HEPSERA®

(adefovir dipivoxil)

Tablets

R_x Only

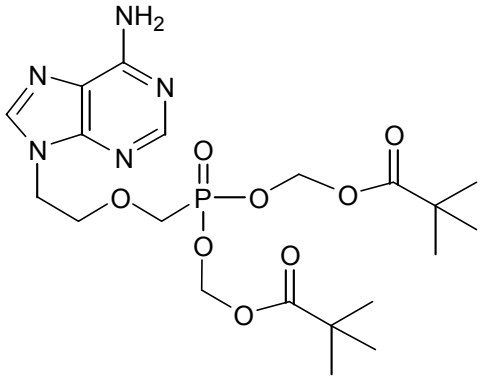
WARNINGS

1. **SEVERE ACUTE EXACERBATIONS OF HEPATITIS HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED ANTI-HEPATITIS B THERAPY INCLUDING HEPSERA®. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ANTI-HEPATITIS B THERAPY. IF APPROPRIATE, RESUMPTION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).**
2. **IN PATIENTS AT RISK OF OR HAVING UNDERLYING RENAL DYSFUNCTION, CHRONIC ADMINISTRATION OF HEPSERA MAY RESULT IN NEPHROTOXICITY. THESE PATIENTS SHOULD BE MONITORED CLOSELY FOR RENAL FUNCTION AND MAY REQUIRE DOSE ADJUSTMENT (SEE WARNINGS AND DOSAGE AND ADMINISTRATION).**
3. **HIV RESISTANCE MAY EMERGE IN CHRONIC HEPATITIS B PATIENTS WITH UNRECOGNIZED OR UNTREATED HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION TREATED WITH ANTI-HEPATITIS B THERAPIES, SUCH AS THERAPY WITH HEPSERA, THAT MAY HAVE ACTIVITY AGAINST HIV (SEE WARNINGS).**
4. **LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).**

DESCRIPTION

HEPSERA is the tradename for adefovir dipivoxil, a diester prodrug of adefovir. Adefovir is an acyclic nucleotide analog with activity against human hepatitis B virus (HBV).

The chemical name of adefovir dipivoxil is 9-[2-[[bis[(pivaloyloxy)methoxy]-phosphinyl]-methoxy]ethyl]adenine. It has a molecular formula of $C_{20}H_{32}N_5O_8P$, a molecular weight of 501.48 and the following structural formula:



Adefovir dipivoxil is a white to off-white crystalline powder with an aqueous solubility of 19 mg/mL at pH 2.0 and 0.4 mg/mL at pH 7.2. It has an octanol/aqueous phosphate buffer (pH 7) partition coefficient (log p) of 1.91.

HEPSERA tablets are for oral administration. Each tablet contains 10 mg of adefovir dipivoxil and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, pregelatinized starch, and talc.

Microbiology

Mechanism of Action:

Adefovir is an acyclic nucleotide analog of adenosine monophosphate which is phosphorylated to the active metabolite adefovir diphosphate by cellular kinases. Adefovir diphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after its incorporation into viral DNA. The inhibition constant (K_i) for adefovir diphosphate for HBV DNA polymerase was 0.1 μM. Adefovir diphosphate is a weak inhibitor of human DNA polymerases α and γ with K_i values of 1.18 μM and 0.97μM, respectively.

Antiviral Activity:

The concentration of adefovir that inhibited 50% of viral DNA synthesis (EC_{50}) in HBV transfected human hepatoma cell lines ranged from 0.2 to 2.5 μM. The combination of adefovir with lamivudine showed additive anti-HBV activity.

Resistance:

Clinical isolates with genotypic changes conferring reduced susceptibility in cell culture to nucleoside analog inhibitors for the treatment of HBV infection have been observed. Genotyping was performed for resistance surveillance annually or on the last available sample on treatment from all adefovir dipivoxil-treated patients with detectable serum HBV DNA. These analyses determined that amino acid substitutions rtN236T and rtA181T/V have been observed in association with adefovir resistance. In cell culture,

the rtN236T mutation demonstrated 4- to 14-fold, the rtA181V mutation 2.5- to 3-fold, and the rtA181T mutation 1.3- to 1.9-fold reduced susceptibility to adefovir.

In HBeAg-positive nucleoside-naïve patients (study GS-98-437, N=171), no adefovir resistance-associated mutations were observed at week 48. Sixty-five patients continued on long term treatment after a median duration on adefovir dipivoxil of 235 weeks (range 110-279 weeks). Sixteen of 38 (42%) patients were identified with adefovir resistance-associated mutations in the setting of virologic failure (confirmed increase of ≥ 1 $\log_{10}$ HBV DNA copies/mL above nadir or never suppressed below10^3 copies/mL). The mutations included rtN236T (n=2), rtA181V (n=4), rtA181T (n=3), rtA181T+rtN236T (n=5), and rtA181V+rtN236T (n=2). In HBeAg-negative nucleoside-naïve patients (study GS-98-438), thirty patients were identified with adefovir resistance-associated mutations with a cumulative probability of 0%, 3%, 11%, 19%, and 30% at 48, 96, 144, 192, and 240 weeks, respectively. Of those 30 patients, 22 had a confirmed increase of ≥1 $\log_{10}$ HBV DNA copies/mL above nadir or never achieved HBV DNA levels below 10^3 copies/mL; an additional 8 patients had an adefovir resistance-associated mutation without virologic failure.

