



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Adefovir dipivoxil

Proprietary Product Name: Hepsera

Sponsor: Gilead Sciences Pty Ltd

June 2010

TGA Health Safety
Regulation

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	29 April 2010
<i>Active ingredient(s):</i>	Adefovir dipivoxil
<i>Product Name(s):</i>	Hepsera
<i>Sponsor's Name and Address:</i>	Gilead Sciences Pty Ltd Level 1, 128 Jolimont Road East Melbourne Vic 3002
<i>Dose form(s):</i>	Tablet
<i>Strength(s):</i>	10 mg
<i>Container(s):</i>	High density polyethylene (HDPE) bottles.
<i>Pack size(s):</i>	30
<i>Approved Therapeutic use:</i>	<p>Hepsera is indicated for the treatment of chronic hepatitis B in patients 12 years of age and older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.</p> <p>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.</p> <p>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.</p>
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	10 mg daily
<i>ARTG Number:</i>	96916

Product Background

Adefovir dipivoxil (ADV) is the active ingredient in Hepsera. It is a diester pro-drug of adefovir, an acyclic nucleotide analogue of adenosine monophosphate, and a potent inhibitor of hepatitis B virus (HBV) replication *in vitro* and *in vivo*.

Hepsera was initially approved for marketing in Australia in 2003 as a once-daily 10 mg tablet for the treatment of chronic hepatitis B (CHB) in the adult population (\geq 18 years of age) with evidence of active viral replication and either evidence of persistent elevations in

serum aminotransferases or histologically active disease. There is currently no paediatric or adolescent indication or dosing recommendations.

This application proposed to extend the current indication of Hepsera to include adolescent patients aged 12 – 17 years.

Hepsera is currently registered in Australia for the treatment of chronic hepatitis B (CHB) in adults. The registered and proposed indications (deletions ~~strike through~~, new text underline) as featured in the draft Australian Product Information (PI) is as follows:

HEPSERA is indicated for the treatment of chronic hepatitis B in patients 12 years of age or older ~~adults~~ with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

For adult patients: this indication is based on histological, virological, biochemical, and serological responses in adult patients with HBeAg+ and HBeAg-/HBV DNA+ 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.

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.

The proposed dose of Hepsera in CHB patients ≥ 12 years of age with adequate renal function is one 10 mg tablet, once daily taken orally, without regard to food.

Hepsera is not proposed for use in children below 12 years of age.

Regulatory Status

The product received initial ARTG Registration in 2003.

A Supplemental New Drug Application (sNDA) to support a new indication for use in adolescent patients aged 12 – 17 years was approved for marketing by the US FDA in December 2007. The indication in the US is essentially identical to the proposed Australian indication.

A Type II variation to register the new adolescent indication (patients 12 to 17 years inclusive) was also submitted to the European Medicines Agency (EMA) in June 2007. During this evaluation the Committee for Medicinal Products for Human Use (CHMP) concluded that the available clinical efficacy and safety data did not allow an assessment of the risk/benefit for Hepsera in the adolescent population. The sponsor subsequently decided not to pursue the adolescent indication. The CHMP agreed to only include paediatric and adolescent efficacy, safety and pharmacokinetic data from the pivotal study **GS-US-013-518** in Sections 4.2, 5.1 and 5.2 of the Hepsera Summary of Product Safety (SPC), and this variation was therefore approved in January 2008.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There is no requirement for a quality evaluation in an application of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There is no requirement for a nonclinical evaluation in an application of this type.

IV. Clinical Findings

Introduction

The clinical submission included the following studies from the sponsor's paediatric development program:

- One pivotal study:
 - **GS-US-103-0518** – a Phase III double-blind, randomised, placebo-controlled study of the efficacy and safety of Hepsera in children and adolescents (aged 2 to < 18) with CHB. This study analysed 173 subjects for a period of 48 weeks from May 2004 (when the first subject was screened) to May 2006 (data cut-off date; that is, the last subject observation for the submitted report). This study also had a subsequent study period (Weeks 49 – 240) in which all subjects were offered the opportunity to receive open-label Hepsera for up to an additional 192 weeks. The open-label period was reported as “on-going” at the time of this submission.
- Three completed clinical pharmacology supportive studies:
 - **GS-02-515 (Formulation A)** – a Phase I randomised, open-label pharmacokinetic study in healthy volunteers to evaluate the bioequivalence between an oral suspension formulation and the marketed 10mg tablet formulation of Hepsera.
 - **GS-02-536 (Formulation B)** – a Phase I pharmacokinetic study in health volunteers to evaluate the bioequivalence of a different oral suspension formulation and marketed 10 mg tablet formulation of Hepsera.
 - **GS-02-517** – a Phase I-II open-label study of the pharmacokinetics and safety of a single marketed 10 mg dose of Hepsera in children and adolescents (aged 2-17) with CHB.

It should be noted that data from these studies concern **all** paediatric age groups and not only the applied for age range of 12 to <18 years.

All studies were performed in accordance with international scientific and ethical standards, including, but not limited to, the International Conference of Harmonization (ICH) guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki.

Evaluator's comments: Oral suspension formulations were developed to allow age and weight-based dosing of paediatric subjects for the purpose of evaluating the efficacy and safety of this drug in this population.

Study **GS-02-517** used Suspension Formulation A to identify the doses to be evaluated for efficacy and safety in paediatric patients. After its completion, changes were made to the flavouring of the oral suspension formulation to improve its palatability. The resulting formulation, Suspension Formulation B, was then evaluated in study **GS-02-536** to establish its bioequivalence to the marketed 10 mg tablet. After bioequivalence of the formulation was said to have been established, the Phase III efficacy and safety study **GS-US-103-0518** used the investigational suspension in 2 – 11 year old subjects and the marketed 10 mg tablet in 12 – 17 year old subjects.

The oral suspension formulation is not being proposed for registration in Australia. The efficacy and safety data presented from bioequivalence studies **GS-02-515** (Formulation A – unflavoured suspension) and **GS-02-536** (Formulation B – flavoured suspension) were

acquired using Hepsera oral suspension in subjects 2 – 11 years of age. These bioequivalence studies were not reviewed in the evaluation.

Pharmacodynamics

No new pharmacodynamic studies were submitted for evaluation.

Pharmacokinetics

The pharmacokinetic data being evaluated is from two studies: **GS-02-517** and **GS-US-103-0518**. The number of Hepsera-treated paediatric subjects with CHB who were included in the pharmacokinetic analyses is presented in Table 1.

Table 1: Paediatric Subjects Included in the Hepsera Pharmacokinetic Evaluation

Study	2-6 Years ^a	7-11 Years ^a	12-17 Years ^a
GS-02-517	12	18	15
GS-US-103-0518	23	36	56

^a Age at first dose

Supportive study: GS-02-517

Study **GS-02-517** was a multi-centre, Phase I – II, open label study conducted to determine a dosage regimen for each paediatric group (from 2 – 17 years) that would produce Hepsera plasma exposure similar to that of adults¹ receiving the approved 10 mg once daily dose. It was conducted to identify the doses to be evaluated in the paediatric efficacy and safety pivotal study.

Forty-seven subjects between the ages of 2 – 17 years with CHB entered this study and were stratified into three age groups. The population included those with CHB and compensated liver disease, hepatitis B e antigen (HBeAg)-positive, with serum HBV DNA $\geq 10^5$ copies/mL and a creatinine clearance ≥ 80 mL/min. A total of 45 subjects were included in the pharmacokinetic evaluation as 2 subjects were never dosed and were excluded from further evaluations. Subjects in the two younger age groups (2 – 6 years and 7 – 11 years) received a single dose of 0.14 mg/kg² and one dose of 0.3 mg/kg³ according to a randomised 2-period crossover design. Subjects in the oldest age group (12 – 17 years) received a single fixed 10mg dose of the Hepsera. Given the pharmacokinetic parameters in the adolescent population were expected to be similar to those of adults, it appears acceptable that the 10 mg adult dose of Hepsera was used as the test dose for subjects in this age group.

This study showed a rapid absorption of Hepsera since measurable adefovir concentrations were seen within 0.5 hours (Figure 1).

Direct comparison of the pharmacokinetic parameters: the maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve from time zero extrapolated to infinite time ($AUC_{0-\infty}$) (also referred to as AUC_{inf}) of adefovir in this paediatric population was comparable with those results obtained in adult CHB subjects in study **GS-00-472** (10mg

¹ The pharmacokinetic profile of adefovir in HBV infected adults following oral administration of 10 mg Hepsera has been established in previous clinical evaluation reports submitted to the TGA.

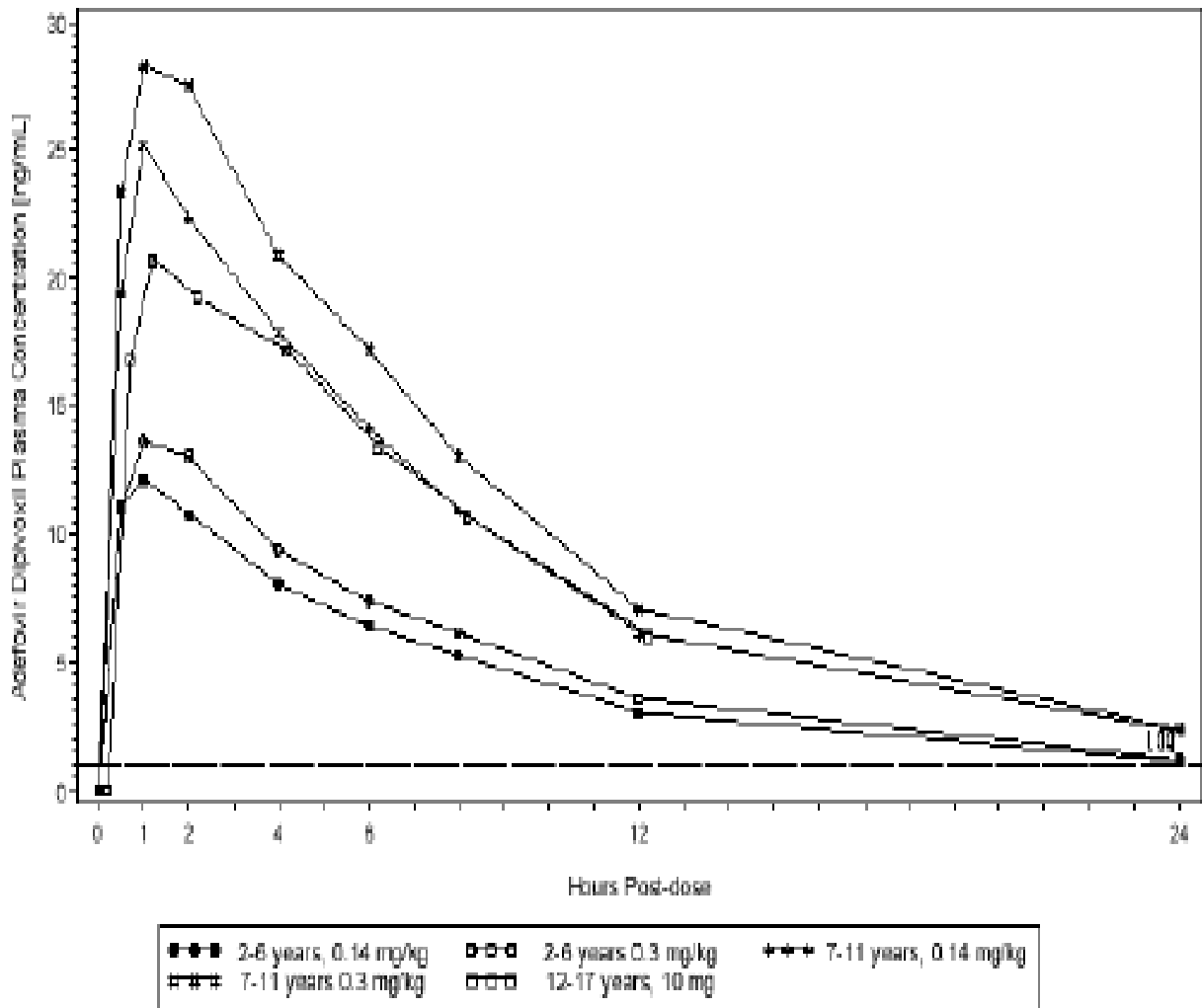
² The current recommended dosage for adults is 10 mg administered once daily. For an average 70 kg adult, this corresponds to approximately 0.14 mg/kg of actual body weight.

