

Product Information: Hepsera® (adefovir dipivoxil 10 mg) Tablets

COMPOSITION

Active: Adefovir dipivoxil

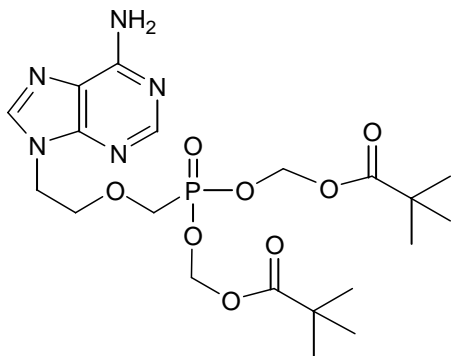
Inactive: croscarmellose sodium, lactose monohydrate, magnesium stearate, pregelatinised maize starch, and talc.

DESCRIPTION

Adefovir dipivoxil is a diester prodrug of adefovir, an acyclic nucleotide analog of adenosine monophosphate with activity against human hepatitis B virus (HBV). Adefovir dipivoxil is designated chemically as 9-[2 [[bis[(pivaloyloxy)-methoxy]phosphinyloxy]ethoxy]ethyl]adenine. It has a molecular formula of C₂₀H₃₂N₅O₈P and a molecular weight of 501.48. Adefovir dipivoxil is a white to off-white crystalline powder with an intrinsic aqueous solubility of 19 mg/mL at pH 2 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.

CAS Registry No.: 142340-99-6

Chemical Structure:



ACTIONS

Adefovir 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 μ M.

Pharmacology

Adefovir diphosphate has an intracellular half-life of 12 to 36 hours in activated and resting lymphocytes. Adefovir diphosphate is a weak inhibitor of human DNA polymerases α and γ with K_i values of 1.18 μ M and 0.97 μ M, respectively.

Microbiology

Adefovir is active against hepadnaviruses *in vitro*, including wild-type and recombinant HBV variants containing lamivudine-resistance associated-mutations (rtL180M, rtM204I, rtM204V, rtL180M +

rtM204V, rtL180M + rtM204V + rtV173L) in the HBV DNA polymerase gene. Adefovir dipivoxil has also demonstrated anti-HBV activity (median reduction in serum HBV DNA of 4.3 log₁₀ copies/mL at week 48) in patients with HBV containing lamivudine-resistance associated-mutations (Study 435). HBV variants with DNA polymerase mutations rtT128N and rtR or W153Q, associated with resistance to hepatitis B immunoglobulin were susceptible to adefovir *in vitro*. The *in vitro* IC₅₀ (concentration of drug which inhibits viral replication by 50%) of adefovir against wild-type HBV is 0.2-2.5 μM in human hepatic cell lines.

Table 1		
Antiviral Sensitivity to Adefovir of Lamivudine-Resistant HBV DNA Polymerase Mutations in Cell Culture		
Mutations/Strains	Fold Resistance¹	
	Adefovir	Lamivudine
Wild-type	1.0	1.0
rtL180M	0.4 - 1.1	2.5 - 18
rtM204I	0.7 - 7.8	380->10,000
rtM204V	0.5 - 8.4	22 - 221
rtL180M/rtM204V	0.4 - 3.8	312->10,000
rtL180M+rtM204V+rtV173L	0.5	>2,500
¹ Fold resistance is defined as the ratio of IC ₅₀ (mutant)/ IC ₅₀ (wild-type): > 10 fold equals resistance. The ranges of fold resistance presented for the cell culture assay reflect the data from 7 independent publications. The clinical significance of these fold changes has not been established.		

