

DATA SHEET

Hepsera® (adefovir dipivoxil 10 mg) Tablets

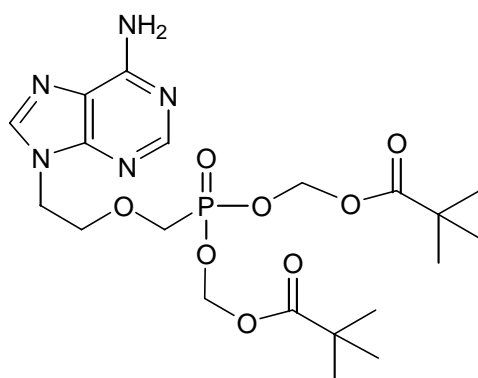
NAME OF THE MEDICINE

HEPSERA

The active ingredient in HEPSERA is adefovir dipivoxil.

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]phosphinyl]methoxy]ethyl]adenine.

Chemical Structure



Molecular formula: $C_{20}H_{32}N_5O_8P$

Molecular weight: 501.48

CAS Registry No.: 142340-99-6

DESCRIPTION

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.

HEPSERA tablets contain croscarmellose sodium, lactose monohydrate, magnesium stearate, pregelatinised maize starch, and talc.

PHARMACOLOGY

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.

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 μM and 0.97 μM , respectively.

Pharmacokinetics

The pharmacokinetics of adefovir have been evaluated in healthy adult volunteers and adult patients with chronic hepatitis B. Adefovir pharmacokinetics are similar between these populations. The pharmacokinetics of adefovir has also been investigated in adult 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 ($\text{AUC}_{0-\infty}$) 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 $\mu\text{g/mL}$. 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.

Gender: Pharmacokinetics of adefovir were similar in male and female patients.

Adolescent Patients: The pharmacokinetics of adefovir were assessed from drug plasma concentrations in 53 HBeAg+ hepatitis B patients with compensated liver disease. The exposure of adefovir following a 48 week daily treatment with HEPSERA in adolescent

patients aged 12 to <18 years ($C_{max} = 21.96$ ng/mL and $AUC_{0-24} = 248.8$ ng.h/mL) was comparable to that observed in adult patients.

Elderly Patients: There are no detailed pharmacokinetic data in the elderly.

Renal impairment: In adults 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 1, the pharmacokinetics of adefovir in patients with varying degrees of renal impairment, following a single 10 mg dose of HEPSERA, are described.

Table 1 Pharmacokinetic Parameters (Mean \pm 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 \pm 3.22	22.4 \pm 4.0	28.5 \pm 8.57	51.6 \pm 10.3
AUC _{0-∞} (ng.hr/mL)	201 \pm 40.8	266 \pm 55.7	455 \pm 176	1240 \pm 629
CL/F (mL/min)	469 \pm 99.0	356 \pm 85.6	237 \pm 118	91.7 \pm 51.3
CL _{renal} (mL/min)	231 \pm 48.9	148 \pm 39.3	83.9 \pm 27.5	37.0 \pm 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.

The pharmacokinetics of adefovir have not been studied in adolescent patients with renal dysfunction.

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 in healthy volunteers following multiple dose administration of HEPSERA (10 mg once daily) in combination with lamivudine (100 mg once daily)(n=18), trimethoprim/ sulfamethoxazole (160/800 mg twice daily)(n=18), paracetamol (1000 mg four times daily)(n=20) and ibuprofen (800 mg three times daily)(n=18). The pharmacokinetics of adefovir have also been evaluated in healthy volunteers following single dose HEPSERA in combination with single dose pegylated interferon α -2a (PEG-IFN) (180 μ g) (n=15). In addition the pharmacokinetics of adefovir have

also been evaluated in post-liver transplantation patients following multiple dose administration of HEPSERA (10 mg once daily) in combination with tacrolimus (n=16).

Adefovir did not alter the pharmacokinetics of lamivudine, trimethoprim/ sulfamethoxazole, paracetamol, tenofovir disoproxil fumarate and ibuprofen. The evaluation of the effect of adefovir on the pharmacokinetics of pegylated interferon α -2a was inconclusive.