³ The sponsor hypothesised that the subjects may need higher doses to achieve similar exposures to that of adults, hence the 0.3 mg/kg dose (approximately double the adult dose).

tablet formulation)⁴. The targeted adult exposure mean (SD [standard deviation]) C_{\max} values were quoted as 18.4 (6.3) ng/mL and $AUC_{0-\infty}$ 220.3 (69.9) ng•hr/mL.

⁴ Open-Label Phase I-II multi-centre study of the pharmacokinetics, safety and anti-viral activity of Hepsera in nucleoside treatment-naive HBV-infected adult subjects.

Figure 1: Median Plot of Hepsera Plasma Concentrations (Dose/Age Groups Overlaid) Linear Scale



In summary:

- Following a 0.14 mg/kg dose of Hepsera for oral suspension, the mean (SD) C_{max} and $AUC_{0-\infty}$ of adefovir in the 2 – 6 years age group were 14.5 (5.3) ng/mL and 104.7 (33.8) ng•hr/mL, respectively. These values are noted to be lower than the targeted adult data.
- Following a 0.3 mg/kg dose of Hepsera for oral suspension, the mean (SD) C_{max} and $AUC_{0-\infty}$ of adefovir in the 2 – 6 years age group were 26.9 (7.9) ng/mL and 224.1 (78.7) ng•hr/mL, respectively. The observed C_{max} is noted to be higher than the targeted C_{max} for the adult dose, but $AUC_{0-\infty}$ is comparable to the adult target.
- Following a 0.14 mg/kg dose of Hepsera for oral suspension, the mean (SD) C_{max} and $AUC_{0-\infty}$ of Hepsera in the 7 – 11 years age group were 14.1 (4.6) ng/mL and 128.5 (53.8) ng•hr/mL, respectively. These values are noted to be lower than the targeted adult exposure data.
- Following a 0.3 mg/kg dose of Hepsera for oral suspension, the mean (SD) C_{max} and $AUC_{0-\infty}$ of adefovir in the 7 – 11 years age group was 33.0 (8.6) ng/mL and 292.4 (101.9)

ng•hr/mL, respectively⁵. These values are noted to be higher than the targeted exposure values, and include data from 7 patients who received a dose greater than 10 mg. Given the unknown clinical impact higher exposure values may cause, it appears reasonable that the sponsor assumed linear pharmacokinetics and applied dose-normalisation at 0.25 mg/kg to provide a C_{max} and $AUC_{0-\infty}$ closer to the adult target dose. The dose of 0.25 mg/kg chosen resulted in a mean C_{max} of 25.74 ng/mL and a mean $AUC_{0-\infty}$ of 227.7 ng•hr/mL, which is closer to the observed adult C_{max} and $AUC_{0-\infty}$.

The rate and extent of adefovir exposure from the 10 mg dose of Hepsera in the 12 – 17 years age group was slightly higher to that observed in adults. Following the Hepsera 10 mg dose, the mean (SD) C_{max} and $AUC_{0-\infty}$ of adefovir for these subjects were 22.8 (4.6) ng/mL and 237.3 (55.9) ng•hr/mL, respectively. Pharmacokinetic parameters from study **GS-02-517** discussed above are summarised in Table 2.

Table 2: Single Dose Adefovir Pharmacokinetics: Study GS-02-517 (Paediatrics)

	Pharmacokinetic parameters: mean (\pm SD) ^(a)	
	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng•hr/mL)
0.14 mg/kg Oral suspension		
2 – 6 year old n=12	14.5 (5.3)	104.7 (33.8)
7 – 11 year old n=18	14.1 (4.6)	128.5 (53.8)
0.3 mg/kg Oral suspension		
2 – 6 year old n=12	26.9 (7.9)	224.1 (78.7)
7 – 11 year old ^(b) n=18	33.0 (8.6)	292.4 (101.9)
7 – 11 year old ^(b)	30.89 (7.35)	273.29 (87.01)
0.25 mg/kg Oral suspension predicted data assuming linear pharmacokinetics		
7 – 11 year old	25.74	227.74
10 mg Oral suspensions		
12 – 17 year old n=15	22.8 (4.6)	237.3 (55.9)
Targeted Adult Exposure 10 mg tablet formulation [Study GS-00-472]^(c)		
Adults n=14	18.4 (6.3)	220.3 (69.9)

(a) Mean (SD) [90% confidence interval], (b) Data normalised to 10mg for those subjects who received a dose of > 10 mg due to weight, (c) Arithmetic mean and SD calculated from single-dose data.

Based on the pharmacokinetic (and safety) results, the sponsor recommended doses of Hepsera in paediatric patients aged 2 – 6 years to be 0.3 mg/kg and in 7 – 11 years to be 0.25 mg/kg for oral suspension, with a maximum total dose of 10 mg. These doses were chosen so as to achieve adefovir target exposure similar to that observed in adults following administration of the 10 mg tablet of Hepsera. The recommended dose for patients aged 12 – 17 years was the current 10 mg Hepsera tablet formulation.

Evaluator's comments:

The targeted adult exposure pharmacokinetic parameters referenced in study **GS-02-517** were based on arithmetic mean and SD results calculated from single-dose data in the final clinical

⁵ Due to the weight of seven subjects, these subjects received doses greater than 10 mg, and “normalising exposure” in these subjects to a 10 mg dose resulted in adjusted C_{max} and $AUC_{0-\infty}$ results.

study report of **GS-00-472**. The data presented here differed to the data published in the final report of study **GS-00-472** which described geometric mean calculations of C_{max} and $AUC_{0-\infty}$ data at Day 1-2 to be 17.47 ng/mL and 210.15 ng•hr/mL, respectively. Also, it was noted that the adult arithmetic mean $AUC_{0-\infty}$ from study **GS-02-517** was incorrectly specified in the final **GS-02-517** clinical study report. The sponsor was requested to clarify these issues and confirmed that, in order to compare the results between studies **GS-00-472** and **GS-02-517**, arithmetic mean and SD of the pharmacokinetic parameters (C_{max} and $AUC_{0-\infty}$) were calculated based on individual pharmacokinetic parameters from the final **GS-00-472** clinical study report. It was also confirmed that the arithmetic mean $AUC_{0-\infty}$ from Study **GS-00-472** was incorrectly specified in the final **GS-02-517** clinical study report and the correct value is 220.34 ng•hr/mL.

Pivotal study: **GS-US-103-0518**

The pharmacokinetic analysis demonstrated adefovir plasma exposure was comparable amongst the three age group cohorts, and all age groups achieved adefovir exposure in the target range. This was based on adefovir plasma concentrations obtained in adult CHB subjects with established efficacy and safety profiles.

Adefovir plasma concentration is characterised by the one-compartment linear model. There appeared to be adequate distribution samples across the dosing intervals for all three age groups. Mean observed and predicted plasma adefovir concentration-time profiles correlated well. The parameters predicted by the one-compartment model, as tabulated below, were generally in agreement with results from the non-compartmental model.

Adefovir plasma exposure appears to be comparable across all age groups. All age groups achieved the target range of adefovir plasma exposure (C_{max} or AUC_{0-24} [area under the concentration versus time curve over the dosing interval at steady-state (that is, from time 0 hours to 24 hours after the dose)]) similar to that identified in adult subjects in study **GS-00-472**. Based on the one-compartment model and pooled mean plasma adefovir concentration data in the 2 – 6, 7 – 11 and 12 – 17 year age groups, the predicted C_{max} values were 17.1 and, 18.5 and 22.0 ng/mL, respectively, and the predicted and AUC_{0-24} values were 210.4, 222.1 and 249.0 ng•h/mL, respectively. When compared to the adult population, adefovir plasma concentration appears comparable in all three paediatric age groups, although a slight increase in pharmacokinetic parameters is noted in the 12 – 17 year age group (Table 3).

Table 3: Pharmacokinetic (Mean C_{max} and AUC_{0-24}) Results: Study GS-US-013-0518 (Paediatrics)

Study Age Group	Pharmacokinetic Parameter	
	C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)
GS-US-103-0518		
2–6 years (0.3 mg/kg suspension) ^a	17.09	210.37
7–11 years (0.25 mg/kg suspension) ^a	18.47	222.09
12–17 years (10-mg tablet) ^a	21.96	248.76
GS-00-472		
Adult (10-mg tablet) ^b	19.71 (8.15)	215.75 (78.61)

Summary of pharmacokinetic studies

Pharmacokinetic results in the dose selection study and pivotal study appear comparable to those reported in the adult population. Each age group achieved target adefovir concentrations. The results presented in these two studies should only be considered of secondary importance; the pharmacokinetic parameters for the current marketed 10 mg tablet formulation, for which the extension of indication is being sought in the adolescent population only, are already established.

Drug Interactions

No drug interaction data were submitted for evaluation.

Efficacy

Pivotal study: GS-US-103-0518

The sponsor's submission provides the interim report for efficacy from this pivotal study, which contains data from the first 48 weeks of treatment. This study presents data in paediatric subjects (ages 2 – 17 years, inclusive, at first dose) with CHB; subjects aged 2 – 11 years at first dose received Hepsera using the investigational oral suspension formulation, and subjects aged 12 – 17 years received Hepsera as the marketed 10 mg tablet. The subsequent study period (Weeks 49 – 240), in which all subjects were offered the opportunity to receive open-label Hepsera for up to an additional 192 weeks, was reported in the sponsor's Clinical Summary as "on-going" at the time of this submission. As of September 2008, approximately 96 subjects were reported to be enrolled in this open-label study.

Design

Study **GS-US-103-0518** is a Phase III, double-blind, randomised, placebo-controlled, parallel-group, multicentre study. This is an on-going study evaluating Hepsera in treatment-naive and treatment-experienced paediatric subjects with CHB (2 – 17 years old at the first dose of study treatment). For the first 48 weeks of treatment, subjects were randomised 2:1 to receive Hepsera or matching placebo. Randomisation was stratified on the basis of age at first dose of study treatment and prior treatment for CHB (prior treatment or no treatment).