In several clinical studies (HBeAg positive, HBeAg negative, pre- and post- liver transplantation with lamivudine resistant HBV and lamivudine resistant HBV co-infected with HIV patients), genotypic and phenotypic analyses were conducted on HBV isolates from 379 of a total of 629 adefovir dipivoxil patients with detectable levels of HBV DNA at week 48. No HBV DNA polymerase mutations associated with resistance to adefovir were identified when patients were genotyped at baseline and at week 48. After 96, 144 and 192 weeks of treatment with adefovir dipivoxil, resistance surveillance was performed for 293, 221 and 67 patients respectively. Two novel conserved site mutations were identified in the HBV polymerase gene (rtN236T and rtA181V), which conferred clinical resistance to adefovir dipivoxil. Resistance to adefovir dipivoxil is delayed and infrequent. The cumulative probabilities of developing these adefovir-associated resistance mutations in all patients treated with adefovir dipivoxil were 0% at 48 weeks and approximately 2%, 7% and 15% after 96, 144 and 192 weeks respectively. These cumulative probabilities combine results in patients receiving adefovir dipivoxil as monotherapy and in combination with lamivudine. In HBeAg negative patients receiving monotherapy adefovir dipivoxil, the cumulative probabilities (life table analysis) of developing these adefovir-associated resistance mutations were approximately 0%, 3%, 11% and 18% after 48, 96, 144 and 192 weeks respectively.

The currently available data both *in vitro* and in patients suggest that HBV expressing the adefovir-associated resistance mutation rtN236T is susceptible to lamivudine. Preliminary data both *in vitro* and in patients suggest the adefovir-associated resistance mutation rtA181V may confer a reduced susceptibility to lamivudine.

No adefovir-associated HIV reverse transcriptase mutations (K65R or K70E) were detected through 48 weeks of ADV 10 mg therapy in 35 HIV/HBV co-infected patients

Pharmacokinetics

The pharmacokinetics of adefovir have been evaluated in healthy volunteers and patients with chronic hepatitis B. Adefovir pharmacokinetics are similar between these populations. The pharmacokinetics of adefovir has also been investigated in patients with hepatic and renal impairment.

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

Absorption: HEPSERA is a dipivaloyloxymethyl ester prodrug of the active ingredient adefovir. Based on a cross-study comparison, the oral bioavailability of adefovir from HEPSERA is approximately 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 \pm 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 T_{max} of adefovir was delayed by approximately 2 hours, but adefovir exposure (C_{max} and AUC) 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 $\leq 4\%$ over the adefovir concentration range of 0.1 to 25 μ g/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.

Excretion: Following oral administration, HEPSERA is rapidly converted to adefovir. Forty-five percent of the dose is recovered as adefovir in the urine over 24 hours after multiple doses of HEPSERA. Adefovir is renally excreted by a combination of glomerular filtration and active tubular secretion. The pharmacokinetics of HEPSERA have been evaluated with a number of drugs that also undergo tubular secretion (See **Drug Interactions**). Co-administration of HEPSERA with other drugs that are eliminated by, or alter tubular secretion may increase serum concentrations of either adefovir or the administered drug.

Linearity/non-linearity: The pharmacokinetics of adefovir are dose proportional over an adefovir dipivoxil dose range of 10 to 60 mg and are not affected by repeat dosing.

Age and gender: Pharmacokinetics of adefovir were similar in male and female patients. There are no detailed pharmacokinetic data 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 haemodialysis, C_{max} , AUC and half-life ($T_{1/2}$) were increased. It is recommended that the dosing interval of HEPSERA is modified in these patients. (See **Dosage and Administration**). In Table 2, the pharmacokinetics of adefovir in patients with varying degrees of renal impairment are described.

Table 2 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 ± 4.0	28.5 ± 8.57	51.6 ± 10.3
AUC _{0-∞} (ng.hr/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 haemodialysis removed approximately 35% of the adefovir dose. The effect of peritoneal dialysis on adefovir removal has not been evaluated.

Hepatic impairment: Pharmacokinetic properties were similar in patients with moderate and severe hepatic impairment compared to healthy volunteers. No change in dosing is required in patients with hepatic impairment.

Drug interactions: At concentrations substantially higher (> 4000 fold) than those observed *in vivo*, adefovir did not inhibit any of the following human CYP 450 isoforms, 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 known elimination pathway of adefovir, the potential for CYP450 mediated interactions involving adefovir 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), paracetamol (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 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, paracetamol, tenofovir disoproxil fumarate or ibuprofen.