The pharmacokinetics of adefovir were unchanged when HEPSERA was co-administered with lamivudine, trimethoprim/ sulfamethoxazole, and paracetamol, tenofovir disoproxil fumarate, tacrolimus and pegylated interferon α -2a. 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.

Microbiology

Resistance to adefovir dipivoxil can result in loss of efficacy and exacerbation of hepatitis B.

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 \log_{10} 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* IC_{50} (concentration of drug which inhibits viral replication by 50%) of adefovir against wild-type HBV is 0.2-2.5 μ M in human hepatic cell lines.

Table 2 Antiviral Sensitivity to Adefovir of Lamivudine-Resistant HBV DNA Polymerase Mutations in Cell Culture

Mutations/Strains	Fold Resistance ¹	
	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/HIV co-infected patients), genotypic 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, 192 and 240 weeks of treatment with adefovir dipivoxil, resistance surveillance was performed for 293, 221, 116 and 64 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%, 14% and 25% after 96, 144, 192 and 240 weeks respectively. These cumulative probabilities combine results in patients receiving adefovir dipivoxil as monotherapy and in combination with lamivudine.

In HBeAg negative patients receiving adefovir dipivoxil monotherapy, the cumulative probabilities (life table analysis) of developing these adefovir-associated resistance mutations were approximately 0%, 3%, 11%, 18% and 29% after 48, 96, 144, 192 and 240 weeks respectively.

In addition, the long term (4 to 5 years) development of resistance to adefovir dipivoxil was significantly lower in patients who had serum HBV DNA below the limit of quantification (less than 1,000 copies/mL) at week 48 as compared to patients with serum HBV DNA above 1,000 copies/mL at week 48.

In HBeAg-positive patients, the incidence of adefovir-associated resistance mutations was 3%, 17%, and 20% after a median duration on adefovir dipivoxil of 135, 189 and 235 weeks respectively.

Studies where adefovir dipivoxil was added to ongoing lamivudine in patients with lamivudine-resistance: In an open-label study of pre- and post-liver transplantation patients with clinical evidence of lamivudine-resistant hepatitis B virus (study 435), the incidence of adefovir-associated resistance (rtN236T or rtA181V) mutations was 0% at 48 weeks. With up to 3 years of exposure, no patients receiving both adefovir dipivoxil and lamivudine developed resistance to adefovir dipivoxil. However, 4 patients who discontinued lamivudine treatment developed the rtN236T mutation while receiving adefovir dipivoxil monotherapy and all experienced serum HBV DNA rebound. All 4 patients who developed the rtN236T mutation in their HBV lost the lamivudine-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-associated mutations were observed in HBV isolates from any of the 15 patients tested after 144 weeks of therapy.

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 and 144 weeks of HEPSERA 10 mg therapy in 35 and 15 HIV/HBV co-infected patients, respectively. Further genotypic analysis from seven patients after 144 weeks of HEPSERA treatment also did not identify the K65R or K70E mutations in these patients.

Clinical resistance in adolescent patients: In a Phase 3 study GS-US-103-0518 (study 518), HBV isolates from 49 of 56 adolescents patients (aged 12 to <18 years) has serum HBV DNA >169 copies/mL and were evaluated for adefovir resistance-associated substitutions. rtN236T and/or rtA181V adefovir resistance-associated substitutions were not observed at 48 weeks. However, the rtA181T substitution was present in baseline and week 48 isolates from two lamivudine-experienced adolescent patients treated with HEPSERA. Assessment for the development of potential drug resistance for those patients that experience virologic failure will continue through the end of the study (maximum treatment duration 240 weeks).

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 anti-HBe 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. At baseline patients had a median total Knodell HAI score of 10, 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

	Study 437		Study 438	
	HEPSERA	Placebo	HEPSERA	Placebo
N ^a	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.

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	36/171 (21% ^c)	0/167 (0%)	63/123 (51% ^c)	0/61 (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 normalization	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.

Table 6 Histological Improvement to Week 96 Study 438*

	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 HEPSERA achieved a reduction in viral load to non-detectable levels (<1000 copies/mL), and 47/64 (73%) of patients had normalisation of ALT levels. In most patients who stopped treatment with HEPSERA, HBV DNA and ALT levels returned towards baseline and there was a reversion of histological improvement.