Inclusion into one of three age groups (2 – 6 years, 7 – 11 years and 12 – 17 years) was based on the subject's age at the first dose of study treatment. Subjects aged 2 – 6 years received investigational oral suspension (Hepsera 0.3 mg/kg) or matching placebo once daily. Subjects aged 7 – 11 years received investigational oral suspension (Hepsera 0.25 mg/kg) or matching placebo once daily. Subjects aged 12 – 17 years received the 10 mg tablet marketed formulation of Hepsera or matching placebo once daily.

The initial double-blind period (Weeks 1 – 48 inclusive) involved a total of 173 who were randomised and treated in the initial double-blind period (35 subjects in the age range 2 – 6 years; 55 subjects in the age range 7 – 11 years; and 83 subjects in the age range 12 – 17 years). This application proposes to extend the current indication of Hepsera to include adolescent patients aged 12 – 17 years only.

Endpoints

Primary:

- The proportion of subjects with serum HBV DNA < 1000 copies/mL and normal alanine aminotransferase (ALT) at the end of blinded treatment (Week 48).

Secondary:

- The proportion of subjects with HBV DNA < 1000 copies/mL;

- The proportion of subjects at Week 48 with HBV DNA < lower limit of quantification (LLQ);
- The observed HBV DNA concentrations, and the change from baseline in that parameter;
- The observed ALT concentrations, and the change from baseline in that parameter;
- The proportion of subjects with normal ALT;
- The proportion of subjects with HBeAg loss⁶ or HBeAg seroconversion⁷;
- The proportion of subjects with HBV DNA < 1000 copies/mL plus normal ALT plus HBeAg seroconversion (in subjects who were HBeAg-positive at baseline); and
- The proportion of subjects with hepatitis B s antigen (hepatitis B surface antigen) [HbsAg] loss.

Evaluator's comments:

The primary efficacy endpoint was changed with Amendment 2 of the study protocol after all subjects completed the blinding period, but before the data were un-blinded. Initially defined as “the proportion of subjects with serum HBV DNA < LLQ of polymerase chain reaction (PCR) based assay and ALT normalisation at week 48 for patients with HBV DNA \geq LLQ and ALT > ULN at baseline” it was changed to “the proportion of subjects with serum HBV DNA < 1000 copies/mL and normal ALT at the end of blinded treatment (Week 48)”. HBV DNA was measured by the Roche COBAS TaqMan HBV assay, with a lower limit of quantification (LLQ) of 29 IU/mL (169 copies/mL). The sponsor was requested to provide adequate justification for this amendment which appears to favour the achievement of the primary endpoint. This change may also prevent a direct comparison of virological response to Hepsera use in already established adult studies (for example, study 437 examined the efficacy of Hepsera in adults with compensated liver disease due to chronic HBV infection and HBV DNA was measured using the Roche Amplicor PCR assay with a LLQ of 400 copies/mL). The sponsor provided a response to the evaluator's request confirming that the change in protocol was made for consistency with the Hepsera development program and was not made to favour the achievement of the primary endpoint. The sponsor was able to more accurately compare efficacy results relating to changes in HBV DNA between the adult and paediatric population, as required.

Statistical methods

The analysis included data through 48 weeks of treatment. The efficacy analysis used the “randomised-to-treat” analysis set, which included all subjects who were randomised and received at least one dose of study medication. The planned analysis of the primary efficacy endpoint was a comparison of the treatment groups using 95% confidence intervals (CIs) of the difference between the groups (as well as comparison between groups with data stratified by age group and by previous treatment for hepatitis B). This statistical method was finalised before un-blinding. After un-blinding the results, the sponsor determined that a statistical exact test would be appropriate in the evaluation of treatment group differences due to the small number of responders in the placebo group. For the analysis of primary endpoint, the results were analysed by study visit, and a Fisher's Exact test was used to evaluate treatment differences between the Hepsera and placebo groups.

It was also planned that the difference between the treatment groups for each of the secondary endpoints would be analysed using 95% CIs of the difference between the groups (using means for continuous endpoints and percentages for categorical endpoints). However,

⁶ Defined as having negative serum HBeAg for subjects with positive serum HBeAg at baseline.

⁷ Defined as having negative serum HBeAg and positive anti-HBe for subjects with positive serum HBeAg at baseline.

after un-blinding the results, due to the small number of responders in the placebo group, the sponsor determined that a statistical exact test would be appropriate in the evaluation of treatment differences. Hence, analysis of categorical secondary endpoints was carried out by study visit and a Fisher's Exact test to evaluate treatment differences between the Hepsera and placebo groups. For continuous secondary endpoints, the 95% CIs were used because they were still deemed appropriate for evaluation of treatment group differences.

Patient enrolment, characteristics and disposition

Enrolment and Disposition

Planned enrolment was 150 subjects (100 Hepsera, 50 placebo). A total of 293 subjects were screened, of whom 173 were randomised and treated (115 Hepsera, 58 placebo). The first subject was randomised on 21 June 2004 and the last was randomised on 08 June 2005. All (100%) placebo-treated subjects and 112 (97%) Hepsera-treated subjects completed 48 weeks of double-blind treatment. The three subjects who discontinued prematurely were in the 12 – 17 year old Hepsera group: 1 subject withdrew due to adverse events (AEs), and 2 subjects withdrew because of non-compliance issues. All the subjects in the 2 – 6 and 7 – 11 year age groups completed the 48-week double-blind treatment period. Thirty subjects had a total of 38 important protocol deviations (24/115 [21%] of Hepsera-treated subjects and 6/58 [10%] of placebo-treated subjects). The efficacy analysis included all randomised subjects who received at least one dose of study medication.

Characteristics

There were no statistically significant differences between the Hepsera and placebo groups in assessed demographic or baseline characteristics, including baseline diseases characteristics. Age distributions were similar in the Hepsera and placebo groups. The majority of subjects were male (Hepsera group 64%; placebo group 67%). The most common racial groups were white Caucasian (Hepsera group 61%; placebo 71%) and Asian (Hepsera group 25%; placebo 21%).

Across all age-groups, slightly more than half of the subjects in both the Hepsera (56%) and placebo (57%) groups had received prior treatment for CHB. At baseline, both groups had similar mean HBV DNA concentrations (Hepsera group 8.74 log₁₀ copies/mL, placebo group 8.67 log₁₀ copies/mL), and the most common HBV genotypes were A (Hepsera group 44%; placebo group 55%) and D (Hepsera group 30%; placebo group 24%).

Subjects in the 2 – 6 year age group differed somewhat from those in the 7 – 11 and 12 – 17 year age groups in both demographic and baseline disease characteristics. The majority of subjects in the 2 – 6 year age group were female, while the majority of subjects in the other age groups were male. In addition, there was a larger percentage of black subjects in the 2 – 6 year Hepsera subgroup (30%) compared with the other subgroups (which ranged from 2% to 8%), and there was a larger percentage of non-Caucasian subjects in the 2 – 6 year Hepsera and placebo age/treatment subgroups compared with the other age/treatment subgroups. Furthermore, compared with the two older age groups, subjects in the 2 – 6 year age group had slightly higher mean HBV DNA concentrations at baseline, and a larger percentage of them were HBV Genotype D. Also a smaller percentage of subjects in the 2 – 6 year age group had received prior treatment for CHB compared with the older subjects.

Regarding serology, 3 subjects at baseline were HBeAg-negative: 1 (8.3%) in the 2 – 6 year placebo group and 2 (3.6%) in the 12 – 17 year Hepsera group despite the pre-defined study inclusion criterion being HBeAg-positive.

The inclusion criterion for baseline serum ALT status was set at ≥ 1.5 times the upper limit of normal (ULN). A total of 9 (5%) subjects, of which 6 (7%) were in the 12 – 17 year age group, had ALT levels less than the ULN. In the 12 – 17 year age Hepsera-treatment group, 4 (7%) subjects had serum ALT levels less than the ULN. Overall, baseline serum ALT levels in the paediatric and adolescent populations ranged from 0.7 to 10.4 x ULN in the Hepsera-treatment groups compared with 0.7 to 7.8 x ULN in the placebo-treatment groups. In the 12 – 17 year age group, baseline serum ALT levels ranged from 0.7 to 10.4 x ULN.

Evaluator's comments:

This application proposes to extend the current indication of Hepsera to include adolescent patients aged 12 – 17 years only. The sample size of evaluable subjects in this target age group is noted to be small (n=83). Several subjects were HBeAg-negative at baseline despite the study serology inclusion criterion requiring HBeAg-positive subjects at screening. There was also significant variability in the baseline serum ALT levels. The clinical setting and the demographic data of this target population at baseline may not be considered fully representative of adolescent patients with CHB and this limits the interpretation of the study data.

Primary efficacy resultsAge Group: 12 – 17 years

- Significantly (p=0.007) more Hepsera-treated subjects (13/56, 23%) than placebo-treated subjects (0/27, 0%) achieved the primary efficacy endpoint.

Age Group: 7 – 11 years

- No significant difference (p=0.083) between Hepsera-treated subjects (6/36, 17%) and placebo-treated subjects (0/19, 0%) even though the primary efficacy endpoint was achieved.

Age Group: 2 – 6 years

- No significant different (p=1.00) between Hepsera-treated subjects (3/23, 13%) and placebo-treated subjects (1/12, 8%) even though the primary efficacy endpoint was achieved.

Pooled (Total) Data:

- Comparing the overall treatment groups, that is, pooled dated across all age groups, significantly (p<0.001) more Hepsera-treated subjects (22/115, 19%) compared with placebo-treated subjects (1/58, 2%) achieved the primary efficacy endpoint; that is, had a serum HBV DNA < 1000 copies/mL and normal ALT at the end of blinded treatment.

A summary of the primary efficacy endpoint results is provided as Table 4.

Table 4: Subjects with HBV DNA < 1000 copies/mL and Normal ALT: Randomised and Treated Analysis Set

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

ADV = adefovir dipivoxil (Hepsera), PLB = placebo

a Age at first dose of study treatment; ranges are inclusive (that is, 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

Secondary efficacy results

The pivotal study examined subjects in three age groups (2 – 6 years, 7 – 11 years and 12 – 17 years). This application is to extend the indication of Hepsera 10 mg tablets to include adolescent patients, aged 12 – 17 years, only. Given this, brief comments on the secondary efficacy results will only be made for the adolescent age group.

*Serum HBV DNA***Change from baseline serum HBV DNA concentration**Age Group: 12 – 17 years

- Hepsera and placebo groups had similar baseline serum HBV DNA concentrations.
- Statistically significant difference was present, with a median change from baseline to end of blinded treatment (Week 48) of -3.46 log₁₀ copies/mL (mean -3.72) for Hepsera-treated subjects compared to a median change of -0.32 log₁₀ copies/mL (mean -0.66) for placebo-treated subjects.

Serum HBV DNA concentration < 1000 copies/mLAge Group: 12 – 17 years

- No subjects had a serum HBV DNA concentration < 1000 copies/mL at baseline.
- For the percentage of subjects with serum HBV DNA < 1000 copies/mL at the end of blinded treatment, there was a statistically significant difference (p=0.007) between the Hepsera-treated subjects (13/56, 23%) and placebo-treated subjects (0/0, 0%).