The pharmacokinetics of adefovir were unchanged when HEPSERA was co-administered with lamivudine, trimethoprim/ sulfamethoxazole, and paracetamol, and tenofovir disoproxil fumarate. When HEPSERA was co-administered 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.

There has been no clinical evaluation of the co-administration of adefovir dipivoxil and tenofovir disoproxil fumarate in HIV/HBV co-infected patients (see also statement on nephrotoxicity under **Precautions**).

Pharmacokinetic/Pharmacodynamic relationship: Adefovir dipivoxil has demonstrated a dose-related significant and sustained anti-HBV effect at doses ranging from 5 mg to 125 mg in phase 1-2 studies of 4 to 12 weeks duration.

Intracellular pharmacokinetics: Adefovir diphosphate has an intracellular half-life of 12 to 36 hours in activated and resting lymphocytes.

Clinical Trials

HEPSERA was compared to placebo in two large controlled trials enrolling patients with chronic hepatitis B and compensated liver function. One study was conducted in patients with HBeAg positive and one study in patients with HBeAg negative disease.

HEPSERA was also studied in an open label trial enrolling chronic hepatitis B patients pre- and post-liver transplantation with lamivudine-resistant HBV and in an active-controlled, double-blind study of patients with lamivudine-resistance HBV and compensated liver function.

Study 437: HBeAg Positive Chronic Hepatitis B adults patients treated with adefovir dipivoxil (10 mg or 30 mg) or placebo.

Study 437 was a randomised, double-blind, placebo-controlled, three-arm study in patients with HBeAg positive chronic hepatitis B. Patients were serum HBsAg positive for a minimum of 6 months and HBeAg positive at screening. At baseline the median age of patients was 33 years, 74% were male, 59% were Asian and 36% were Caucasian, and 24% had prior interferon- α . Patients had a median total Knodell histology activity index (HAI) score of 10 and a median serum HBV DNA level of 8.36 log₁₀ copies/mL and a median ALT level of 2.3 times the upper limit of normal.

Study 438: Presumed Precore Mutant (HBeAg negative/anti-HBe positive/ HBV DNA positive) Chronic Hepatitis B adults patients treated with adefovir dipivoxil (10 mg) or placebo.

Study 438 was a randomised (2:1), double-blind, placebo-controlled, two arm study in patients who were HBeAg negative and HBV DNA positive at screening. At baseline the median age of patients was 46 years, 83% were male, 66% were Caucasian and 30% were Asian and 41% had prior interferon- α therapy. Patients had a median total Knodell HAI score of 10 and a median baseline serum HBV DNA level of 7.08 log₁₀ copies/mL and a median ALT level 2.3 times the upper limit of normal.

The primary efficacy parameter in both studies was histological response. Assessable, paired biopsies at baseline and week 48 were available for 88% and 91% of patients in studies 437 and 438 respectively. Other measures of response included change in serum HBV DNA, change in ALT, HBeAg loss and HBeAg seroconversion (437 only). The results are shown in Tables 3-5.

Table 3				
Histologic Improvement at Week 48				
N ^a	Study 437		Study 438	
	HEPSERA	Placebo	HEPSERA	Placebo
	168	161	121	57
Improvement ^b	89/168 (53% ^d)	41/161 (25%)	78/121 (64% ^d)	20/57 (35%)
No Improvement	63/168 (37%)	108/161 (67%)	35/121 (29%)	36/57 (63%)
Missing/ Unassessable ^c Data	16/168 (10%)	12/161 (7%)	8/121 (7%)	1/57 (2%)

a: Intent To Treat population (patients with ≥ 1 dose of study drug) with assessable baseline biopsies.
b: Histological improvement defined as ≥ 2 point decrease in the Knodell necro-inflammatory score with no worsening of the Knodell fibrosis score.
c: Post-baseline missing/unassessable biopsies for the primary analysis were considered as treatment failures.
d: p < 0.001 comparison of Placebo vs. Hepsera 10 mg.