Table 7 Change in Serum HBV DNA and Percent of Patients with HBV DNA <1000 c/mL and ALT Normalisation at Week 48 and Week 96 Study 438

	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)
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 and non-missing value at time point.

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 time point. ULN for ALT was defined as 43 IU/L for males and 34 IU/L for females.

Long Term Safety and Efficacy Study (LTSES) component of Study 438

Patients who received placebo during the first 48 weeks and HEPSERA during the second 48 weeks and patients who received HEPSERA during the first and second 48 weeks continued on HEPSERA for up to 144 additional weeks for a total of up to 192 weeks of treatment (192-week cohort) or up to 240 weeks of treatment (240-week cohort), respectively. Those patients receiving placebo during weeks 49 to 96 were not eligible to enter the Long Term Safety and Efficacy Study (LTSES). 125 patients entered and were analysed as part of the LTSES, covering a total duration of exposure to HEPSERA of up to 240 weeks.

HBV DNA levels were undetectable in 53 of 69 (77%), 51 of 65 (78%) and 37 of 55 (67%) of patients following treatment with HEPSERA for 144, 192, and 240 weeks respectively. ALT normalization was attained in 43 of 64 (67%), 44 of 59 (75%), and 38 of 55 (69%) of patients following treatment with HEPSERA for 144, 192, and 240 weeks respectively. Similar percentages of undetectable DNA and ALT normalization were observed at weeks 144 and 192 for patients who received HEPSERA in the 192-week cohort. The results are based on remaining patients at each time point rather than all participating patients, as such these results should be interpreted with caution due to implicit survival bias.

Twelve of 22 (55%) patients treated with HEPSERA in the 192-week cohort and 17 of 24 (71%) patients treated in the 240-week cohort had an improved Ishak Fibrosis Score. In the combined 192-week and 240-week cohorts, 7 of 12 patients (58%) with bridging fibrosis or cirrhosis at baseline had an improved Ishak Fibrosis Score of ≥ 2 points after 192 weeks of treatment or 240 weeks of treatment with HEPSERA. The results are based on remaining patients at each time point rather than all participating patients, as such these results should be interpreted with caution due to implicit survival bias.

In both cohorts, 6 of 125 patients (5%) who received HEPSERA experienced HBsAg loss. Five of these 6 patients also achieved and maintained HBsAg seroconversion (HBsAg-/HBsAb+).

A 29% cumulative probability of developing a resistance mutation by week 240 was identified, with a 13% incidence between 193 and 240 weeks of HEPSERA treatment (see Microbiology). Eleven patients who developed genotypic resistance were then treated with lamivudine, all 10 of the patients with HBV DNA subsequently measured demonstrated a response (≥ 1 log₁₀ c/mL drop) to the lamivudine. The decreases in serum HBV DNA in patients harbouring the rtN236T or the rtA181V variants from the start of lamivudine treatment to the last available data ranged from 2.0 to 6.2 log₁₀ copies per mL.

Pre- and Post-liver Transplantation Patients:

HEPSERA was also evaluated in an open-label, uncontrolled study in 467 chronic hepatitis B patients aged 16 to 75 years old, pre- (n=226) and post- (n=241) liver transplantation with clinical evidence of lamivudine-resistant HBV (Study 435). At baseline, 60% of pre-liver transplantation patients were classified as Child-Pugh-Turcotte score of Class B or C which is indicative of moderate to severe decompensated liver disease. Median baseline HBV DNA was 7.4 and 8.2 log₁₀ copies/mL, and median baseline ALT values were 77 (1.8 x ULN) and 82 (2.0 x ULN) IU/L in pre- and post-liver transplantation patients, respectively. Treatment with HEPSERA 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. HEPSERA showed similar efficacy regardless of the patterns of lamivudine-resistant HBV DNA polymerase mutations at baseline. The mean improvement in CPT scores in post-transplantation cohort at 48 weeks was 0.2 ± 0.6 in Class A patients at baseline, compared to 2.3 ± 1.6 in patients who were Class B or C at baseline.

In the pre-transplantation cohort, 61/226 (27%) underwent on-study liver transplant.