In an open-label study of pre- and post-liver transplantation patients (study GS-98-435), 129 patients with clinical evidence of lamivudine-resistant hepatitis B virus at baseline were evaluated for adefovir resistance-associated mutations. The incidence of adefovir resistance-associated (rtN236T or rtA181T/V) mutations was 0% at 48 weeks. Four patients developed the rtN236T mutation after 72 weeks of adefovir dipivoxil therapy. Development of the rtN236T mutation was associated with serum HBV DNA rebound. All 4 patients who developed the rtN236T mutation in their HBV had discontinued lamivudine therapy before the development of genotypic resistance and all 4 lost the lamivudine resistance-associated mutations present at baseline. In a study of 35 HIV/HBV co-infected patients with lamivudine-resistant HBV (study 460i) who added adefovir dipivoxil to lamivudine, no adefovir resistance-associated mutations were observed in HBV isolates from 15/35 patients tested up to 144 weeks of therapy.

Cross-resistance:

Recombinant HBV variants containing lamivudine-resistance-associated mutations (rtL180M, rtM204I, rtM204V, rtL180M + rtM204V, rtV173L + rtL180M + rtM204V) were susceptible to adefovir in cell culture. Adefovir dipivoxil has also demonstrated anti-HBV activity (median reduction in serum HBV DNA of 4.3 $\log_{10}$ copies/mL) in patients with HBV containing lamivudine-resistance-associated mutations (study 435). Adefovir also demonstrated in cell culture activity against HBV variants with entecavir resistance-associated mutations (rtT184G, rtS202I, rtM250V). HBV variants with DNA polymerase mutations rtT128N and rtR153Q or rtW153Q associated with resistance to hepatitis B virus immunoglobulin were susceptible to adefovir in cell culture.

HBV expressing the adefovir resistance-associated mutation rtN236T showed no change in susceptibility to entecavir in cell culture, and a 2- to 3-fold decrease in lamivudine susceptibility. HBV mutants with the adefovir resistance-associated mutation rtA181V showed a range of decreased susceptibilities to lamivudine of 4.2- to

14-fold and a 12-fold decrease in susceptibility to entecavir. In patients with the rtA181V mutation (n=2) or the rtN236T mutation (n=3), a reduction in serum HBV DNA of 2.4 to 3.1 and 2.0 to 5.1 $\log_{10}$ copies/mL, respectively, was observed when treatment with lamivudine was added to treatment with adefovir dipivoxil.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of adefovir have been evaluated in healthy volunteers and patients with chronic hepatitis B. Adefovir pharmacokinetics are similar between these populations.

Absorption:

Adefovir dipivoxil is a diester prodrug of the active moiety adefovir. Based on a cross study comparison, the approximate oral bioavailability of adefovir from HEPSERA is 59%.

Following oral administration of a 10 mg single dose of HEPSERA to chronic hepatitis B patients (N=14), the peak adefovir plasma concentration (C_{max}) was 18.4 ± 6.26 ng/mL (mean ± SD) and occurred between 0.58 and 4.00 hours (median=1.75 hours) post dose. The adefovir area under the plasma concentration-time curve ($AUC_{0-\infty}$) was 220 ± 70.0 ng•h/mL. Plasma adefovir concentrations declined in a biexponential manner with a terminal elimination half-life of 7.48 ± 1.65 hours.

The pharmacokinetics of adefovir in subjects with adequate renal function were not affected by once daily dosing of 10 mg HEPSERA over seven days. The impact of long-term once daily administration of 10 mg HEPSERA on adefovir pharmacokinetics has not been evaluated.

Effects of Food on Oral Absorption:

Adefovir exposure was unaffected when a 10 mg single dose of HEPSERA was administered with food (an approximately 1000 kcal high-fat meal). HEPSERA may be taken without regard to food.

Distribution:

In vitro binding of adefovir to human plasma or human serum proteins is ≤4% over the adefovir concentration range of 0.1 to 25 μg/mL. The volume of distribution at steady-state following intravenous administration of 1.0 or 3.0 mg/kg/day is 392 ± 75 and 352 ± 9 mL/kg, respectively.

Metabolism and Elimination:

Following oral administration, adefovir dipivoxil is rapidly converted to adefovir. Forty-five percent of the dose is recovered as adefovir in the urine over 24 hours at steady

state following 10 mg oral doses of HEPSERA. Adefovir is renally excreted by a combination of glomerular filtration and active tubular secretion **(see DRUG INTERACTIONS)**.

Special Populations:

Gender

The pharmacokinetics of adefovir were similar in male and female patients.

Race

The pharmacokinetics of adefovir have been shown to be comparable in Caucasians and Asians. Pharmacokinetic data are not available for other racial groups.

Pediatric and Geriatric Patients

Pharmacokinetic studies have not been conducted in children or in the elderly.

Renal Impairment

In subjects with moderately or severely impaired renal function or with end-stage renal disease (ESRD) requiring hemodialysis, $C_{max,}$ AUC, and half-life ($T_{1/2}$) were increased compared to subjects with normal renal function. It is recommended that the dosing interval of HEPSERA be modified in these patients **(see DOSAGE AND ADMINISTRATION)**.