Categorical assessment of serum HBV DNA concentration

Subjects were categorised based on serum HBV DNA concentration at the end of blinded treatment (that is, < 169 copies/mL; ≥ 169 but < 1000 copies/mL; ≥ 1000 but < 10⁴ copies/mL; ≥ 10⁴ but < 10⁵ copies/mL; ≥ 10⁵ but < 10⁶ copies/mL; ≥ 10⁶ copies/mL). The LLQ of the HBV DNA assay was 169 copies/mL. Overall, older subjects were more likely to have a HBV DNA < 1000 copies/mL than younger subjects at the end of blinded treatment.

Age Group: 12 – 17 years

- Only 7% (4/56) of Hepsera-treated subjects compared with 0% (0/27) of placebo-treated subjects achieved a HBV DNA < LLQ of 169 copies/mL. Furthermore, similar proportions of Hepsera-treated subjects achieved a serum HBV DNA < 1000 copies/mL (23%, 13/56) when compared to those that achieved a serum HBV DNA ≥ 10⁵ but < 10⁶ copies/mL (25%, 14/56) and ≥ 10⁶ copies/mL (27%, 15/56). The magnitude of the observed response to Hepsera-treatment in this age group is not robust.

*Serum ALT***Changes from baseline in serum ALT concentration**Age Group: 12 – 17 years

- The median change from baseline to end of blinded treatment (Week 48) in the serum ALT concentration was -53.0 U/L in Hepsera-treated vs -12.0 U/L in placebo-treated subjects.
- The difference between the Hepsera and placebo groups in the change from baseline to Week 48 was statistically significant.

Normal serum ALT concentrationAge Group: 12 – 17 years

- At baseline there was no difference ($p=0.1000$) between the proportion of Hepsera-treated subjects (4/56, 7%) and placebo-treated subjects (2/27, 7%) that had a normal ALT.
- Significantly ($p<0.001$) more Hepsera-treated subjects (34/56, 61%) than placebo-treated subjects (5/27, 19%) had a normal ALT half-way through blinded treatment (Week 24).
- At the end of blinded treatment (Week 48), 64% (36/56) of Hepsera-treated subjects had a normal ALT compared with 22% (6/27) of placebo-treated subjects, and this difference was significant ($p<0.001$).

HBeAg Serology

HBeAg seroconversion was defined as loss of HBeAg and appearance of antibody to HBeAg (anti-HBe). Two (2/56, 3.6%) subjects in the Hepsera-treatment 12 – 17 year old group were HBeAg-negative at baseline.

HBeAg Seroconversion plus HBV DNA < 1000 copies plus Normal ALT

Age Group: 12 – 17 years

- Only Hepsera-treated subjects achieved the endpoint compared with placebo-treated subjects (7%, 4/54 vs 0%, 0/27), however this finding is not robust and the difference between the two treatments was not statistically significant ($p=0.30$).

HBeAg seroconversion or HBeAg Loss

Age Group: 12 – 17 years

- There was no difference ($p=1.00$) between the two treatments in the proportion of subjects with HBeAg seroconversion (Hepsera-treated subjects 11%, 6/54 vs placebo-treated subjects 11%, 3/27) or HBeAg loss (Hepsera-treated subjects 13%, 7/54 vs placebo-treated subjects 11%, 3/27) at the end of blinded treatment.

HBsAg Serology

HBsAg seroconversion was defined as loss of HBsAg and appearance of antibody to HBsAg (anti-HBs).

Age Group: 12 – 17 years

- One female subject in the Hepsera-treatment group (2%, 1/56) experienced HBsAg seroconversion (HBsAg-positive/HBeAg-positive at baseline, HBsAg negative/anti-HBs-positive at Week 12, and remained HBsAg-negative/anti-HBs-positive throughout all future assessments; at Week 12 HBeAg-negative but became anti-HBe-positive at Week 24 and remained HBeAg-negative/anti-HBe-positive throughout all future assessments).

Clinical Virology

Age Group: 12 – 17 years

- No subject developed the rtA181V or rtN236T mutation associated with adefovir resistance over the blinded treatment period.
- The rtA181T mutation was identified in two lamivudine-experienced subjects in this age group in the Hepsera group at baseline and at the end of the blinded treatment; the effects of Hepsera on serum HBV DNA and ALT in these subjects did not differ significantly from the effects observed in other subjects.⁸

⁸ The rtA181T substitution was present at baseline in a total of 3 subjects enrolled in the pivotal trial: 1 subject from the 7 – 11 year old cohort, and 2 subjects from the 12 – 17 year old cohort.

Conclusions regarding efficacy

This application is seeking to extend the indication of Hepsera 10 mg tablets, administered daily, for use in those aged 12 – 17 years only. From the efficacy findings in study **GS-US-103-0518**, the use of Hepsera, when compared to placebo, in the adolescent age group:

- Demonstrated a statistically significant difference (23% vs 0%, $p=0.007$) in achieving the primary efficacy endpoint; that is achieving a serum HBV DNA < 1000 copies/mL and a normal serum ALT at the end of 48-weeks of blinded treatment.
- For the percentage of adolescent subjects with serum HBV DNA < 1000 copies/mL at the end of blinded treatment, there was a statistically significant difference ($p=0.007$) between Hepsera-treated (13/56, 23%) vs placebo-treated subjects (0/0, 0%). However, categorical analysis of serum HBV DNA concentrations demonstrated a similar proportion of adolescent subjects who achieved HBV DNA $\geq 10^5$ but < 10^6 copies/mL (25%, 14/56) and those with $\geq 10^6$ copies/mL when treated with Hepsera (15/56, 27%). Undetectable HBV DNA levels using the Roche COBAS TaqMan HBV PCR assay was only achieved in 4 (7%) Hepsera-treated adolescent subjects. The magnitude of virological response does not appear to be a robust finding in this age group and the significance of persisting detectable serum HBV DNA in treated adolescent subjects is uncertain.
- There was no difference ($p=1.00$) between Hepsera vs placebo treatment in the proportion of subjects with HBeAg seroconversion (11%, 6/54⁹ vs 11%, 3/27) or HBeAg loss (13%, 7/54 vs 11%, 3/27) at the end of blinded treatment. Furthermore, only 1 adolescent subject in the Hepsera-treatment group (2%, 1/56) experienced HBsAg seroconversion throughout the blinded study period.
- No subject developed the rtA181V or rtN236T mutation associated with adefovir resistance over the blinded treatment period. However, the rtA181T mutation was identified in two lamivudine-experienced adolescent subjects in the Hepsera-treatment group at baseline and at the end of the blinded treatment.¹⁰ The effects of Hepsera on serum HBV DNA and serum ALT in these subjects did not differ significantly from the effects observed in other subjects. There is no long term resistance data available beyond the blinded study period.

Although superior efficacy of Hepsera over placebo in achieving the primary endpoint (virological and biochemical response) is evident, methodological issues relating to overall sample size, heterogeneity of subject disease status at baseline, and amendments made to the primary efficacy endpoint and statistical analysis plan at the end of the blinded treatment phase, may limit the interpretation of these findings. Given HBeAg seroconversion is a more reliable predictor of long-term virological outcome, serological response to Hepsera-treatment should have also been demonstrated, if efficacy was to shown robustly.

Safety

Safety data from the Phase I-II single-dose pharmacokinetic study in paediatric CHB subjects (**GS-02-517**) was supportive only. A total of 17 of 45 subjects (38%) treated with Hepsera experienced 35 events. Most events were of mild severity. One serious adverse event (SAE) was reported (concussion/orbital fracture, assessed as not related to study drug) and no deaths

⁹ Analysis included only subjects who were HBeAg-positive at study baseline. Two Hepsera-treated subjects (2/56, 3.6%) were HBeAg-negative at baseline.

¹⁰ A total of 3 subjects; 1 subject from 7 – 11 years, and 2 subjects from 12 – 17 years.

were reported. Adverse events (AEs) reported by more than 1 subject were abdominal pain, headache, and fatigue. Nine AEs in 5 subjects were assessed as possibly related to Hepsera; all of which were mild in severity. One subject discontinued study due to an AE. No notable or unexpected changes in serum chemistry, haematology, vital signs, or physical examination findings were reported.

This remainder of this section on safety will focus on the data package submitted for evaluation from the pivotal study (**GS-US-101-0518**) and discussion will focus on:

- Safety data presented from all age group cohorts (2 – 17 years) treated with Hepsera or placebo during the double-blind treatment period, which included analysis from all randomised subjects from the three different age groups who received at least one dose of study medication (randomised-and-treated analysis set) from the double-blind treatment period (Week 0 to 48);
- Safety data from the first portion of the open-label period (reported up to June 2007), which represents approximately one additional year of treatment with Hepsera, with the primary focus the 12 – 17 year group, the age range in which the extension of indication is being sought. For subjects who received placebo during double-blind treatment and started Hepsera treatment in open-label treatment, treatment-emergent adverse events (TEAEs), changes from baseline, and marked laboratory abnormalities were identified relative to the start of Hepsera treatment (rather than the start of placebo treatment at study baseline); and
- Analysis of vital sign data completed for all subjects (height/weight/body mass index [BMI]/Z scores) for up to Week 96 of treatment.

Pivotal study: GS-US-013-0518

Patient exposure

Double Blind Phase

A total of 173 paediatric and adolescent subjects with CHB were initially enrolled in the double blind phase of study **GS-US-103-0518**, and received at least one dose of study treatment. The median duration of study treatment was 48 weeks in both the Hepsera and placebo groups. In total, 97% (112/115) of Hepsera treated subjects completed the blinded treatment period compared to 100% (58/58) of those in the placebo cohort. For those aged 12 – 17 years, 95% (53/56) of Hepsera treated subjects compared to 100% (27/27) of those receiving placebo completed the blinded treatment period. In the age/treatment sub-groups, the median duration of treatment ranged from 47.9 to 48.1 weeks. For those aged 12 – 17 years, the median (\pm SD) duration of treatment was 46.1 (8.19) for the Hepsera-treatment group compared to 48.0 (0.30) for those in the placebo-treatment group.

Open-Label Phase

The open-label portion of this study is on-going. The median exposure of Hepsera for subjects in the 12 – 17 year group was 96 weeks, with approximately 96¹¹ subjects remaining on the study as of September 2008.

Adverse events

The sponsor judged and reported the severity of each AE as mild (Grade 1), moderate (Grade 2), severe (Grade 3) or life threatening (Grade 4).

¹¹ Of these 96 subjects, 19 open-label Hepsera, 20 combination open-label Hepsera plus lamivudine (in the 12 – 17 year age with prior lamivudine experience), and 57 off drug after confirmed HBeAg seroconversion.

Double Blind Period

Eighty three percent (83%, 143/173) of subjects in both the Hepsera and placebo groups reported at least one AE, most of which were Grade 1 or 2 (mild to moderate) and judged by the sponsor to be unrelated to the study treatment. The most frequently reported AEs¹² in either treatment group (Hepsera and placebo) were: nasopharyngitis (25.4%, 44/173), cough (16.8%, 29/173), headache (13.3%, 23/173), pharyngitis (12.7%, 22/173), upper respiratory track infection (12.1%, 21/173), pyrexia (11.6%, 20/173) and abdominal pain (11.0%, 19/173). The rate of occurrence of these AEs in the Hepsera group were not statistically different from the rate in the placebo group (Table 5).