Treatment Beyond 48 Weeks:

In the pre-liver transplantation cohort, 33 of the 177 patients that had detectable HBV DNA levels (≥ 1000 copies/mL) at baseline were still on study at the 96 week time point; 25 of these patients had achieved undetectable HBV DNA levels (< 1000 copies/mL) at 96 weeks. Also in the pre-liver transplant cohort, 19 of the 149 patients that had ALT $>$ ULN at baseline were still on study at the 96 week time point; 16 of those patients had ALT normalization at 96 weeks.

In the post-liver transplantation cohort, of the 202 patients that had detectable HBV DNA levels (≥ 1000 copies/mL) at baseline, 94 patients were still on study at the 96 week time point and 45 patients at the 144 week time point; 61 of these patients at 96 weeks and 35 patients at 144 weeks achieved undetectable HBV DNA levels (< 1000 copies/mL) at those time points. Also in the post-liver transplant cohort, of the 156 patients that had ALT $>$ ULN at baseline, 66 patients were still on study at the 96 week time point and 26 patients at the 144 week time point; 46 of these patients at 96 weeks and 15 patients at 144 weeks had ALT normalization at those time points.

The estimated probability of survival in the pre-liver transplant population was 84% by week 48 and 77% by week 96. In the post-liver transplant population the estimated probabilities were 91% by week 48, 88% by week 96 and 87% by week 144. Sixty-seven patients (14.3%) died during treatment or within 30 days of last study dose: 27 (11%) of 241 patients in the post-transplant cohort, 40 (18%) of 226 of patients in the pre-transplant cohort. Forty-seven (70%) of the deaths occurred in the first 24 weeks of the study. Immediate causes of death were related to complications of end-stage liver disease or transplantation surgery in the majority of patients and were judged to be unrelated to HEPSERA treatment.

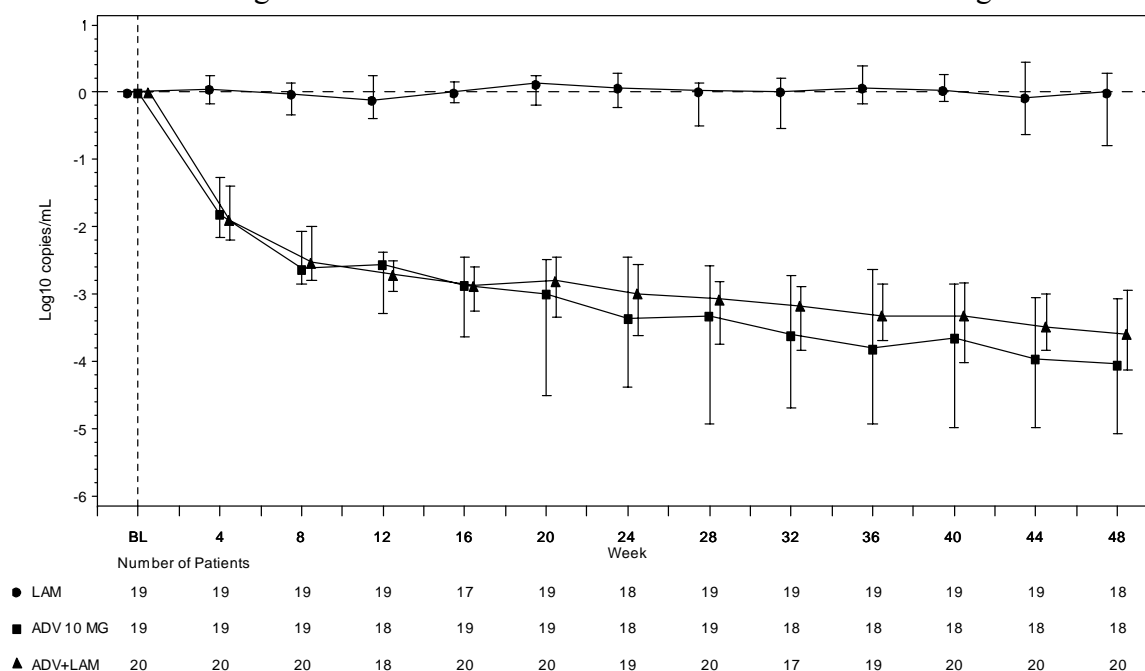
Table 8 Efficacy in Pre- and Post- Liver Transplantation Patients at Week 48 and Week 96 Study 435