The pharmacokinetics of adefovir in non-chronic hepatitis B patients with varying degrees of renal impairment are described in Table 1. In this study, subjects received a 10 mg single dose of HEPSERA.

Table 1. Pharmacokinetic Parameters (Mean ± SD) of Adefovir in Patients with Varying Degrees of Renal Function

Renal Function Group	Unimpaired	Mild	Moderate	Severe
Baseline creatinine clearance (mL/min)	**>80 (N=7)**	**50–80 (N=8)**	**30–49 (N=7)**	**10–29 (N=10)**
C_{max} (ng/mL)	17.8 ± 3.22	22.4 ± 4.04	28.5 ± 8.57	51.6 ± 10.3
AUC $_{0-\infty}$ (ng•h/mL)	201 ± 40.8	266 ± 55.7	455 ± 176	1240 ± 629
CL/F (mL/min)	469 ± 99.0	356 ± 85.6	237 ± 118	91.7 ± 51.3
CL_{renal} (mL/min)	231 ± 48.9	148 ± 39.3	83.9 ± 27.5	37.0 ± 18.4

A four-hour period of hemodialysis removed approximately 35% of the adefovir dose. The effect of peritoneal dialysis on adefovir removal has not been evaluated.

Hepatic Impairment

The pharmacokinetics of adefovir following a 10 mg single dose of HEPSERA have been studied in non-chronic hepatitis B patients with hepatic impairment. There were no substantial alterations in adefovir pharmacokinetics in patients with moderate and severe hepatic impairment compared to unimpaired patients. No change in HEPSERA dosing is required in patients with hepatic impairment.

Drug Interactions:

Adefovir dipivoxil is rapidly converted to adefovir in vivo. At concentrations substantially higher (>4000-fold) than those observed in vivo, adefovir did not inhibit any of the common human CYP450 enzymes, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Adefovir is not a substrate for these enzymes. However, the potential for adefovir to induce CYP450 enzymes is unknown. Based on the results of these in vitro experiments and the renal elimination pathway of adefovir, the potential for CYP450 mediated interactions involving adefovir as an inhibitor or substrate with other medicinal products is low.

The pharmacokinetics of adefovir have been evaluated following multiple dose administration of HEPSERA (10 mg once daily) in combination with lamivudine (100 mg once daily), trimethoprim/sulfamethoxazole (160/800 mg twice daily), acetaminophen (1000 mg four times daily), and ibuprofen (800 mg three times daily) in healthy volunteers (N=18 per study). The pharmacokinetics of adefovir have also been evaluated following single dose HEPSERA (10 mg) in combination with multiple dose tenofovir disoproxil fumarate (300 mg daily) in healthy volunteers (N=22).

Adefovir did not alter the pharmacokinetics of lamivudine, trimethoprim/sulfamethoxazole, acetaminophen, tenofovir disoproxil fumarate, or ibuprofen.

The pharmacokinetics of adefovir were unchanged when HEPSERA was coadministered with lamivudine, trimethoprim/sulfamethoxazole, acetaminophen, and tenofovir disoproxil fumarate. When HEPSERA was coadministered with ibuprofen (800 mg three times daily) increases in adefovir C_{max} (33%), AUC (23%) and urinary recovery were observed. This increase appears to be due to higher oral bioavailability, not a reduction in renal clearance of adefovir.

INDICATIONS AND USAGE

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

This indication is based on histological, virological, biochemical, and serological responses in adult patients with HBeAg+ and HBeAg- chronic hepatitis B with compensated liver function, and in adult patients with clinical evidence of

lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function.

Description of Clinical Studies

HBeAg-Positive Chronic Hepatitis B:

Study 437 was a randomized, double-blind, placebo-controlled, three-arm-study in patients with HBeAg-positive chronic hepatitis B that allowed for a comparison between placebo and HEPSERA. The median age of patients was 33 years. Seventy-four percent were male, 59% were Asian, 36% were Caucasian, and 24% had prior interferon-α treatment. At baseline, patients had a median total Knodell Histology Activity Index (HAI) score of 10, a median serum HBV DNA level as measured by the Roche Amplicor Monitor polymerase chain reaction (PCR) assay (LLOQ = 1000 copies/mL) of 8.36 $\log_{10}$ copies/mL and a median ALT level of 2.3 times the upper limit of normal.

HBeAg-Negative (Anti-HBe Positive/HBV DNA Positive) Chronic Hepatitis B:

Study 438 was a randomized, double-blind, placebo-controlled study in patients who were HBeAg-negative at screening, and anti-HBe positive. The median age of patients was 46 years. Eighty-three percent were male, 66% were Caucasian, 30% were Asian and 41% had prior interferon-α treatment. At baseline, the median total Knodell HAI score was 10, the median serum HBV DNA level as measured by the Roche Amplicor Monitor PCR assay (LLOQ = 1000 copies/mL) was 7.08 $\log_{10}$ copies/mL, and the median ALT was 2.3 times the upper limit of normal.

The primary efficacy endpoint in both studies was histological improvement at week 48; results of which are shown in Table 2.