¹² AEs frequency reported $\geq 10\%$.

Table 5: Adverse Events in at Least 5% of Subjects in Either Treatment Groups (Double-Blinded Treatment Study GS-US-103-0518)

AEs ^a by System Organ Class and Preferred Term (n, %)	2–6 Years ^b		7–11 Years ^b		12–17 Years ^b		Total	
	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)	ADV (n=115)	PLB (n=58)
Subjects with ≥ 1 AE	21 (91%)	11 (92%)	28 (78%)	18 (95%)	46 (82%)	19 (70%)	95 (83%)	48 (83%)
Gastrointestinal Disorders								
Abdominal Pain	0	0	4 (11%)	5 (26%)	6 (11%)	4 (15%)	10 (9%)	9 (16%)
Diarrhea	1 (4%)	2 (17%)	5 (14%)	2 (11%)	2 (4%)	0	8 (7%)	4 (7%)
Vomiting	3 (13%)	3 (25%)	0	1 (5%)	1 (2%)	1 (4%)	4 (4%)	5 (9%)
Toothache	0	0	0	1 (5%)	1 (2%)	2 (7%)	1 (< 1%)	3 (5%)
General Disorders and Administration-Site Conditions								
Pyrexia	8 (35%)	2 (17%)	4 (11%)	2 (11%)	3 (5%)	1 (4%)	15 (13%)	5 (9%)
Infections and Infestations								
Nasopharyngitis	8 (35%)	3 (25%)	8 (22%)	7 (37%)	14 (25%)	4 (15%)	30 (26%)	14 (24%)
Pharyngitis	0	0	6 (17%)	4 (21%)	9 (16%)	3 (11%)	15 (13%)	7 (12%)
Upper Respiratory Tract Infection	5 (22%)	4 (33%)	4 (11%)	4 (21%)	4 (7%)	0	13 (11%)	8 (14%)
Rhinitis	1 (4%)	2 (17%)	2 (6%)	4 (21%)	2 (4%)	3 (11%)	5 (4%)	9 (16%)
Bronchitis	1 (4%)	2 (17%)	3 (8%)	1 (5%)	4 (7%)	1 (4%)	8 (7%)	4 (7%)
Influenza	0	0	1 (3%)	3 (16%)	3 (5%)	0	4 (4%)	3 (5%)
Gastroenteritis	0	1 (8%)	0	2 (11%)	1 (2%)	0	1 (< 1%)	3 (5%)
Nervous System Disorders								
Headache	2 (9%)	2 (17%)	6 (17%)	1 (5%)	7 (13%)	5 (19%)	15 (13%)	8 (14%)
Respiratory, Thoracic, and Mediastinal Disorders								
Cough	7 (30%)	4 (33%)	6 (17%)	6 (32%)	4 (7%)	2 (7%)	17 (15%)	12 (21%)
Pharyngo-laryngeal Pain	2 (9%)	1 (8%)	2 (6%)	1 (5%)	3 (5%)	2 (7%)	7 (6%)	4 (7%)
Epistaxis	1 (4%)	0	0	2 (11%)	1 (2%)	3 (11%)	2 (2%)	5 (9%)
Skin and Subcutaneous Tissue Disorders								
Rash	2 (9%)	1 (8%)	0	0	1 (2%)	2 (7%)	3 (3%)	3 (5%)

Randomized-and-Treated analysis set; treatment-emergent events

ADV = adefovir dipivoxil, PLB = placebo

- a Treatment-emergent events; each subject is counted only once per preferred term; table includes all AEs reported for ≥ 5% of the subjects in a treatment group (summed across age groups)
- b Age at first dose of study treatment; ranges are inclusive (i.e., 2 to < 7 years; ≥ 7 to < 12 years; ≥ 12 to < 18 years).

Open-label Period

No new AEs were identified during the reported period and there were no age-related patterns of clinical concern. Seventy two percent (72.2%, 122/169)¹³ of paediatric subjects experienced AEs, most of which were mild or moderate (Grade 1 or 2) and unrelated to study treatment (Table 6). Overall, the most frequently reported AEs were similar to those in the double-blind period: nasopharyngitis (24.3%, 41/169), headache 16.1% (27/169), pharyngitis

¹³ Included all Hepsera data set (data from Hepsera-treatment combined over the 48-week double-blind period and from the open-label period (up to June 2007)).

(14.2%, 24/169), abdominal pain (12.4%, 21/169), cough (12.4%, 21/169), upper respiratory track infection (11.2%, 19/169) and pyrexia (11.2%, 19/169). In the 12 – 17 year age group, 71.3% (57/80) of subjects had at least one AE with Hepsera-treatment in the double-blind and open-label periods. Again, most of these AEs were mild or moderate (Grate 1 or 2) and judged to be unrelated to treatment.

Table 6: Adverse Events in at Least 5% of Adefovir Dipivoxil-Treated Subjects, Combined Across Age Groups (GS-US-103-0518: Double-Blind Plus Open-Label to June 2007)

AEs* by System Organ Class and Preferred Term (n, %)	Adefovir Dipivoxil Treatment							
	2–6 Years ^b		7–11 Years ^b		12–17 Years ^b		Total	
	DB (48 wk) (n=23)	DB+OL (Update) (n=34)	DB (48 wk) (n=36)	DB+OL (Update) (n=55)	DB (48 wk) (n=56)	DB+OL (Update) (n=80)	DB (48 wk) (n=115)	DB+OL (Update) (n=169)
Subjects with ≥ 1 AE	21 (91%)	26 (77%)	28 (78%)	39 (71%)	47 (84%)	57 (71%)	96 (84%)	122 (72%)
Gastrointestinal Disorders								
Abdominal Pain	0	1 (3%)	4 (11%)	9 (16%)	6 (11%)	11 (14%)	10 (9%)	21 (12%)
Diarrhea	1 (4%)	1 (3%)	5 (14%)	5 (9%)	2 (4%)	2 (3%)	8 (7%)	8 (5%)
General Disorders and Administration-Site Conditions								
Pyrexia	8 (35%)	9 (27%)	4 (11%)	7 (13%)	3 (5%)	3 (4%)	15 (13%)	19 (11%)
Infections and Infestations								
Nasopharyngitis	8 (35%)	12 (35%)	8 (22%)	12 (22%)	14 (25%)	17 (21%)	30 (26%)	41 (24%)
Pharyngitis	0	2 (6%)	6 (17%)	9 (16%)	9 (16%)	13 (16%)	15 (13%)	24 (14%)
Upper Respiratory Tract Infection	5 (22%)	5 (15%)	4 (11%)	7 (13%)	4 (7%)	7 (9%)	13 (11%)	19 (11%)
Rhinitis	1 (4%)	1 (3%)	2 (6%)	3 (6%)	2 (4%)	5 (6%)	5 (4%)	9 (5%)
Bronchitis	1 (4%)	1 (3%)	3 (8%)	4 (7%)	4 (7%)	5 (6%)	8 (7%)	10 (6%)
Influenza	0	4 (12%)	1 (3%)	2 (4%)	3 (5%)	4 (5%)	4 (4%)	10 (6%)
Nervous System Disorders								
Headache	2 (9%)	3 (9%)	6 (17%)	9 (16%)	7 (13%)	15 (19%)	15 (13%)	27 (16%)
Respiratory, Thoracic, and Mediastinal Disorders								
Cough	7 (30%)	8 (24%)	6 (17%)	7 (13%)	5 (9%)	6 (8%)	18 (16%)	21 (12%)
Pharyngo-laryngeal Pain	2 (9%)	2 (6%)	2 (6%)	5 (9%)	3 (5%)	4 (5%)	7 (6%)	11 (7%)

Randomized and Treated analysis set

Contents of this table: This table includes all treatment-emergent AEs reported for either ≥ 5% of adefovir-dipivoxil-treated subjects in the 48-week analysis (combined across age groups) or ≥ 5% of the subjects in the All ADV (see definition below) set (combined across age groups).

AE = adverse event, DB = double blind, OL = open label, wk = week

DB (48 wk) = data from ADV-treated subjects in first 48 weeks of study (i.e., double-blind period)

DB+OL (Update) = "All ADV" data set (i.e., data from ADV treatment combined over the 48-week double-blind period and from the open-label period up to June 2007)

a Treatment-emergent AEs; each subject is counted only once per treatment and preferred term.

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

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Adverse reactions (drug-related adverse events)

Double Blind Period

A total of 13.9% (16/115) of Hepsera treated subjects and 10.3% (6/58) of placebo treated subjects had at least one drug-related AE; the difference between these two treatment groups was not deemed to be statistically significant.

Open Label Period

A total of 12.4% (21/169) subjects experienced at least one drug-related AE during treatment with Hepsera. In the 12 – 17 year age group, a total of 12.5% (10/80) of subjects experienced at least one drug-related AE with Hepsera treatment. Of these, between Week 48 and Week 96, new drug-related AEs reported included: hepatitis (1%), candidiasis (1%), serum creatine phosphokinase (CPK) increase (3%) and depression (1%).

Of particular interest, across the whole study:

- No AEs suggested adverse effects on renal function.
- Four Hepsera-treated subjects (3.5%, 4/115) and three placebo-treated subjects (5.2%, 3/58) had AEs related to hepatic status or function during the double-blind period. For those treated with Hepsera, only one AE was classified as a drug-related SAE; all other hepatic AEs in this treatment group were non-serious, and none resulted in hepatic decompensation. In the open-label period, a total of 7 subjects (4.1%, 7/169) had AEs related to hepatic status or function¹⁴ with Hepsera treatment, however none of these subjects showed evidence of hepatic decompensation.
- A higher rate of AEs related to appetite/food intake occurred in those subjects treated with Hepsera. In response to a request from the European Medicines Agency (EMA), an analysis of Z-score data on weight/height/BMI for up to 96 weeks of treatment for all subjects was performed.¹⁵ The report, along with an independent expert opinion, concluded that Hepsera-treatment had no effect on height Z-scores but mean changes from baseline in weight and BMI Z-scores were measurably lower in Hepsera-treated subjects compared to placebo. These differences were statistically significant, but were not considered to be clinically significant.
- In the 12 – 17 year group, AEs in the “psychiatric disorders” system organ class were reported for six subjects over the course of Hepsera-treatment, of which four were listed as SAEs, and of these, one subject was classified as treatment related. The explanation for this finding is unclear, but given this index subject had pre-morbid psychiatric issues, this result might not be robust. It is difficult at this stage to suggest that Hepsera therapy in adolescent subjects is correlated with the occurrence of exacerbation of pre-existing psychiatric illness.

Withdrawals (discontinuations) due to adverse events

Double Blind Period

One subject developed a SAE (abnormal behaviour) in the Hepsera-treated group which resulted in permanent discontinuation of treatment.

Open-label Period

One subject permanently discontinued study treatment because of a drug related AE (depression).

Deaths and other Serious Adverse Events

Double Blind Period

There were no reported deaths in the double-blind period of the study.