Efficacy Parameter	Pre-liver transplantation n=226		Post-liver transplantation n=241	
	48 Weeks	96 Weeks	48 Weeks	96 Weeks
Mean \pm SD change in HBV DNA from baseline (log ₁₀ copies/mL)	-3.7 \pm 1.6 (n=117)	-3.9 \pm 1.5 (n=35)	-4.0 \pm 1.6 (n=164)	-4.5 \pm 1.5 (n=96)
Proportion with undetectable HBV DNA (≤ 1000 copies/mL) ¹	77/109	25/33	64/159	61/94
Stable or improved Child-Pugh-Turcotte score	86/90	6/6	107/115	60/63
Normalisation of: ²				
ALT	61/82	16/19	56/110	46/66
Albumin	43/54	16/17	21/26	11/12
Bilirubin	38/66	12/19	29/38	19/22
Prothrombin time	39/46	- ³	5/9	- ³
HBeAg loss ⁴	15/31	7/8	30/98	29/50
HBeAg Seroconversion ⁵	7/31	3/8	11/98	17/50

1. Denominator is the number of patients with serum HBV DNA ≥ 1000 copies/mL at baseline using the Roche Amplicor PCR Assay (LLOQ = 1000 copies/mL) and non-missing value at week 48 or 96 assessment as appropriate. 2. Denominator is number of patients with abnormal values at baseline and non-missing value at week 48 or 96 assessment as appropriate. 3. Very few patients had prothrombin time data beyond 48 weeks. 4. Defined as the loss of HBeAg regardless of anti-HBe status. Denominator is the number of patients HBeAg+ and non-missing value at week 48 or 96 assessment as appropriate. Excludes post-transplant data for patients who were waitlisted and had on-study transplants. 5. Defined as loss of HBeAg and gain of anti-HBe; denominator is the number of patients HBeAg+ at baseline and non-missing value at week 48 or 96 assessment as appropriate. Excludes post-transplant data for patients who were waitlisted and had on-study transplants. Results should be interpreted with caution due to implicit survival bias at each time point.

Efficacy in Lamivudine Resistant Virus:

In Study 461, a double-blind, active controlled study in 59 chronic hepatitis B adult 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.

Study 493 was a double-blind, active controlled study in patients with chronic hepatitis B who had developed a YMDD variant hepatitis B virus with evidence of reduced response to lamivudine. Stratum A [HBeAg-positive, compensated patients (n=78)] were randomised 1:1 to receive either HEPSERA once daily or placebo in addition to once daily 100mg lamivudine. Stratum B [HBeAg-positive or negative, decompensated, (n=38)] was open label with patients receiving HEPSERA in addition to once daily 100mg lamivudine. The study had an initial treatment period of 52 weeks but was extended to 104 weeks as a follow-on study with blinding and randomised treatments unchanged. Disease progression was defined

in the protocol as increase in Child-Pugh-Turcotte of 2 or more points at consecutive visits (4 weeks apart), spontaneous bacterial peritonitis, bleeding gastric/esophageal varices or hepatocellular carcinoma. The proportion of patients with hepatitis B disease progression during the study was greater for the Stratum A placebo + lamivudine treatment group (18%) than for the HEPSERA + lamivudine treatment group (3%). For Stratum B, 11% of patients had disease progression.

After 104 weeks of treatment, the Stratum A HEPSERA + lamivudine active arm showed a lower incidence (52% (17/33)) of detectable YMDD variant HBV compared to lamivudine + placebo (92% (22/24)). Seven of 31 (23%) Stratum B patients with viral genome assessment had detectable YMDD variant HBV at week 104.