Histological improvement was observed more frequently in patients treated with HEPSEARA than in those treated with placebo after 48 weeks of treatment. The absolute differences in response rates were 27.5% for study 437 and 30.3% for study 438.

There was an increased proportion of patients treated with HEPSEARA whose fibrosis regressed and a decreased proportion of patients treated with HEPSEARA whose fibrosis progressed when compared to patients receiving placebo (See Table 4.).

Table 4				
Changes in Ishak Fibrosis Score at Week 48				
	Study 437		Study 438	
	HEPSERA	Placebo	HEPSERA	Placebo
Number of adequate biopsy pairs	(n=152)	(n=149)	(n=113)	(n=56)
Ishak Fibrosis Score				
Improved*	52/152 (34%)	28/149 (19%)	38/113 (34%)	8/56 (14%)
Unchanged	83/152 (55%)	89/149 (60%)	70/113 (62%)	28/56 (50%)
Worsened*	17/152 (11%)	32/149 (21%)	5/113 (4%)	20/56 (36%)

* Change of 1 point or more in Ishak Fibrosis Score

Blinded, ranked assessments of both necro-inflammatory activity and fibrosis at baseline and at week 48 demonstrated that patients treated with HEPSEARA had improved necro-inflammation and fibrosis compared to patients treated with placebo.

Serum HBV DNA levels were reduced at week 48 in the group receiving HEPSERA compared to placebo (see Table 5).

In Study 437, HBeAg seroconversion (12%) and HBeAg loss (24%) were observed more frequently in patients receiving HEPSERA than in patients receiving placebo (6% and 11%, respectively) after 48 weeks of treatment.

Table 5				
Change in Serum HBV DNA, ALT Normalisation, HBeAg Loss and Seroconversion at Week 48				
	Study 437		Study 438	
	HEPSERA (n=171)	Placebo (n=167)	HEPSERA (n=123)	Placebo (n=61)
HBV DNA Proportion undetectable by PCR ^a	21% ^c	0%	51% ^c	0%
Mean Change ± SD serum HBV DNA (log ₁₀ copies/mL)	-3.57 ± 1.64	-0.98 ± 1.32	-3.65 ± 1.14	-1.32 ± 1.25
ALT normalisation	81/168 (48% ^c)	26/164 (16%)	84/116 (72% ^c)	17/59 (29%)
HBeAg loss	41/171 (24% ^d)	17/161 (11%)	NA ^b	NA ^b
HBeAg Seroconversion	20/171 (12% ^e)	9/161 (6%)	NA ^b	NA ^b
a: Lower limit of quantification- Roche Amplicor™ polymerase chain reaction assay <400 copies/mL b: Patients with HBeAg _{negative} disease cannot undergo HBeAg seroconversion c: p < 0.001 d: p = 0.001 e: p < 0.05				

Treatment beyond 48 weeks:

In Study 437 with continued treatment beyond 48 weeks, maintenance of reductions in serum HBV DNA, and increases in ALT normalization, HBeAg loss and HBeAg seroconversion were observed.

In Study 438, patients who received HEPSERA during the first 48 weeks were re-randomised (2:1) in a blinded manner to continue on HEPSERA or receive placebo for an additional 48 weeks, whereas patients previously in the placebo arm commenced on HEPSERA. Measures of response included change in serum HBV DNA and change in ALT. Histology was only reported on a subset of patients at Week 96 as biopsy at this time point was optional. Of the 179 patients enrolled in the second 48 weeks of the study, 96% had assessable biopsies at baseline and Week 48 and 27% had assessable biopsies at baseline, Week 48 and Week 96. The results to Week 96 are presented in Tables 6 and 7.