Table 2. Histological Response at Week 48*

	Study 437		Study 438	
	HEPSERA 10 mg (N=168)	**Placebo (N=161)**	**HEPSERA 10 mg (N=121)**	**Placebo (N=57)**
Improvement**	53%	25%	64%	35%
No Improvement	37%	67%	29%	63%
Missing/Unassessable Data	10%	7%	7%	2%

* Intent-to-Treat population (patients with ≥1 dose of study drug) with assessable baseline biopsies.

** Histological improvement defined as ≥2 point decrease in the Knodell necro-inflammatory score with no worsening of the Knodell fibrosis score.

Table 3 illustrates the changes in Ishak Fibrosis Score by treatment group.

Table 3. Changes in Ishak Fibrosis Score at Week 48

Number of Adequate Biopsy Pairs	Study 437		Study 438	
	HEPSERA 10 mg (N=152)	Placebo (N=149)	HEPSERA 10 mg (N=113)	Placebo (N= 56)
Ishak Fibrosis Score				
Improved*	34%	19%	34%	14%
Unchanged	55%	60%	62%	50%
Worsened*	11%	21%	4%	36%

*Change of 1 point or more in Ishak Fibrosis Score.

At week 48, improvement was seen in respect to mean change in serum HBV DNA (log_{10} copies/mL), normalization of ALT, and HBeAg seroconversion as compared to placebo in patients receiving HEPSERA (Table 4).

Table 4. Change in Serum HBV DNA, ALT Normalization, and HBeAg Seroconversion at Week 48

	Study 437		Study 438	
	HEPSERA 10 mg (N=171)	Placebo (N=167)	HEPSERA 10 mg (N=123)	Placebo (N=61)
Mean change ± SD in serum HBV DNA from baseline (log_{10} copies/mL)	-3.57 ± 1.64	-0.98 ± 1.32	-3.65 ± 1.14	-1.32 ± 1.25
ALT normalization	48%	16%	72%	29%
HBeAg seroconversion	12%	6%	NA*	NA*

* Patients with HBeAg-negative disease cannot undergo HBeAg seroconversion.

Treatment Beyond 48 Weeks:

In study 437, continued treatment with HEPSERA to 72 weeks resulted in continued maintenance of mean reductions in serum HBV DNA observed at week 48. An increase in the proportion of patients with ALT normalization was also observed in study 437. The effect of continued treatment with HEPSERA on seroconversion is unknown.

In study 438, patients who received HEPSERA during the first 48 weeks were re-randomized in a blinded manner to continue on HEPSERA or receive placebo for an additional 48 weeks. At week 96, 50 of 70 (71%) of patients who continued treatment with HEPSERA had undetectable HBV DNA levels (<1000 copies/mL), and 47 of 64

(73%) of patients had ALT normalization. HBV DNA and ALT levels returned towards baseline in most patients who stopped treatment with HEPSERA.

Pre- and Post-Liver Transplantation Patients:

HEPSERA was also evaluated in an open-label, uncontrolled study of 467 chronic hepatitis B patients pre- (N=226) and post- (N=241) liver transplantation with clinical evidence of lamivudine- resistant hepatitis B virus (study 435). At baseline, 60% of pre-liver transplantation patients were classified as Child-Pugh-Turcotte score of Class B or C. The median baseline HBV DNA as measured by the Roche Amplicor Monitor PCR assay (LLOQ = 1000 copies/mL) was 7.4 and 8.2 $\log_{10}$ copies/mL, and the median baseline ALT was 1.8 and 2.0 times the upper limit of normal in pre- and post-liver transplantation patients, respectively. Results of this study are displayed in Table 5. Treatment with HEPSERA resulted in a similar reduction in serum HBV DNA regardless of the patterns of lamivudine-resistant HBV DNA polymerase mutations at baseline. The significance of the efficacy results listed in Table 5 as they relate to clinical outcomes is not known.

Table 5. Efficacy in Pre- and Post-Liver Transplantation Patients at Week 48

Efficacy Parameter*	**Pre-Liver Transplantation (N=226)**	**Post-Liver Transplantation (N=241)**
Mean change ± SD in HBV DNA from baseline ($\log_{10}$ copies/mL)	–3.7 ± 1.6 (n=117)	–4.0 ± 1.6 (n=164)
**Proportion with undetectable HBV DNA (< 1000 copies/mL)	77/109 (71%)	64/159 (40%)
Stable or improved Child-Pugh-Turcotte score	86/90 (96%)	107/115 (93%)
Normalization of: ***		
ALT	61/82 (74%)	56/110 (51%)
Albumin	43/54 (80%)	21/26 (81%)
Bilirubin	38/68 (58%)	29/38 (76%)
Prothrombin time	39/46 (85%)	5/9 (56%)

* Data are missing for 29% (HBV DNA) and 37% to 45% (CPT Score, Normalization of ALT, Albumin, Bilirubin, and PT) of total patients enrolled in the study.

** Denominator is the number of patients with serum HBV DNA ≥ 1000 copies/mL at baseline using the Roche Amplicor Monitor PCR Assay (LLOQ = 1000 copies/mL) and non-missing value at week 48.