At weeks 100 and 104 of treatment, 76% of subjects receiving Hepsera in addition to lamivudine versus 13% receiving lamivudine and placebo in Stratum A had serum HBV DNA concentrations $\leq 10^5$ copies/mL or a ≥ 2 log₁₀ reduction from baseline. Eighty seven percent (87%) of Stratum B patients had an HBV DNA response at weeks 100 and 104. Forty-nine percent of HEPSERA + lamivudine patients versus 10% had an ALT response; 64% of Stratum B patients had an ALT response. At week 104, HBeAg loss and seroconversion were observed in similar proportions of Stratum A subjects in the HEPSERA + lamivudine treatment groups (18% and 12%, respectively) compared to the placebo + lamivudine treatment group (12% and 9%, respectively). At week 104, 38% of Stratum B subjects exhibited HBeAg loss and 15% seroconverted.

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

Efficacy in Paediatric (2 to <12 years) and Adolescent (12 to <18 years) Patients:

Study 518 was a phase 3, double-blind, randomized, placebo-controlled, study in which 170 HBeAg+ and 3 HBeAg- paediatric patients (aged 2 to <12) or adolescent patients (aged 12 to <18) with chronic hepatitis B and elevated ALT were randomised 2:1 (115 receiving HEPSERA and 58 receiving placebo) for a period of 48 weeks. Randomisation was stratified by prior treatment and age 2 to <7 years old (cohort 1, n=35), 7 to <12 years old (cohort 2, n=55) and 12 to <18 years old (cohort 3, n=83). All patients in cohort 3 received 10 mg tablet formulation; all patients in cohorts 1 and 2 received an investigational suspension formulation (0.3 mg/kg/day cohort 1, 0.25 mg/kg/day cohort 2) once daily. This study has a subsequent open-label period (week 49 to 240) which is currently ongoing.

The primary efficacy endpoint was HBV DNA <1000 copies/mL plus normalization of ALT at the end of week 48.

In cohort 3 (n=83), significantly more patients treated with HEPSERA achieved the primary efficacy endpoint at the end of 48 weeks of blinded treatment (23%) when compared to the placebo-treated patients (0%), see Table 9. The proportion of patients from cohorts 1 and 2 who responded to treatment with HEPSERA was not statistically significant when compared to the placebo arm, although the adefovir plasma concentrations in these patients were comparable to those observed in older patients. Overall, 22 of 115 (19%) of paediatric (aged 2 to <12 years) or adolescent patients (aged 12 to <18 years) who received HEPSERA vs 1 of 58 (2%) of placebo treated patients responded to treatment by week 48.

Table 9 Results of Primary Endpoint (HBV DNA <1000 copies/mL and Normal ALT)

	HBV DNA < 1000 copies/mL and Normal ALT		p-value ^c
	Baseline N (%)	End of Blinded Treatment ^b N (%)	
12-17 Years^a			
Hepsera (N=56)	0 (0)	13 (23)	p=0.007
Placebo (N=27)	0 (0)	0 (0)	
7-11 Years^a			
Hepsera (N=36)	0 (0)	6 (17)	p=0.082
Placebo (N=19)	0 (0)	0 (0)	
2-6 Years^a			
Hepsera (N=23)	0 (0)	3 (13)	p=0.64
Placebo (N=12)	0 (0)	1 (8)	
Pooled (Total)			
Hepsera (N=115)	0 (0)	22 (19)	P<0.001
Placebo (N=58)	0 (0)	1 (2)	

^a Age at first dose of study treatment; ranges are inclusive (i.e., 2 to < 7 years; ≥ 7 to < 12 years; ≥ 12 to < 18 years)

^b Week 48 data: if Week 48 was missing, Week 44 was carried forward, if Week 44 was missing, missing=failure

^c Fisher's exact test (Hepsera vs placebo at end of blinded treatment); missing = failure analysis

INDICATIONS

HEPSERA is indicated for the treatment of patients 12 years and older with chronic hepatitis B infection and evidence of hepatitis B viral replication.

For adult patients 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 adult patients with clinical evidence of lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function.

For adolescent patients (12 to <18 years of age), the indication is based on virological and biochemical responses in patients with HBeAg+ chronic hepatitis B virus with compensated 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

HEPSERA should not be administered concurrently with VIREAD (tenofovir disoproxil fumarate), TRUVADA (tenofovir disoproxil fumarate/emtricitabine combination tablet), or ATRIPLA (tenofovir disoproxil fumarate/emtricitabine/efavirenz combination tablet).