	HEPSERA (to Wk 48) & HEPSERA (to Wk 96)			HEPSERA (to Wk 48) & Placebo (to Wk 96)			Placebo (to Wk 48) & HEPSERA (to Wk 96)		
	0-48 wks	48-96 wks	0-96 wks	0-48 wks	48-96 wks	0-96 wks	0-48 wks	48-96 wks	0-96 wks
Histological Improvement**	65% (48/74)	37% (7/19)	79% (15/19)	76% (29/38)	0% (0/9)	25% (2/8)	35% (19/55)	70% (14/20)	57% (12/21)
No Histological Improvement	35% (26/74)	63% (12/19)	21% (4/19)	24% (9/38)	100% (9/9)	75% (6/8)	65% (36/55)	30% (6/20)	43% (9/21)

* ITT population. Missing/unassessable biopsies are excluded.
** Improvement defined as ≥ 2 -point decrease in Knodell necro-inflammatory score with no worsening in fibrosis score.

At week 96, 50/70 (71%) of patients receiving continued treatment with HEPSEARA achieved a reduction in viral load to non-detectable levels (<1000 copies/mL), and 73% of patients had normalisation of ALT levels. In most patients who stopped treatment with HEPSEARA, HBV DNA and ALT levels returned towards baseline and there was a reversion of histological improvement.

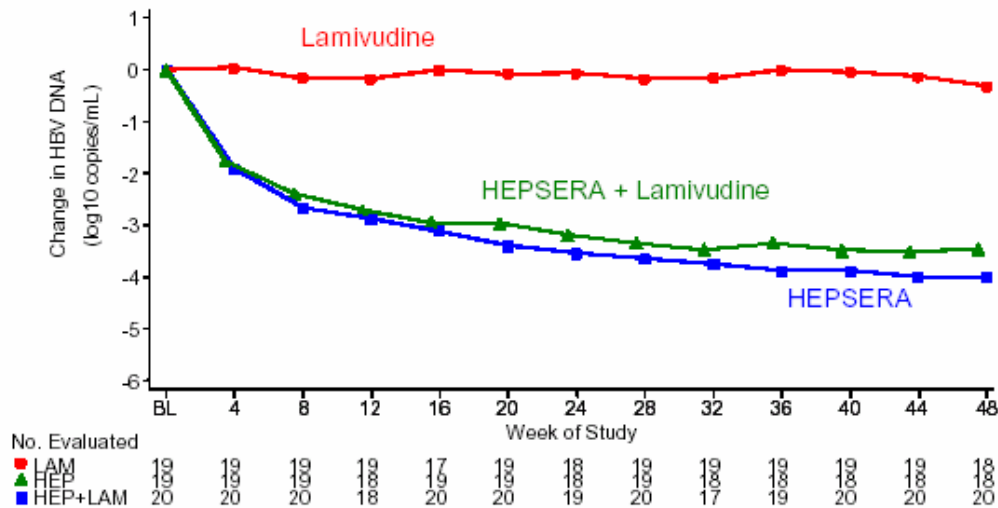
	HEPSERA (to Wk 48) & HEPSERA (to Wk 96)		HEPSERA (to Wk 48) & Placebo (to Wk 96)		Placebo (to Wk 48) & HEPSERA (to Wk 96)	
	Wk 48	Wk 96	Wk 48	Wk 96	Wk 48	Wk 96
HBV DNA Proportion undetectable by PCR ^a , n/N (%) ^b	68% (53/78)	71% (50/70)	67% (26/39)	8% (3/38)	4% (2/56)	76% (37/49)
Mean Change \pm SD serum HBV DNA (log ₁₀ copies/mL)	-3.42 \pm 0.99 (n=78)	-3.35 \pm 1.18 (n=70)	-3.46 \pm 1.14 (n=39)	-1.34 \pm 1.24 (n=38)	-1.33 \pm 1.23 (n=56)	-3.71 \pm 1.05 (n=49)
ALT normalisation (< ULN), n/N (%) ^c	75% (54/72)	73% (47/64)	79% (31/39)	32% (12/38)	33% (18/54)	80% (40/50)

a: Roche Amplicor™ polymerase chain reaction assay (LLOQ = 1000 copies/mL).
b: n = no. of patients with HBV DNA < 1000 copies/mL at time point, N= no. of patients with HBV DNA \geq 1000 copies/mL at baseline.
c: n = no. of patients with ALT levels < ULN at time point, N= no. of patients with ALT levels > ULN at baseline and non-missing values at week 48. ULN for ALT was defined as 43 IU/L for males and 34 IU/L for females.