*** Denominator is patients with abnormal values at baseline and non-missing value at week 48.

Clinical Evidence of Lamivudine Resistance:

In study 461, a double-blind, active controlled study in 59 chronic hepatitis B patients with clinical evidence of lamivudine-resistant hepatitis B virus, patients were randomized to receive either HEPSERA monotherapy or HEPSERA in combination with lamivudine 100 mg or lamivudine 100 mg alone. At week 48, the mean ± SD decrease in serum HBV DNA as measured by the Roche Amplicor Monitor PCR assay (LLOQ = 1000 copies/mL) was 4.00 ± 1.41 $\log_{10}$ copies/mL for patients treated with HEPSERA and 3.46 ± 1.10 $\log_{10}$ copies/mL for patients treated with HEPSERA in combination with lamivudine. There was a mean decrease in serum HBV DNA of 0.31 ± 0.93 $\log_{10}$ copies/mL in patients receiving lamivudine alone. ALT normalized in 47% of patients treated with HEPSERA, in 53% of patients treated with HEPSERA in combination with lamivudine, and 5% of patients treated with lamivudine alone. The significance of these findings as they relate to clinical outcomes is not known.

CONTRAINDICATIONS

HEPSERA is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

WARNINGS

Exacerbations of Hepatitis after Discontinuation of Treatment

Severe acute exacerbation of hepatitis has been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with HEPSERA. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least several months in patients who discontinue HEPSERA. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

In clinical trials of HEPSERA, exacerbations of hepatitis (ALT elevations 10 times the upper limit of normal or greater) occurred in up to 25% of patients after discontinuation of HEPSERA. These events were identified in studies GS-98-437 and GS-98-438 (N=492). Most of these events occurred within 12 weeks of drug discontinuation. These exacerbations generally occurred in the absence of HBeAg seroconversion, and presented as serum ALT elevations in addition to re-emergence of viral replication. In the HBeAg-positive and HBeAg-negative studies in patients with compensated liver function, the exacerbations were not generally accompanied by hepatic decompensation. However, patients with advanced liver disease or cirrhosis may be at higher risk for hepatic decompensation. Although most events appear to have been self-limited or resolved with re-initiation of treatment, severe hepatitis exacerbations, including fatalities, have been reported. Therefore, patients should be closely monitored after stopping treatment.

Nephrotoxicity

Nephrotoxicity characterized by a delayed onset of gradual increases in serum creatinine and decreases in serum phosphorus was historically shown to be the

treatment-limiting toxicity of adefovir dipivoxil therapy at substantially higher doses in HIV-infected patients (60 and 120 mg daily) and in chronic hepatitis B patients (30 mg daily). Chronic administration of HEPSERA (10 mg once daily) may result in delayed nephrotoxicity. The overall risk of nephrotoxicity in patients with adequate renal function is low. However, this is of special importance in patients at risk of or having underlying renal dysfunction and patients taking concomitant nephrotoxic agents such as cyclosporine, tacrolimus, aminoglycosides, vancomycin and non-steroidal anti-inflammatory drugs **(see ADVERSE REACTIONS)**.

It is important to monitor renal function for all patients during treatment with HEPSERA, particularly for those with pre-existing or other risks for renal impairment. Patients with renal insufficiency at baseline or during treatment may require dose adjustment **(see DOSAGE AND ADMINISTRATION)**. The risks and benefits of HEPSERA treatment should be carefully evaluated prior to discontinuing HEPSERA in a patient with treatment-emergent nephrotoxicity.

HIV Resistance

Prior to initiating HEPSERA therapy, HIV antibody testing should be offered to all patients. Treatment with anti-hepatitis B therapies, such as HEPSERA, that have activity against HIV in a chronic hepatitis B patient with unrecognized or untreated HIV infection may result in emergence of HIV resistance. HEPSERA has not been shown to suppress HIV RNA in patients; however, there are limited data on the use of HEPSERA to treat patients with chronic hepatitis B co-infected with HIV.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals.

A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with HEPSERA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS

Since adefovir is eliminated by the kidney, co-administration of HEPSERA with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either adefovir and/or these co-administered drugs.

Apart from lamivudine, trimethoprim/sulfamethoxazole, acetaminophen, and tenofovir disoproxil fumarate, the effects of co-administration of HEPSERA with drugs that are

excreted renally, or other drugs known to affect renal function have not been evaluated **(see CLINICAL PHARMACOLOGY)**.

Patients should be monitored closely for adverse events when HEPSERA is co-administered with drugs that are excreted renally or with other drugs known to affect renal function.

Ibuprofen 800 mg three times daily increased adefovir exposure by approximately 23%. The clinical significance of this increase in adefovir exposure is unknown **(see CLINICAL PHARMACOLOGY)**.

While adefovir does not inhibit common CYP450 enzymes, the potential for adefovir to induce CYP450 enzymes is not known.

The effect of adefovir on cyclosporine and tacrolimus concentrations is not known.

Duration of Treatment

The optimal duration of HEPSERA treatment and the relationship between treatment response and long-term outcomes such as hepatocellular carcinoma or decompensated cirrhosis are not known.