¹⁴ Hepatic AEs were exacerbations of CHB following discontinuation of Hepsera-treatment, or transient ALT elevations that resolved following continued use of Hepsera.

¹⁵ Z-score: Standard scores are also called z-values, z-scores, normal scores, and standardized variables; the use of "Z" is because the normal distribution is also known as the "Z distribution". They are most frequently used to compare a sample to a standard normal deviate

A total of 6.1% (7/115) Hepsera-treated subjects had at least one SAE compared with 8.6% (5/58) of placebo-treated subjects. There was only one¹⁶ SAE related to hepatic status or function in the Hepsera-treatment group. There was no SAEs related to renal dysfunction.

Open-label Period

There have been no reported deaths during the open-label period of the study.

For this period, there were 35 SAEs reported in 25 subjects in the 12 – 17 year group, 15 SAEs in 12 subjects in the 7 – 11 year group, and 18 SAEs in 10 subjects in the 2 – 6 year age group.

Laboratory abnormalities

Laboratory abnormalities were rated as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (potentially life threatening), according to criteria defined in the study protocol. Most graded abnormalities in laboratory parameters were mild or moderate, and there appeared to be no patterns of change in the Hepsera group that were of clinical concern.

Biochemistry

CPK

An increase in CPK was the most common marked laboratory abnormality in the double-blind phase. Overall, three male Hepsera-treated subjects (2.6%, 3/115) reported elevated CPK levels; none of which led to an interruption of treatment, but one event was reported as an AE. In the placebo-treated subjects one subject (1.7%, 1/27) also reported a marked abnormality. All subjects were in the 12 – 17 year group.

In the open-label phase, the most common marked laboratory abnormality during Hepsera treatment was elevated CPK levels. This occurred with six subjects (7.5%, 6/80) in the 12 – 17 year group; all of whom had no clinical symptoms or findings, and the abnormality resolved during on-going Hepsera treatment. In three of the six subjects, the abnormalities occurred during the first 48-weeks of the study, as discussed above. All six subjects were male, and given elevated CPK levels generally resolved rapidly in these subjects, these findings may be benign and explained by the activity level of adolescent males.

Renal function

There were no remarkable findings in laboratory parameters related to renal function in Hepsera-treated subjects in the double-blind phase. In the 12 – 17 year group, one Hepsera-treated subject had a confirmed increase of at least 0.3 mg/dL in serum creatinine, however this subject's creatinine concentration values were rated as Grade 1; there was no associated decrease in serum phosphorus, and the event was not reported as an AE. No Hepsera-treated subjects had a confirmed serum phosphorus concentration less than 2 mg/dL. In the 12 – 17 year group, one Hepsera-treated subject had an unconfirmed abnormality in serum phosphorus, which was the only serum phosphorus concentration < 2 mg/dL and the only treatment-emergent Grade 3 or Grade 4 abnormality in phosphorus. The number of subjects that reported other serum biochemistry/electrolyte abnormalities in the two treatment groups is too small to make a meaningful comparison between treatment groups.

¹⁶ One female subject in the 2 – 6 year age group had a drug-related Grade 3 SAE which resolved during on-going Hepsera-treatment. This subject received Hepsera during the double-blind period. This was the only SAE related to hepatic status or function in the Hepsera-treatment group.

In the open-label period, there were no remarkable findings in laboratory parameters related to renal function in Hepsera-treated subjects. No change in serum phosphorus was reported as an AE and no subject had a marked abnormality in serum phosphorus.

Hepatic function

No Hepsera-treated subject showed evidence of hepatic decompensation during the double-blind period. Three Hepsera-treated subjects had serum ALT elevations that met the protocol-established definition of a severe hepatic flare, but none resulted in interruption or discontinuation of study treatment. Of these three subjects, one subject in the 2 – 6 year age group developed a treatment-related Grade 3 SAE (increased hepatic enzymes that resolved during continuing Hepsera treatment).

In the open-label period, no Hepsera-treated subject showed evidence of hepatic decompensation. One subject had a post-treatment exacerbation of hepatitis B that met the protocol definition for a severe hepatic flare. This subject was in the 12 – 17 year group, had a SAE of hepatitis (post-treatment exacerbation of hepatitis B) approximately three months after Hepsera-treatment was discontinued because of depression (discussed earlier); there were no concomitant changes in total bilirubin or albumin.

Serum Amylase and Lipase

Six (5.2%, 6/115) Hepsera-treated subjects had treatment-emergent Grade-3 abnormalities in serum amylase during the double-blind period: the serum lipase level was in the normal range in four of the six subjects at the time of the Grade-3 amylase elevation.

In the open-label period, across all age groups, nine (5.3%, 9/169) subjects had treatment-emergent Grade-3 abnormalities in serum amylase.

Haematology

The number of subjects with abnormalities in prothrombin time or full blood examination recorded was small to make a meaningful comparison between treatment groups during the double-blind period.

In the open-label period, no haematological abnormalities of clinical significance were noted.

Post-marketing experience

Hepsera is currently approved for use in the adult population in 81 countries, and its use has been approved for marketing in the US adolescent population (12 – 17 years) since 2007. To date, its cumulative exposure is estimated to be 411,106 patient-years of treatment, of which 109,193 patient-years of treatment was covered during the most current Periodic Safety Update Report (PSUR) period (21 September 2007 – 20 September 2008).

Safety issues for Hepsera which are under close monitoring include renal toxicity, resistance, post-treatment hepatic flare, pancreatitis and lactic acidosis.

A total of 151 case reports (107 spontaneous, 44 serious, drug-related reports from clinical trials), were received as published in the most current period of safety update available to the TGA: this included 70 serious unlisted, 30 serious listed, 29 non-serious and 22 non-serious cases. In the paediatric and adolescent populations, 8 reports of post-treatment hepatic flare from study **GS-US-103-0518** were received by the sponsor during this safety update period, all of which were considered listed per the current Hepsera company core safety information (CCSI).¹⁷ The event resolved spontaneously in 7 of these cases, with the remaining case still

¹⁷ The company core safety information (CCSI) is all relevant safety information contained within the company core data sheet (CCDS) and forms the basis for determining whether an adverse event is listed or unlisted.

reported as on-going at the time of reporting. Of note, no spontaneous AE reports in children or adolescents have been received from the US or from other countries using Hepsera off-label.

No actions have been taken for safety reasons by the sponsor or any regulatory agency as reported during the most current PSUR period. All AEs in the paediatric population are reported as being monitored closely.

Conclusions regarding safety

From the safety data reported in study **GS-US-103-0518**:

- Hepsera appears to be well tolerated in the paediatric and adolescent populations, with AEs generally similar in treatment and placebo groups.
- A signal towards higher rates of AEs related to appetite/food intake is noted in those subjects treated with Hepsera. At week 48 and 96, mean changes from baseline in weight and BMI Z-scores tended to decrease in Hepsera-treated subjects. The clinical significance of these results in the long term is uncertain. However, across the whole study, no SAEs related to appetite/food intake have been recorded in subjects in any age group of the study.
- A signal towards several AEs related to psychiatric disorders was reported in adolescent subjects receiving Hepsera-treatment. Psychiatric disorders (of any kind) are currently not listed in the Hepsera Australian Product Information (PI) as an adverse effect. At this stage, the explanation for this is unclear, and this signal may not be a robust finding given there is insufficient evidence to confirm whether the use of Hepsera in adolescent subjects plays a direct role in the occurrence of new-onset psychiatric disorders. However, given no long-term safety data are available, precipitation of pre-existing psychiatric conditions due to Hepsera-treatment cannot be fully excluded.
- In general, no major safety concern regarding renal toxicity or hepatic decompensation in Hepsera-treated adolescent subjects has been identified.
- Overall, the safety profile of Hepsera in adolescent subjects (aged 11 – 17 years) appears comparable to the known safety profile in the adult population.

Clinical Summary and Conclusions

The Sponsor's submission, collectively known as the Paediatric Development Program for Hepsera, included a total of four studies for evaluation: three completed pharmacology studies (**GS-02-515**, **GS-02-517** and **GS-02-536**) and an on-going efficacy and safety pivotal study (**GS-US-103-0518**).

This application is seeking to extend the indication of Hepsera 10 mg tablets, administered daily, for use in adolescent patients aged 12 – 17 years only. The clinical studies submitted for this extension of indication complied with the guidelines and directives for GCP for clinical trials and were conducted with appropriate ethical principles, and in accordance with associated global regulations and guidelines.

Pharmacokinetic results in the dose selection study (**GS-02-517**) and pivotal study (**GS-US-103-0518**) appear comparable to those reported in the adult population. Each age group achieved target adefovir concentrations. The results presented in these two studies should only be considered of secondary importance. The pharmacokinetic parameters for the current marketed 10 mg tablet formulation, for which the extension of indication is being sought in the adolescent population only, is already established.

From the efficacy findings in the pivotal study (**GS-US-103-0518**), it is reasonable to say that the use of Hepsera over placebo demonstrated antiviral activity with biochemical responses in adolescent subjects with chronic replicative hepatitis B infection. The use of Hepsera, when compared to placebo, demonstrated a significant difference (23% vs 0%, $p=0.007$) in achieving the primary efficacy endpoint of obtaining a serum HBV DNA < 1000 copies/mL and a normal serum ALT at the end of 48-weeks of blinded treatment. However, the

magnitude of virological response to undetectable levels was only achieved in 4 (7%) adolescent subjects treated with Hepsera and this does not appear to be a robust finding. The significance of persisting detectable serum HBV DNA in treated adolescent subjects is therefore uncertain. Furthermore, given HBeAg seroconversion is a reliable predictor of long-term virological outcome, serological response to Hepsera treatment should have also been demonstrated. Resistance to Hepsera in this age group was not detected during the study, and it is unknown if a longer duration of therapy could result in emergence of resistance. On-going evaluation and monitoring regarding resistance beyond the blinded study period is therefore required.

Hepsera appears to be well tolerated in the adolescent population, with AEs generally similar in treatment and placebo groups. At the time of the submission of this application, the clinical safety profile of Hepsera use in the adolescent population appeared consistent with that already established in the adult population. The safety profile is in accordance with that expected from known class effects, and this is reflected in the safety information that has been reported in the post-marketing period. In particular, no major safety concerns regarding renal toxicity or hepatic decompensation in adolescent subjects treated with Hepsera has been identified. However, a signal towards higher rates of AEs related to appetite/food intake and psychiatric disorders is noted in those subjects treated with Hepsera. At this stage the precipitation of these signals due to Hepsera use cannot be fully excluded and the significance of these findings in the long-term is uncertain. On-going evaluation and monitoring of safety over a longer period of therapy is required.

Although superior efficacy of Hepsera over placebo in achieving the primary endpoint (virological and biochemical response) was demonstrated during the blinded treatment period in study **GS-US-103-0518**, several methodological limitations highlighted in the body of this report may limit the interpretation of these efficacy findings. Given this, caution should be exercised in extrapolating the finding from the data presented in this evaluation, and the sponsor should address these concerns in response to this report.