Pre- and Post-liver Transplantation Patients: HEPSEARA was also evaluated in an open-label, uncontrolled study in 324 chronic hepatitis B patients pre- (n=128) and post- (n=196) liver transplantation with clinical evidence of lamivudine-resistant HBV (Study 435). Median baseline HBV DNA was 7.4 and 8.2 log₁₀ copies/mL, and median baseline ALT values were 75 (1.8 x ULN) and 83 (2.1 x ULN) IU/L in pre- and post-liver transplantation patients, respectively. Treatment with HEPSEARA resulted in a reduction in serum HBV DNA from baseline at week 48. Improvements were seen in Child-Pugh-Turcotte score, with normalisation of ALT, albumin, bilirubin and prothrombin time at week 48, as shown in Table 8. HEPSEARA showed similar efficacy regardless of the patterns of lamivudine-resistant HBV DNA polymerase mutations at baseline. The clinical significance of these findings as they relate to histological improvement is not known.

Table 8 Efficacy in Pre- and Post- Liver Transplantation Patients at Week 48 Study 435		
Efficacy Parameter	Pre-liver transplantation	Post-liver transplantation
Mean \pm SD change in HBV DNA from baseline (log ₁₀ copies/mL)	-3.8 \pm 1.4 (n=21)	-4.1 \pm 1.6 (n=86)
HBV DNA (below lower limit of assay quantification*)	17/21 (81%)	29/86 (34%)
Stable or improved Child-Pugh-Turcotte score	24/26 (92%)**	52/54 (96%)
Normalisation of: ***		
ALT	13/17 (76 %)	35/72 (49 %)
Albumin	13/16 (81 %)	13/17 (76 %)
Bilirubin	9/18 (50 %)	18/24 (75 %)
Prothrombin time	10/12 (83 %)	1/5 (20 %)
* Lower limit of quantification of either < 400 copies/mL or < 1000 copies/mL ** 24 week data *** Denominator is number of patients with abnormal values at baseline		

Efficacy in Lamivudine Resistant Virus: In Study 461, a double-blind, active controlled study in 59 chronic hepatitis B patients with clinical evidence of lamivudine-resistant (YMDD-mutant) hepatitis B virus, patients were randomised to receive either HEPSERA monotherapy, HEPSERA in combination with lamivudine 100 mg, or lamivudine 100 mg alone. At week 48, the mean \pm SD decrease in serum HBV DNA was 4.00 ± 1.41 log₁₀ copies/mL for patients treated with HEPSERA and 3.46 ± 1.10 log₁₀ copies/mL for patients treated with HEPSERA in combination with lamivudine. These were significant reductions when compared to the mean decrease in serum HBV DNA of 0.31 ± 0.93 log₁₀ copies/mL in patients receiving lamivudine alone ($p < 0.001$). ALT normalised 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 mean changes in serum HBV DNA over time are summarised in Figure 1 below.



Monotherapy with HEPSERA resulted in a progressive loss of YMDD mutations through 48 weeks; 7 patients (37%) in this treatment group had reverted to wild-type HBV at week 48. Continuation of lamivudine therapy, either as monotherapy or in combination with HEPSERA resulted in the maintenance of YMDD mutations with only one patient in the combination treatment arm reverting to HBV without YMDD mutations through 48 weeks of treatment. Loss of YMDD mutations in the HEPSERA-treated patients was not associated with serum HBV DNA increases or ALT flares. There was no evidence of the development of adefovir-associated resistance mutations in the HBV polymerase during 48 weeks of treatment with HEPSERA either alone or in combination with lamivudine.

There is no clinical data in patients co-infected with hepatitis C or delta virus.

INDICATIONS

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-/HBVDNA+ chronic hepatitis B with compensated liver function, and in adults patients with clinical evidence of lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function.

CONTRAINDICATIONS

HEPSERA is contraindicated in patients with known hypersensitivity to adefovir, adefovir dipivoxil or to any of the excipients in adefovir dipivoxil tablets.