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 recommended that creatinine clearance is calculated in all patients prior to initiating therapy with HEPSERA. 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.

The efficacy and safety of HEPSERA have not been studied in patients less than 18 years of age with different degrees of renal impairment and no data are available on which to make dosage recommendations in these patients (see **DOSAGE AND ADMINISTRATION**).

Caution should therefore be exercised when prescribing HEPSERA to patients with underlying renal dysfunction and renal function in these patients should be closely monitored.

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.

Clinical Resistance

Resistance to adefovir dipivoxil can result in viral load rebound which may result in exacerbation of hepatitis B and, in the setting of diminished hepatic function, lead to liver decompensation and possible fatal outcome.

In order to reduce the risk of resistance in patients receiving adefovir dipivoxil monotherapy, a modification of treatment should be considered if serum HBV DNA remains above 1000 copies/mL at or beyond 1 year of treatment. In lamivudine-resistant patients, in order to reduce the risk of resistance, adefovir dipivoxil should be used in combination with lamivudine and not as adefovir dipivoxil monotherapy.

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: The safety, efficacy and pharmacokinetics of HEPSERA in adolescent patients (aged 12 to <18 years) were evaluated in a double-blind randomized, placebo-controlled study (518) in 83 adolescent patients with chronic hepatitis B and compensated liver disease. The proportion of patients treated with HEPSERA who achieved the primary efficacy endpoint of serum HBV DNA <1,000 copies/mL and normal ALT levels at the end of 48 weeks blinded treatment was significantly greater (23%) when compared to placebo-treated patients (0%). (See **CLINICAL STUDIES**).

Paediatric patients aged 2 to <12 years were also evaluated in Study 518 (n=90). The efficacy of HEPSERA was not significantly different from placebo in patients less than 12 years of age. The clinical data available are insufficient to draw definitive conclusions on the benefit/risk ratio of HEPSERA treatment in children below 12 years of age with chronic hepatitis B

HEPSERA is not recommended for use in children below 12 years of age.

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 tacrolimus 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 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 placebo-controlled studies (437 and 438) in which 522 patients with chronic hepatitis B and compensated liver disease received double-blind treatment with HEPSERA (n = 294) or placebo (n = 228) for 48 weeks. Adverse reactions considered at least possibly related to treatment in the first 48 weeks of treatment are listed below, by body system organ class and frequency. Frequencies are defined as very common ($\geq 1/10$) or common ($\geq 1/100, < 1/10$).

Nervous system disorders:

Common: headache

Gastrointestinal disorders:

Common: nausea, flatulence, diarrhoea, dyspepsia, abdominal pain

General disorders and administration site conditions:

Very common: asthenia

A summary of adverse events reported in the first 48 weeks is provided in Table 10. Adverse events in the HEPSERA and placebo groups occurred with similar frequency.

Table 10 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%

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.

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.

A summary of grade 3 and 4 laboratory abnormalities during the first 48 weeks is provided in Table 11.

Table 11 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%

With extended treatment in 125 HBeAg negative patients (up to 240 weeks duration), 4 patients had confirmed increases in serum creatinine of at least 0.5 mg/dL from baseline with 1 patient discontinuing from the study due to the elevated serum creatinine concentration. No patients had confirmed serum phosphorus levels of \leq 2.0 mg/dL.

With extended treatment in 65 HBeAg positive patients (up to 234 weeks duration), 6 patients had confirmed increases in serum creatinine of at least 0.5 mg/dL from baseline with 2 patients discontinuing from the study due to the elevated serum creatinine concentration.

Confirmed serum phosphorus levels of ≤ 2.0 mg/dL were observed in two patients, neither of whom discontinued from the study (see **Special Risk Patients** section below for changes in serum creatinine in patients with underlying renal insufficiency at baseline).

Special Risk Patients

Pre- and Post-transplantation lamivudine-resistant liver disease:

Pre- (n=226) and post- (n=241) liver-transplantation patients with chronic hepatitis B and lamivudine-resistant HBV were treated in an open-label study with 10 mg adefovir dipivoxil once daily for up to 203 weeks (Study 435) with a median time on treatment of 51 and 99 weeks, respectively.