Animal Toxicology

Renal tubular nephropathy characterized by histological alterations and/or increases in BUN and serum creatinine was the primary dose-limiting toxicity associated with administration of adefovir dipivoxil in animals. Nephrotoxicity was observed in animals at systemic exposures approximately 3–10 times higher than those in humans at the recommended therapeutic dose of 10 mg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral carcinogenicity studies of adefovir dipivoxil in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the therapeutic dose for HBV infection. In both mouse and rat studies, adefovir dipivoxil was negative for carcinogenic findings. Adefovir dipivoxil was mutagenic in the in vitro mouse lymphoma cell assay (with or without metabolic activation). Adefovir induced chromosomal aberrations in the in vitro human peripheral blood lymphocyte assay without metabolic activation. Adefovir dipivoxil was not clastogenic in the in vivo mouse micronucleus assay and adefovir was not mutagenic in the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli* strains in the presence or absence of metabolic activation. In reproductive toxicology studies, no evidence of impaired fertility was seen in male or female rats at systemic exposure approximately 19 times that achieved in humans at the therapeutic dose.

Pregnancy

Pregnancy Category C:

Reproduction studies conducted with adefovir dipivoxil administered orally have shown no embryotoxicity or teratogenicity in rats at doses producing systemic exposures approximately 23 times that achieved in humans at the therapeutic dose of 10 mg/day, or in rabbits at systemic exposures 40 times that in the human.

When adefovir was administered intravenously to pregnant rats at doses associated with notable maternal toxicity (systemic exposure 38 times that in the human), embryotoxicity and an increased incidence of fetal malformations (anasarca, depressed eye bulge, umbilical hernia and kinked tail) were observed. No adverse effects on development were seen with adefovir administered intravenously to pregnant rats at a systemic exposure 12 times that in the human.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, HEPSERA should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits.

Pregnancy Registry

To monitor fetal outcomes of pregnant women exposed to HEPSERA, a pregnancy registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Labor and Delivery

There are no studies in pregnant women and no data on the effect of HEPSERA on transmission of HBV from mother to infant. Therefore, appropriate infant immunizations should be used to prevent neonatal acquisition of hepatitis B virus.

Lactating Women

It is not known whether adefovir is excreted in human milk. Mothers should be instructed not to breast-feed if they are taking HEPSERA.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of HEPSERA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised when prescribing to elderly patients since they have greater frequency of decreased renal or cardiac function due to concomitant disease or other drug therapy.

ADVERSE REACTIONS

Assessment of adverse reactions is based on two studies (437 and 438) in which 522 patients with chronic hepatitis B received double-blind treatment with HEPSERA (N=294) or placebo (N=228) for 48 weeks. With extended therapy in the second 48 week treatment period, 492 patients were treated for up to 109 weeks, with a median time on treatment of 49 weeks.

Patients who received HEPSERA beyond week 48 in Study 438 reported adverse reactions similar in nature and severity to those reported in the first 48 weeks of treatment. With increased HEPSERA exposure, the incidence of adverse events related to treatment increased only slightly.

In addition to specific adverse events described under the WARNINGS section, all treatment-related clinical adverse events that occurred in 3% or greater of HEPSERA-treated patients compared with placebo are listed in Table 6. A summary of grade 3 and 4 laboratory abnormalities during therapy with HEPSERA compared with placebo is listed in Table 7.

Table 6. Treatment-Related Adverse Events (Grades 1–4) Reported in ≥3% of All HEPSERA-Treated Patients in the Pooled 437–438 Studies (0–48 Weeks)

	HEPSERA 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%

Laboratory Abnormalities

Table 7. Grade 3–4 Laboratory Abnormalities Reported in ≥1% of All HEPSERA-Treated Patients in the Pooled 437–438 Studies (0–48 Weeks)

	HEPSERA 10 mg (N=294)	Placebo (N=228)
ALT (>5 × ULN)	20%	41%
Hematuria (≥3+)	11%	10%
AST (>5 × ULN)	8%	23%
Creatine kinase (>4 × ULN)	7%	7%
Amylase (>2 × ULN)	4%	4%
Glycosuria (≥3+)	1%	3%

In patients with adequate renal function, increases in serum creatinine ≥0.3 mg/dL from baseline were observed in 4% of patients treated with HEPSERA 10 mg daily compared with 2% of patients in the placebo group at week 48. No patients developed a serum creatinine increase ≥0.5 mg/dL from baseline by week 48. By week 96, 10% and 2% of HEPSERA-treated patients, by Kaplan-Meier estimate, had increases in serum creatinine ≥0.3 mg/dL and ≥0.5 mg/dL from baseline, respectively (no placebo-controlled results were available for comparison beyond week 48). Of the 29 of 492 patients with elevations in serum creatinine ≥0.3 mg/dL from baseline, 20 out of 29 resolved on continued treatment (≤0.2 mg/dL from baseline), 8 of 29 remained unchanged and 1 of 29 resolved on discontinuing treatment **(see Special Risk Patients section below for changes in serum creatinine in patients with underlying renal insufficiency at baseline)**.