PRECAUTIONS

Post-treatment Exacerbations of Hepatitis

Severe acute exacerbation of hepatitis has been reported in patients with discontinuation of anti-hepatitis B therapy, including HEPSERA. Patients who discontinue the drug should be

monitored at repeated intervals over a period of time for hepatic function. 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. 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.

Changes in Renal Function

Adefovir is eliminated by renal excretion, therefore adjustments to the dosing interval of HEPSERA are recommended in patients with renal insufficiency (See **DOSAGE AND ADMINISTRATION**).

Nephrotoxicity

Chronic administration of HEPSERA (10 mg once daily) may result in nephrotoxicity. Nephrotoxicity characterised 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). 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.

Caution should be exercised when HEPSERA is administered concomitantly with nephrotoxic agents.

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 unrecognised 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).

Use in children: Safety and efficacy of HEPSERA in pediatric patients have not been established. HEPSERA should not be administered to children and adolescents under the age of 18.

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

Drug Interactions

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, paracetamol, ibuprofen 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 Pharmacokinetics**).

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 and no dose adjustment is recommended (**See Pharmacokinetics**).

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

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity studies in mice and rats receiving adefovir have been conducted. In mice, at oral dose levels of 1, 3, or 10 mg/kg/day, no treatment-related increases in tumor incidence were found at 10 mg/kg/day (systemic exposure (AUC) was approximately 10 times that achieved in humans at a therapeutic dose of 10 mg/day). In rats dosed at oral levels of 0.5, 1.5, or 5 mg/kg/day, no drug-related increase in tumor incidence was observed (systemic exposure (AUC) at the high dose was approximately four times that at the human therapeutic dose). 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 was not clastogenic in the *in vivo* mouse micronucleus assay at oral doses up to 2,000 mg/kg and it 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 oral doses up to 30 mg/kg/day (systemic exposure (AUC) approximately 19 times that achieved in humans at the therapeutic dose).

Use in Pregnancy

Pregnancy Category B3

Reproduction studies conducted with adefovir dipivoxil administered orally have shown no embryotoxicity or teratogenicity in rats at doses up to 35 mg/kg/day (systemic exposure (AUC) at least 23 times that achieved in humans at the therapeutic dose of 10 mg/day), or in rabbits at 20 mg/kg/day (systemic exposure (AUC) 40 times humans).

When adefovir was administered intravenously to pregnant rats at doses associated with notable maternal toxicity (20 mg/kg/day, systemic exposure (AUC) at least 38 times human), embryotoxicity and an increased incidence of foetal 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 2.5 mg/kg/day (systemic exposure (AUC) 12 times 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.

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 immunisations should be used to prevent neonatal acquisition of hepatitis B virus.

Use in Lactation

It is not known whether adefovir is excreted in human or animal milk. Mothers should be instructed not to breastfeed if they are taking HEPSERA.

Effects on ability to drive and use machines: No studies on the effects on ability to drive or use machines have been performed.

ADVERSE REACTIONS

Adults with Compensated Liver Disease

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.

Treatment-Related Adverse Events:

A summary of the most frequently reported treatment-related adverse events of HEPSERA is provided in Table 9. Adverse events in the HEPSERA and placebo groups occurred with similar frequency.

Table 9 Treatment-Related Adverse Events (Grades 1-4) Reported In \geq 3% of HEPSERA-Treated Patients in the Pooled 437-438 Studies (0-48 weeks)		
	HEPSERA n = 294	Placebo n = 228
Asthenia	13%	14%
Headache	9%	10%
Abdominal pain	9%	11%
Nausea	5%	8%
Flatulence	4%	4%
Diarrhoea	3%	4%
Dyspepsia	3%	2%

Laboratory Abnormalities:

In patients with adequate renal function, no patients developed a serum creatinine increase \geq 0.5 mg/dL from baseline by week 48. By week 96, 2% of HEPSERA-treated patients, by Kaplan-Meier estimate, had increases in serum creatinine \geq 0.5 mg/dL from baseline (**see Special Risk Patients section below for changes in serum creatinine in patients with underlying renal insufficiency at baseline**).

