

- Patients with chronic hepatitis B (HBsAg positive) with evidence of viral replication (detectable HBV DNA) and either evidence of persistent elevations in serum aminotransferases or histological disease
- AND
- Patients with clinical evidence of lamivudine-resistant chronic hepatitis B, defined as $\geq 1 \log_{10}$ increase in HBV DNA over the nadir HBV DNA while on lamivudine
- AND
- Patients who are not allergic to any product component

2. **Summary of Efficacy Trials**

- In two Phase III double-blinded, randomized, placebo-controlled clinical trials involving HBeAg positive and negative chronic hepatitis B patients, adefovir dipivoxil 10 mg daily significantly improved histologic, virologic, biochemical, and serological response rates for up to 48 weeks of treatment.

	Adefovir dipivoxil 10 mg/day	Placebo
Histologic Improvement¹	53-64%*	25-35%
Virologic Response²	21-51%*	0%
Biochemical Response³	48-72%*	16-29%
HBeAg Seroconversion⁴	12%**	6%

¹ Defined as ≥ 2 point decrease in the Knodell necroinflammatory score without concurrent worsening in the Knodell fibrosis score

² Undetectable serum levels of HBV DNA (<400 copies/mL, Roche Amplicor™ PCR assay)

³ Normalization of ALT levels

⁴ Defined as loss of HBeAg and appearance of anti-HBe

*p < 0.001 compared to placebo, **p < 0.01 compared to placebo

- In a double-blinded, randomized, active-controlled clinical trial involving lamivudine-resistant chronic hepatitis B patients, adefovir dipivoxil 10 mg daily for 48 weeks reduced viral loads, and improved biochemical and serological response rates compared to lamivudine monotherapy. There appeared to be no additional benefit from continued lamivudine use in combination with adefovir dipivoxil.
- To date, there appears to be little evidence of adefovir resistance mutations with up to 48 weeks of treatment.

3. **Safety Issues**

Pooled adverse effects between adefovir dipivoxil 10 mg daily and placebo are similar 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.

Patients should be offered HIV antibody testing prior to initiating adefovir dipivoxil to prevent emergence of HIV resistance in unrecognized or untreated HIV infection.

In chronic hepatitis B patients with adequate renal function, 10% and 2% of patients treated with adefovir dipivoxil 10 mg daily for up to 96 weeks had an increase in serum creatinine 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 underlying renal dysfunction at baseline or when there are other risk factors for renal dysfunction during treatment (i.e. concomitant nephrotoxic agents). Renal function should be monitored routinely for all patients while on treatment, and the dose of the adefovir dipivoxil should be adjusted accordingly.

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, but has not been reported with adefovir dipivoxil. Adefovir dipivoxil should be discontinued immediately in any patient that develops clinical signs or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

There are no clinical trials using adefovir dipivoxil in pregnant women; therefore, it should be used only if benefits outweigh the risks.

4. **Dosage**

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.

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