Special Risk Patients

Pre- (N=226) and post-liver transplantation patients (N=241) with chronic hepatitis B and clinical evidence of lamivudine-resistant hepatitis B virus were treated in an open-label study with HEPSERA for up to 203 weeks in study 435, with a median time on treatment of 51 and 99 weeks, respectively. Changes in renal function occurred in pre- and post-liver transplantation patients with risk factors for renal dysfunction, including concomitant use of cyclosporine and tacrolimus, renal insufficiency at baseline, hypertension, diabetes, and on-study transplantation. Therefore, the contributory role of HEPSERA to these changes in renal function is difficult to assess. Increases in serum creatinine ≥ 0.3 mg/dL from baseline were observed in 37% and 53% of pre-liver transplantation patients by weeks 48 and 96, respectively, by Kaplan-Meier estimates. Increases in serum creatinine ≥ 0.3 mg/dL from baseline were observed in 32% and 51% of post-liver transplantation patients by weeks 48 and 96, respectively, by Kaplan-Meier estimates. Serum phosphorus values < 2.0 mg/dL were observed in 3/226 (1.3%)

of pre-liver transplantation patients and in 6/241 (2.5%) of post-liver transplantation patients by last study visit. Four percent (19 of 467) of pre- and post-liver transplantation patients discontinued HEPSERA due to renal events.

The most common treatment-related adverse events reported in pre- and post-liver transplantation patients treated with HEPSERA with a 2% frequency or higher and potential causal relationship with HEPSERA include:

Metabolism and Nutrition Disorders: hypophosphatemia

Nervous System Disorders: headache

Gastrointestinal Disorders: nausea, vomiting, diarrhea, abdominal pain

Skin and Subcutaneous Tissue Disorders: rash, pruritis

Renal and Urinary Disorders: increased creatinine, abnormal renal function, renal failure

General Disorder and Administration Site Conditions: asthenia

OVERDOSAGE

Doses of adefovir dipivoxil 500 mg daily for 2 weeks and 250 mg daily for 12 weeks have been associated with gastrointestinal side effects. If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Following a 10 mg single dose of HEPSERA, a four-hour hemodialysis session removed approximately 35% of the adefovir dose.

DOSAGE AND ADMINISTRATION

The recommended dose of HEPSERA in chronic hepatitis B patients with adequate renal function is 10 mg, once daily, taken orally, without regard to food. The optimal duration of treatment is unknown.

Dose Adjustment in Renal Impairment:

Significantly increased drug exposures were seen when HEPSERA was administered to patients with renal impairment **(see Pharmacokinetics)**. Therefore, the dosing interval of HEPSERA should be adjusted in patients with baseline creatinine clearance <50 mL/min using the following suggested guidelines (see Table 8). The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated.

Additionally, it is important to note that these guidelines were derived from data in patients with pre-existing renal impairment at baseline. They may not be appropriate for

patients in whom renal insufficiency evolves during treatment with HEPSERA. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 8. Dosing Interval Adjustment of HEPSERA in Patients with Renal Impairment

	Creatinine Clearance (mL/min)*			
	≥50	20–49	10–19	Hemodialysis Patients
Recommended dose and dosing interval	10 mg every 24 hours	10 mg every 48 hours	10 mg every 72 hours	10 mg every 7 days following dialysis

* Creatinine clearance calculated by Cockcroft-Gault method using lean or ideal body weight.

The pharmacokinetics of adefovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients.

HOW SUPPLIED

HEPSERA is available as tablets. Each tablet contains 10 mg of adefovir dipivoxil. The tablets are white and debossed with “10” and “GILEAD” on one side and the stylized figure of a liver on the other side. They are packaged as follows: Bottles of 30 tablets (NDC 61958-0501-1) containing desiccant (silica gel) and closed with a child-resistant closure.

Store in original container at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

Do not use if seal over bottle opening is broken or missing.

Gilead Sciences, Inc.

Foster City, CA 94404

April 2006

PATIENT INFORMATION

HEPSERA® (hep-SER-rah)

Generic Name: (adefovir dipivoxil) tablets

Read this information carefully before you start taking HEPSERA. Read and check for new information each time you get more HEPSERA. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about HEPSERA?

1. **Some people who stop taking HEPSERA get a very serious hepatitis.** This usually happens within 12 weeks after stopping. You will need to have regular blood tests to check for liver function and hepatitis B virus levels if you stop taking HEPSERA.
2. **HEPSERA may cause a severe kidney problem called nephrotoxicity.** It usually happens in people that already have a kidney problem, but it can happen to anyone that uses HEPSERA. You will need to have regular blood tests to check for kidney function while you are taking HEPSERA.
3. **If you get or have HIV that isn't being treated with medicines, HEPSERA may increase the chances your HIV infection cannot be helped with usual HIV medicines.** This can happen if you get or have HIV and don't know it, or if your HIV is not being treated while you are taking HEPSERA. You should get an HIV test before you start taking HEPSERA and anytime after that when there's a chance you were exposed to HIV.
4. **Some people who have taken medicines like HEPSERA that are called nucleoside or nucleotide analogs have developed a serious condition called lactic acidosis** (build up of an acid in the blood). Lactic acidosis is a medical emergency and must be treated in the hospital. **Call your doctor right away if you get any of the following signs of lactic acidosis:**

   - You feel very weak or tired.
   - You have unusual (not normal) muscle pain.
   - You have trouble breathing.
   - You have stomach pain with nausea and vomiting.
   - You feel cold, especially in your arms and legs.
   - You feel dizzy or lightheaded.
   - You have a fast or irregular heartbeat.

Some people who have taken medicines like HEPSERA have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). **Call your doctor right away if you get any of the following signs of liver problems.**

- Your skin or the white part of your eyes turns yellow (jaundice).
- Your urine turns dark.