A summary of grade 3 and 4 laboratory abnormalities is provided in Table 10.

Table 10 Grade 3-4 Laboratory Abnormalities Reported in \geq 1% of All HEPSERA-Treated Patients in the Pooled 437-438 Studies (0-48 weeks)		
	HEPSERA n=294	Placebo N=228
ALT ($>$ 5 x ULN)	20%	41%
Haematuria (\geq 3+)	11%	10%
AST ($>$ 5 x ULN)	8%	23%
CK ($>$ 4 X ULN)	7%	7%
Amylase ($>$ 2 x ULN)	4%	4%
Glycosuria (\geq 3+)	1%	3%

Special Risk Patients

Pre- (n=128) and post-liver transplantation patients (n=196) 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 129 weeks, with a median time on treatment of 19 and 56 weeks, respectively. The majority

of these patients had some degree of underlying renal insufficiency at baseline or other risk factors for renal dysfunction during treatment. Increases in serum creatinine ≥ 0.5 mg/dL from baseline were observed in 16% of these patients by week 48 and 31% by week 96 by Kaplan-Meier estimates. Of the 324 patients treated, elevations in serum creatinine ≥ 0.5 mg/dL from baseline was observed in 41 patients. 7 of 41 resolved on continued treatment (≤ 0.3 mg/dL from baseline), 18 of 41 remained unchanged and 16 of 41 had not resolved. Additionally, decreases in serum phosphorus were observed in 4% of these patients by week 48, and 6% by week 96 by Kaplan-Meier estimates. One percent (3 of 324) of pre- and post-liver transplantation patients discontinued HEPSERA due to renal events.

Due to the presence of multiple concomitant risk factors for renal dysfunction in these patients, the contributory role of HEPSERA to these changes in serum creatinine and serum phosphorus is difficult to assess.

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

Body as a whole: asthenia, abdominal pain, headache, fever

Gastrointestinal: nausea, vomiting, diarrhoea, flatulence, hepatic failure

Metabolic and Nutritional: increases in ALT and AST, abnormal liver function

Respiratory: increased cough, pharyngitis, sinusitis

Skin and Appendages: pruritus, rash

Urogenital: increases in creatinine, renal failure, renal insufficiency

DOSAGE AND ADMINISTRATION

Adults: The recommended dose of HEPSERA is one tablet, once daily taken orally, without regard to food. Doses higher than those recommended must not be administered. The optimum duration of treatment is unknown.

Children and adolescents: The safety and efficacy of HEPSERA in patients under the age of 18 years have not been established. HEPSERA should not be administered to children or adolescents.

Elderly: No data are available to support a dose recommendation for patients over the age of 65 years. In general, caution should be exercised when prescribing to elderly patients, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal insufficiency: 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 11). The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Additionally, it is important to note that these guidelines are for 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 11				
Dosing interval adjustments of HEPSERA in patients with renal impairment				
	Creatinine Clearance (mL/min)*			
	≥ 50	20-49	10-19	Haemodialysis 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 has not been evaluated in non-haemodialysis patients with creatinine clearance < 10 mL/min, therefore, no dosing recommendation is available for these patients.

Hepatic impairment: Pharmacokinetic properties were similar in patients with moderate and severe hepatic impairment compared to healthy volunteers. No change in dosing is required in patients with hepatic impairment.

OVERDOSAGE

Daily doses of adefovir dipivoxil 500 mg 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.

Adefovir can be removed by haemodialysis (see Pharmacokinetics, *Renal Impairment*). The elimination of adefovir by peritoneal dialysis has not been studied.

PRESENTATION

HEPSERA are white, flat-faced tablets debossed with “10” and “GILEAD” on one side and the stylised figure of a liver on the other side.

HEPSERA is supplied in high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and desiccant (silica gel).

POISONS SCHEDULE OF THE DRUG: S4

NAME AND ADDRESS OF SPONSOR

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