However, the primary goal of therapy in this target population is control of viral replication, and the management principles and selection of patients for treatment in this age group should be considered generally the same as for those with adults. This is particularly relevant when determining the acceptable risk in comparison to demonstrated benefit in this population. There is without doubt that therapy should always be individualised, with regular monitoring to identify resistance, decompensation, and response. Given this, and with the knowledge that Hepsera has been marketed for use in US adolescent patients for the past two years with no significant safety issues reported in the post-marketing period, it appears reasonable to register the use of Hepsera for the proposed indication based on the submitted preliminary clinical data.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There is no requirement for a quality evaluation in an application of this type.

Nonclinical

There is no requirement for a nonclinical evaluation in an application of this type.

Clinical

The paediatric development program included three completed pharmacology studies and one ongoing pivotal efficacy and safety study. During the development program, two oral suspensions, formulation A and B of adefovir (ADV) (only different in taste) were evaluated.

Bioequivalence studies: Studies GS-02-515 and GS-02-536

These studies were Phase I, open-label, randomised, crossover studies in which healthy adult subjects received a single 10 mg (5 mL) dose of ADV suspension formulation A (study GS-02-515) or ADV suspension formulation B (study GS-02-536), and in a separate study period, a single 10 mg ADV tablet. There was a 7-day washout period. A total of 24 subjects enrolled in Study -515 and 22 completed the study. In study -536 twenty were enrolled, and 17 completed the study. In both studies, the 90% CIs for the geometric mean ratios of the oral suspension formulations / tablet $AUC_{0-\infty}$, AUC_{0-last} , and C_{max} were within the range of 80% to 125%, demonstrating that the suspension formulation A and B and the tablet formulation were bioequivalent. There were no safety concerns from these studies.

Dose-finding study: Study GS-02-517

GS-02-517 was a Phase I-II, multi-centre, open-label study conducted to determine a dosage regimen for each paediatric group (2-17 years) that would produce ADV plasma exposures similar to that of adults receiving the approved dose of 10 mg once daily (in Study GS-00-472). Two different doses were assessed in the 2–6 years and 7–11 years age groups, one dose of 0.14 mg/kg and one dose of 0.3 mg/kg with a 7-day washout period. Subjects in the oldest age group (12 – 17 years) received a single fixed 10mg dose.

The inclusion criteria were paediatric subjects aged 2-17 years with CHB and compensated liver disease, HBeAg positive, serum hepatitis B virus (HBV) DNA ≥ 105 copies/ml, and creatinine clearance ≥ 80 ml/min. A total of 47 patients were enrolled, 2 discontinued before receiving study medication. Data from 45 patients were analysed (12 aged 2-6 years, 18 aged 7-11 years and 15 aged 12-17 years).

The study showed that the ADV exposure in adolescents (12 – 17 years) receiving 10 mg dose was similar to those observed in adults., The mean C_{max} and $AUC_{0-\infty}$ in adolescents were 22.8 ng/ml and 237.3 ng.hr/ml respectively, compared to 18.4 ng/ml and 220.3 ng.hr/ml in adult patients (study GS-00-472). In children aged 2-6 years and 7-11 years, the mean values of AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} following a 0.14 mg/kg of ADV were much lower (40 to 60 %) than in the targeted adult values. In children aged 2-6 years, the mean values of AUC_{0-t} and $AUC_{0-\infty}$ following a 0.3 mg/kg of ADV were comparable to adults whereas the mean C_{max} was 46 % higher than the adult values. In children aged 7–11 years, the mean values of AUC_{0-t} , $AUC_{0-\infty}$ were approximately 25 % higher than the adult values and the mean C_{max} values are 80% higher than the adult values. Based on these results, the following dosing regimens were proposed for paediatric patients and were then used in the pivotal study (Table 7):

Table 7: Recommended dosing regimens proposed for paediatric patients

Age ranges	Dose regimens
2 to 6 years old	0.3 mg/kg (up to 10mg/day)
7 to 11 years old	0.25 mg/kg*

12-17 years old	10 mg/day
*the 0.3 mg/kg resulted in a C_{max} and $AUC_{0-\infty}$ higher than those achieved in adults. Assuming linear pharmacokinetics, a dose of 0.25 mg/kg appeared to provide a C_{max} and $AUC_{0-\infty}$ closer to the adult target dose - C_{max} 25.74 ng/ml, $AUC_{0-\infty}$ 227.74 ng.hr/ml	

Pivotal Study: Study GS-US-103-518

This was a Phase III, randomised, double-blinded study. The study assessed the efficacy, safety, and the pharmacokinetics (PK) of ADV treatment in paediatric CHB patients. The interim report containing 48 weeks data is submitted. The study subjects were randomised in a 2:1 ratio to receive ADV or placebo. Randomisation was stratified by age at the first dose (2–6, 7–11, and 12–17 years, inclusive) and by prior treatment history (had prior treatment or no prior treatment). The daily doses were based on age and weight (Table 7). The adolescent group received 10mg tablet or matching placebo while the two younger groups received oral suspension or matching placebo.

The 48 weeks double blinded phase of the study involved a total of 173 paediatric CHB patients. The key inclusion criteria were:

- Treatment- naïve and treatment-experienced paediatric subjects (from age 2 to < 18 years) with evidence of active hepatitis B and compensated liver disease.
- HBsAg positive for at least 6 months and HBeAg positive
- serum HBV DNA \geq 105 copies/ml.
- Serum ALT levels \geq 1.5 upper limit of normal (ULN) at both initial and confirmatory screening visits
- creatinine clearance \geq 80 ml/min.
- seronegative for HIV, Hepatitis C Virus (HCV) and Hepatitis D Virus (HDV).

PK in paediatrics and adults

The PK results from paediatric patients (GS-US-103-0518) and adult patients (GS-00-472) are summarised in Table 3. The plasma exposure was similar among the three paediatric age groups with slightly higher AUC and C_{max} in the older children. The dosing regimens used in paediatric patients in Study GS-US-103-518 were considered adequate based on the PK results, as the plasma concentrations of ADV were comparable in the three paediatric age groups, and each age group achieved the target ADV concentrations reported in adult CHB patients.

Efficacy results

The primary objective of this pivotal study was to assess the efficacy of ADV following 48 weeks treatment in paediatric CHB patients (2 to < 18 years) in comparison to placebo. The primary endpoint was the proportion of subjects achieving serum HBV DNA < 1000 copies/ml and normal ALT. A summary of the patients' disposition is present in Table 8 below:

Table 8: Patients' disposition in Study GS-US-103-0518

	2-6 years		7-11 years		12-17 years		Total	
	ADV (n=23)	Placebo (n=12)	ADV (n=36)	Placebo (n=19)	ADV (n=56)	Placebo (n=27)	ADV (n=115)	Placebo (n=58)
Randomised and treated	23	12	36	19	56	27	115	58
Completed 48 weeks	23 (100%)	12 (100%)	36 (100%)	19 (100%)	53 (95%)	27 (100%)	112 (97%)	58 (100%)
Discontinued prematurely:	0	0	0	0	3 (5%)	0	3 (3%)	0
▪ Adverse events	0	0	0	0	1 (2%)	0	1 (<1%)	0
▪ Non compliance	0	0	0	0	2 (4%)	0	2 (2%)	0

There were no statistically significant differences between the ADV and placebo groups with regard to demographic or baseline characteristics.

The evaluator noted that in the targeted age group (12-17 years), ALT levels ranged from 0.7 to 10.4 ULN, and 6 subjects (7%) had normal ALT at baseline although the inclusion criterion required ALT \geq 1.5 ULN. In addition, 3 subjects were HBeAg negative at baseline (1 in placebo 2-6 years, 2 in ADV 12-17 years) despite the inclusion criterion required subjects with positive HBeAg.

The evaluator commented that the sample size of the target group (12-17 years old) was small (n=83), and there was also significant variability in the baseline serum ALT levels in the study population. The clinical setting and the demographic data of this target population may not be considered fully representative of adolescent patients with active CHB, and this may limit the interpretation of the study data.

Results of the primary endpoint: HBV DNA < 1000 copies/ml and normal ALT

The primary efficacy endpoint results are summarised in Table 4. Significantly more ADV-treated subjects in the 12–17 years age group achieved the primary endpoint (23% vs 0%, p = 0.007). There were no statistical significant differences between the ADV- and the placebo-treated subjects in the two younger age groups. The significant differences in the pooled group (19% vs 2%; p < 0.001) appeared to be mainly driven by the subjects in the older age group (12-17 years).

The evaluator noted that the primary endpoint was initially defined as “the proportion of subjects with serum HBV DNA < LLQ of PCR based assay and ALT normalisation at Week 48 for patients with HBV DNA \geq LLQ and ALT > ULN at baseline”. It was changed to “the proportion of subjects with serum HBV DNA < 1000 copies/mL and normal ALT at Week 48”. This change was documented in the Amendment 2 of the protocol and it was after all subjects completed the blinding period, but before the data was un-blinded. This amendment appears to favour the achievement of the primary endpoint.

Results of some of the secondary endpoints

Since the sponsor only seeks to extend the indication to adolescent group aged 12-17 years, the evaluator focused the discussion of secondary endpoints in this target age group.

Change from baseline in serum HBV DNA: Statistically significant difference was present, with a median change of -3.46 log₁₀ copies/mL (mean -3.72) for Hepsera-treated subjected compared to a median change of -0.32 log₁₀ copies/mL (mean -0.66) for placebo-treated subjects.

Serum HBV DNA < 1000 copies/mL: For the percentage of subjects with serum HBV DNA < 1000 copies/mL at Week 48, there was a statistically significant difference ($p = 0.007$) between the Hepsera-treated subjects (13/56, 23%) and placebo-treated subjects (0/0, 0%).

Categorical assessment of serum HBV DNA concentration: Subjects were categorised based on serum HBV DNA concentration at Week 48 (i.e. < 169 copies/mL; ≥ 169 but < 1000 copies/mL; ≥ 1000 but < 104 copies/mL; ≥ 104 but < 105 copies/mL; ≥ 105 but < 106 copies/mL; ≥ 106 copies/mL). The LLQ of the HBV DNA assay was 169 copies/mL. In the age group of 12 – 17 years, only 7% of ADV-treated subjects compared with 0% of placebo-treated subjects achieved a HBV DNA < LLQ (169 copies/mL). Furthermore, similar proportions of ADV-treated subjects achieved a serum HBV DNA < 1000 copies/mL (23%) when compared to those that achieved a serum HBV DNA ≥ 105 but < 106 copies/mL (25%) and ≥ 106 copies/mL (27%). The magnitude of the observed response to Hepsera-treatment in this age group is not robust.

HBeAg seroconversion: For the target age group of 12 – 17 years, there was no difference between the two treatment groups in the proportion of subjects with HBeAg seroconversion (11% vs 11%, $p = 1.00$) at the end of blinded treatment.