Adverse events considered possibly related to treatment were:

Metabolism and nutrition disorders:

Common: hypophosphataemia

Nervous system disorders:

Common: headache

Gastrointestinal disorders:

Common: nausea, vomiting, diarrhoea, abdominal pain

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Renal and urinary disorders:

Very common: increased creatinine

Common: abnormal renal function, renal failure

General disorders and administration site conditions:

Common: asthenia

Changes in renal function occurred in wait-listed 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. Increases in serum creatinine ≥ 0.5 mg/dL from baseline were observed in 18%, 35%, and 35% of pre-liver transplantation patients by weeks 48, 96, and 144, respectively, by Kaplan-Meier estimates. Increases in serum creatinine ≥ 0.5 mg/dL from baseline were observed in 12%, 28%, and 30% of post-liver transplantation patients by weeks 48, 96, and 144, respectively, by Kaplan-Meier estimates. Elevations in serum creatinine ≥ 0.5 mg/dL from baseline resolved (≤ 0.3 mg/dL increase from baseline) in 8 of 39 (21%) patients in the pre-liver transplantation cohort and in 14 of 43 (33%) patients in the post-liver transplantation cohort by the last study visit. 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.

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.

Paediatric (2 to <12 years) and Adolescent (12 to <18 years) Patients:

Assessment of adverse reactions is based on a placebo-controlled study (study 518) in which 173 paediatric patients aged (2 to <12 years) or adolescent patients (aged 12 to <18 years) with chronic hepatitis B and compensated liver disease received double-blind treatment with HEPSERA (n=115), or placebo (n=58) for 48 weeks (see CLINICAL TRIALS).

The safety profile of HEPSERA in adolescent patients 12 to <18 years of age (n=56) was similar to that observed in adults. No paediatric patients treated with HEPSERA developed a confirmed serum creatinine increase ≥ 0.5 mg/dL or confirmed phosphorous decrease to < 2 mg/dL from baseline at week 48.

However a signal towards a higher rate of decreased appetite and/or food intake was observed in the HEPSERA arm as compared to the placebo arm. Ongoing evaluation and monitoring of safety and long-term resistance data over a longer period of therapy in children and adolescent patients is required.

Post-Marketing Experience

In addition to adverse reaction reports from clinical trials the following possible adverse reactions have also been identified during post-approval use of adefovir dipivoxil. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Hepatobiliary Disorders

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment with HEPSERA.

Metabolism and nutrition disorders:

Hypophosphataemia

Gastrointestinal disorders

Pancreatitis

Musculoskeletal and connective tissue disorders:

Osteomalacia (manifested as bone pain and infrequently contributing to fractures and myopathy, both associated with proximal renal tubulopathy).

Renal and urinary disorders:

Renal failure, proximal renal tubulopathy, Fanconi syndrome

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 recommended dose of HEPSERA in chronic hepatitis B patients ≥ 12 years of age with adequate renal function is one tablet, once daily taken orally,

without regard to food. HEPSERA is not recommended for use in children below 12 years of age.

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 adults 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 12). 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 12 Dosing Interval Adjustments of HEPSERA in Patients with Renal Impairment

	Creatinine Clearance (mL/min)*			
	≥ 50	30-49	10-29	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.

No clinical data are available to make dosing recommendations in adolescent patients with renal insufficiency (see **PRECAUTIONS**).

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.

Clinical Resistance: In order to reduce the risk of resistance in patients receiving adefovir dipivoxil monotherapy, a modification of treatment should be considered if serum HBV DNA remains above 1000 copies/mL at or beyond 1 year of treatment. In lamivudine-resistant patients, in order to reduce the risk of resistance, adefovir dipivoxil should be used in combination with lamivudine and not as adefovir dipivoxil monotherapy.

OVERDOSAGE

Daily doses of adefovir dipivoxil 500 mg for 2 weeks and 250 mg 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 AND STORAGE CONDITIONS

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).

HEPSERA should be stored in its original container below 25 °C.

MEDICINE CLASSIFICATION

Prescription Medicine.

NAME AND ADDRESS OF SPONSOR

Gilead Sciences (NZ)
Level 35, 23-29 Albert Street
Auckland
New Zealand

DATE OF PREPARATION

28 September 2011