- Your bowel movements (stools) turn light in color.
- You don't feel like eating food for several days or longer.
- You feel sick to your stomach (nausea).
- You have lower stomach pain.

You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleoside analog medicines [Combivir® (zidovudine plus lamivudine), Emtriva® (emtricitabine), Epivir®, Epivir-HBV® (lamivudine), Hivid® (zalcitabine), Retrovir® (zidovudine), Trizivir® (zidovudine plus lamivudine plus abacavir), Videx® (didanosine), Viread® (tenofovir disoproxil fumarate), Zerit® (stavudine), and Ziagen® (abacavir)] for a long time.

What is HEPSERA?

HEPSERA is a medicine used to treat adults with continuing (chronic) infections with active hepatitis B virus. HEPSERA has not been studied in adults over the age of 65 or in children.

- HEPSERA will not cure your chronic hepatitis B.
- HEPSERA may help lower the amount of hepatitis B virus in your body.
- HEPSERA may lower the ability of the virus to multiply and infect new liver cells.
- We do not know if HEPSERA will reduce your chances of getting liver cancer or liver damage (cirrhosis) from chronic hepatitis B.
- We do not know how long HEPSERA may help your hepatitis. Sometimes viruses change in your body and medicines no longer work. This is called drug resistance.
- HEPSERA does not stop you from spreading hepatitis B to others by sex or sharing needles. So practice safe sex and needle use.

Who should not take HEPSERA?

- Do not take HEPSERA if you are allergic to any of the ingredients in HEPSERA. The active ingredient in HEPSERA is adefovir dipivoxil. See the end of this leaflet for a complete list of all the ingredients in HEPSERA.

Tell your doctor if:

- **You are pregnant.** We do not know if HEPSERA can harm your unborn child. You and your doctor will need to decide if HEPSERA is right for you. If you take HEPSERA and you are pregnant, talk to your doctor about how you can be on the HEPSERA pregnancy registry.
- **You are breast-feeding.** We do not know if HEPSERA can pass through your milk and if it can harm your baby. You will need to choose either to breast feed or take HEPSERA, but not both.
- **You have kidney problems now or had them before.** Your dose and schedule of HEPSERA may be reduced. Blood tests will need to be done regularly to see how your kidneys are working.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how HEPSERA works, **especially medicines that affect how your kidneys work**.

HEPSERA can affect how your other medicines work. Your dose of HEPSERA and the other medicines may be changed. **Do not take any other medicines while you are taking HEPSERA, unless your doctor has told you it is okay.**

How should I take HEPSERA?

- Your doctor will tell you how much HEPSERA to take.
- Your doctor will tell you when and how often to take HEPSERA.
- Take HEPSERA the same time each day that your doctor tells you. If you forget to take HEPSERA, take it as soon as you remember that day. Do not take more than 1 dose of HEPSERA in a day. Do not take 2 doses at the same time. Call your doctor or pharmacist if you are not sure what to do.
- **Do not** change your dose of HEPSERA or stop HEPSERA without talking to your doctor. Your hepatitis may get worse if you change doses or stop.
- You may take HEPSERA with or without food.
- When your HEPSERA supply gets low, call your doctor or pharmacy for a refill. **Do not run out of HEPSERA.**
- If you take too much HEPSERA, call your local poison control center or emergency room right away.

Some patients get worse or very serious hepatitis B symptoms when they stop taking HEPSERA (see, "What is the most important information I should know about HEPSERA?"). We don't know how long you should use HEPSERA. You and your doctor will need to decide when it is best for you to stop taking HEPSERA. After you stop taking HEPSERA, your doctor will still need to check your health and take blood tests to check your liver for a few months.

What should I avoid while taking HEPSERA?

Avoid doing things that can spread hepatitis B since HEPSERA doesn't stop you from passing the infection to others.

- Do not share needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.
- Do not have any kind of sex without protection. Practice "safe sex" using condoms and dental dams.

What are the possible side effects of HEPSERA?

HEPSERA can cause the following serious side effects: (see, "What is the most important information I should know about HEPSERA?")

1. **a very serious hepatitis if you stop taking it**
2. **a severe kidney problem called nephrotoxicity**
3. **increase your chance of developing a form of HIV that cannot be treated with usual HIV medicines**
4. **lactic acidosis and liver problems**

The most common side effects of HEPSERA are weakness, headache, stomach pain, and nausea. The most common side effects in patients with liver transplants and

chronic hepatitis B are weakness, headache, stomach pain, and itching. Some patients with liver transplants also had changes in the way their kidneys worked.

These are not all of the possible side effects of HEPSERA. For more information, ask your doctor or pharmacist.

General information about the safe and effective use of HEPSERA:

Medicines are sometimes prescribed for conditions not mentioned in patient information leaflets. Do not use HEPSERA for a condition for which it was not prescribed. Do not give HEPSERA to other people, even if they have the same symptoms that you have.

This leaflet summarizes the most important information about HEPSERA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about HEPSERA that is written for health professionals.

HEPSERA Tablets should be stored at room temperature and should be stored in their original container.

Do not use if seal over bottle opening is broken or missing.

What are the Ingredients of HEPSERA?

Active Ingredient: adefovir dipivoxil

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, pregelatinized starch, and talc

℞ **Only**

April 2006

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