HBeAg seroconversion + HBV DNA < 1000 copies/ml + ALT normalisation: A combined analysis of HBeAg seroconversion, HBV DNA < 1000 copies/ml and ALT normalisation was presented in Table 9 below:

Table 9: HBeAg seroconversion, HBV DNA < 1000 copies/ml and ALT normalisation

HBeAg seroconversion, HBV DNA < 1000 copies/ml and Normal ALT	2-6 years		7-11 years		12-17 years		Total	
	ADV (n=23)	Placebo (n=12)	ADV (n=36)	Placebo (n=19)	ADV (n=56)	Placebo (n=27)	ADV (n=115)	Placebo (n=58)
Baseline (n, %)	0	0	0	0	0	0	0	0
Week 24 (n, %)	0	0	2 (6%)	0	2 (4%)	0	4 (4%)	0
End of blinded treatment (n,%) ^a	3 (13%)	0	5 (14%)	0	4 (7%)	0	12 (11%)	0
	p=0.54		p=0.15		p=0.30		p=0.009	

The difference between ADV and placebo-treated groups was not statistically significant in any of the age groups. For the age group of 12 – 17 years, only 4 ADV-treated subjects (7%) had a positive response, however the difference between the two treatment groups was not statistically significant ($p = 0.30$).

Resistance analysis: No subject developed the rtA181V or rtN236T mutation associated with ADV resistance over the 48 weeks of treatment. However, 5 ADV-treated patients (3 lamivudine-experienced and 2 naïve patients) developed mutations other than those versus none in placebo group. Three lamivudine-experienced patients on ADV presented enrichment of the rtA181T mutation at week 48. The relationship between rtA181T mutation and phenotypic resistance to adefovir is under close monitoring for adult patients. It cannot be excluded that the development of rtA181T is a preliminary step of rtA181V emergence.

Safety results

The evaluator discussed the safety data from the pivotal study with the initial 48 weeks and the first portion of the open label period which represent one additional year of treatment.

Hepsera (ADV) appears to be well tolerated in the paediatric and adolescent populations, with AEs generally similar in treatment and placebo groups. A signal towards higher rates of AEs related to appetite/food intake is noted in those subjects treated with ADV. At week 48 and 96, mean changes from baseline in weight and BMI Z-scores tended to decrease in ADV-treated subjects. A signal towards several AEs related to psychiatric disorders was reported in adolescent subjects receiving treatment. However, there is insufficient evidence to confirm whether the use of ADV in adolescents plays a direct role in the occurrence of new-onset psychiatric disorders at this stage. As no long-term safety data are available, precipitation of pre-existing psychiatric conditions due to treatment cannot be fully excluded.

No major safety concerns regarding renal toxicity or hepatic decompensation in ADV-treated adolescent subjects has been identified. The evaluator also reviewed the recent PSUR where no actions have been taken for any safety reasons. Overall, the safety profile in adolescent subjects appears comparable to the known safety profile in the adult population.

Risk-Benefit Analysis

Evaluator's recommendation

With the knowledge that Hepsera has been marketed for use in US adolescent patients for the past two years with no significant safety issues reported in the post-marketing period, it appears reasonable to register the use of Hepsera for the proposed indication based on the submitted preliminary clinical data.

Delegate's comments

Although the evaluator recommends approval of Hepsera for the treatment of adolescent CHB patients, a number of concerns with regard to the methodological limitations of the pivotal study have been raised during the evaluation, and these concerns are reiterated below:

Study population: In the targeted study group of adolescent aged 12-17 years, the baseline ALT levels ranged from 0.7 to 10.4 ULN which indicated that part of this small population did not have an active disease at inclusion and that there was an important variability in the severity of the disease. The study population may not be representative of a population with active, progressive disease for which treatment should be considered in clinical practice.

Sample size: The sample size of the target group (12 to 17 years) in the pivotal study was small with a total of 83 subjects (56 ADV, 27 placebo). There was also an important variability in the baseline disease status of these studied subjects as discussed above.

Primary endpoint: Initially the primary efficacy endpoint was defined as the "proportion of subjects with serum HBV DNA < LLQ and ALT normalisation at Week 48" and was then changed to "the proportion of subjects with serum HBV DNA < 1000 copies/ml and normal ALT at Week 48". This change appears to favour the achievement of the endpoint. In addition, as there is a high rate of spontaneous seroconversion in the paediatric population, it would be preferable to include the HBeAg seroconversion as a primary efficacy endpoint.

Efficacy results: Although a statistically significant difference was observed with regard to the primary efficacy endpoint, a more stringent criteria of virological response, such as undetectable HBV-DNA or HBV-DNA < 400 copies/ml should have been used. For the target age group of 12 – 17 years, there was no difference ($p = 1.00$) between the two treatments in the proportion of subjects with HBeAg seroconversion.

Risk of resistance: The risk of emergence of resistance with long term use of ADV is not clear. Compared to adults, the chronic hepatitis B infection in paediatric patients has a more benign course and a relatively higher annual rate of spontaneous and durable seroconversion. There is therefore a particular need to obtain robust evidence on the benefit of the treatment and to have reassurance on its safety profile before granting an approval for any treatment in the paediatric CHB patients. In view of the above-mentioned limitations of the submitted study, including the uncertainty of the representativeness of the study population, the appropriateness of the primary efficacy endpoint, the unconvincing efficacy results in the target age group of 12 to <18 years old (in particular in term of HBeAg seroconversion), and the uncertainties with regard to the risk of resistance development with long term use, the Delegate was of opinion that the results from the pivotal study do not allow a definitive conclusion to be drawn regarding the benefit/risk balance of this treatment in adolescents CHB patients.

Delegate's conclusion and proposed action

The Delegate therefore proposed to reject the application of extending the treatment indication to adolescent CHB patients. However, the clinical trial information in paediatric patients can be included in the PI. The information included should highlight the limitations

of the efficacy observed in the overall paediatric population and should discourage the off label use of this product.

The evaluator has recommended many changes to the proposed PI statements with regards to the paediatric use, and the recommended changes reflect correctly the clinical trial data.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, disagreed with the Delegate's proposal. The committee recommended approval for the following indication:

Hepsera is indicated for the treatment of chronic hepatitis B in patients 12 years of age or older adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

For adult patients: this indication is based on histological, virological, biochemical, and serological responses in adult patients with HBeAg+ and HBeAg-/HBV DNA+ 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

In making this recommendation the ACPM noted the limited numbers in the studies of the 12 to 17 years age group and that in this subgroup the results for the primary endpoint were of borderline statistical significant in the pivotal clinical study. The ACPM concluded that evidence of the safety and efficacy of the formulation and the dosage regimen for the proposed new indication for the 12 years and older has been sufficiently demonstrated.

While further noting that the evidence indicated no substantial differences to the adult efficacy and toxicity, the ACPM encouraged further assessment of Hepsera in patients in the 7-11 year age subgroup. The ACPM noted a trend toward efficacy in children <12 years of age is limited by low statistical power and would consider an extension of indication if further data supporting efficacy were presented in this age group.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Hepsera 10 mg tablet containing adefovir dipivoxil for the following indication:

Hepsera is indicated for the treatment of chronic hepatitis B in patients 12 years of age and older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

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.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published.
For the current Product Information please refer to the TGA website at www.tga.gov.au.

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

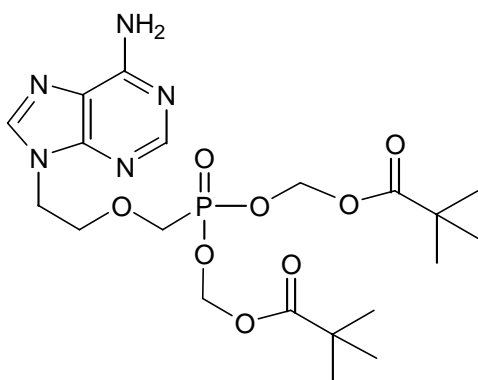
NAME OF THE MEDICINE

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: C₂₀H₃₂N₅O₈P

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 μM .

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 ± 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
$AUC_{0-\infty}$ (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.

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 multiple dose tenofovir disoproxil fumarate (300 mg daily) (n=22) and 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 4.1 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 rtR153Q 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 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 IC₅₀ (mutant)/ IC₅₀ (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 adolescent patients (aged 12 to <18 years) had 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

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. Hepsersa 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 HEPSERA 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 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 AmplicorTM 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 ± 1.6 (n=117)	-3.9 ± 1.5 (n=35)	-4.0 ± 1.6 (n=164)	-4.5 ± 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 \geq 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.

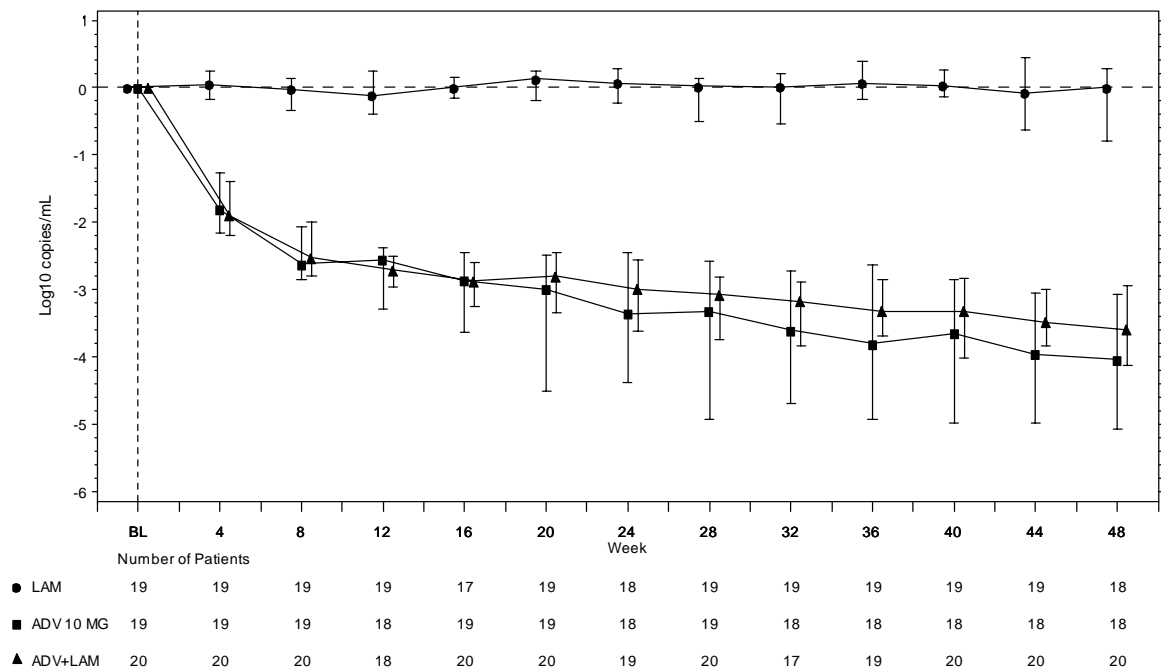
4. Defined as the loss of HBeAg regardless of anti-HBe status. Denominator is the number of patients HBeAg+ and non-missing value at week 48 or 96 assessment as appropriate. Excludes post-transplant data for patients who were waitlisted and had on-study transplants.

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 $4.00 \pm 1.41 \log_{10}$ copies/mL for patients treated with HEPSERA and $3.46 \pm 1.10 \log_{10}$ 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 $0.31 \pm 0.93 \log_{10}$ 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 $\geq 2 \log_{10}$ 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)	
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^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 chronic hepatitis B in patients 12 years of age and older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

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 ration 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: hypophosphatemia

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 phosphorus 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:

Myopathy, osteomalacia (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

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

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