

Product Monograph

Pr HEPSERA[®]

Adefovir Dipivoxil Tablets

(10 mg)

Antiviral Agent

Gilead Sciences, Inc.
Foster City, CA 94404
USA

Date of Revision: August 19, 2020

Gilead Sciences Canada, Inc.
Mississauga ON L5N 2W3

www.gilead.com

Submission Control No.: 236397

TABLE OF CONTENTS

| | |
|--|----|
| PART I. HEALTH PROFESSIONAL INFORMATION..... | 3 |
| SUMMARY PRODUCT INFORMATION | 3 |
| INDICATIONS AND CLINICAL USE | 3 |
| CONTRAINDICATIONS | 3 |
| WARNINGS AND PRECAUTIONS..... | 4 |
| ADVERSE REACTIONS..... | 7 |
| DRUG INTERACTIONS | 11 |
| DOSAGE AND ADMINISTRATION | 12 |
| OVERDOSAGE | 13 |
| ACTIONS AND CLINICAL PHARMACOLOGY | 13 |
| STORAGE AND STABILITY | 16 |
| SPECIAL HANDLING INSTRUCTIONS..... | 16 |
| DOSAGE FORMS, COMPOSITION AND PACKAGING..... | 16 |
| PART II. SCIENTIFIC INFORMATION | 17 |
| CLINICAL TRIALS..... | 17 |
| DETAILED PHARMACOLOGY | 24 |
| MICROBIOLOGY | 24 |
| PHARMACEUTICAL INFORMATION..... | 25 |
| TOXICOLOGY | 26 |
| REFERENCES | 27 |
| PART III. CONSUMER INFORMATION..... | 28 |

PART I. HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedical Ingredients |
|-------------------------|------------------------|--|
| Oral | Tablet 10 mg | pregelatinized starch (gluten free), lactose monohydrate |

For a complete listing, see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

HEPSERA® (adefovir dipivoxil) is indicated for the treatment of chronic hepatitis B in adults with compensated and decompensated liver disease with evidence of active viral replication, and either evidence of histologically active disease or elevation in serum aminotransferases (ALT or AST).

This indication is based on data from:

- two randomized, double-blind, placebo-controlled studies in adult patients with HBeAg+ and HBeAg- chronic hepatitis B with compensated liver function evaluating histological response
- and a non-placebo controlled study in pre- and post-liver transplantation patients, with either compensated or decompensated liver function, and an active-controlled study in patients with lamivudine-resistant hepatitis B and compensated liver function, evaluating virological response. The clinical significance of a reduction in serum HBV DNA with respect to histological improvement could not be evaluated.

CONTRAINDICATIONS

HEPSERA is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product. **For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.**

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Severe acute exacerbations of hepatitis have been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with HEPSERA (adefovir dipivoxil). Hepatic function should be monitored closely in patients who discontinue anti-hepatitis B therapy. If appropriate, resumption of anti-hepatitis B therapy may be warranted (see WARNINGS).
- Chronic administration of HEPSERA may result in nephrotoxicity. It is important to monitor renal function before and during treatment with HEPSERA (see WARNINGS). Patients at risk for or having underlying renal dysfunction and patients taking nephrotoxic agents are particularly at risk and should be monitored closely. Patients with renal insufficiency at baseline or during treatment may require dose adjustment (see DOSAGE AND ADMINISTRATION).
- HIV resistance may emerge in chronic hepatitis B patients with unrecognized or untreated human immunodeficiency virus (HIV) infection treated with anti-hepatitis B therapies, such as therapy with HEPSERA, that may have activity against HIV (see WARNINGS).
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals (see WARNINGS).

General

HEPSERA should not be administered concurrently with VIREAD[®] (tenofovir disoproxil fumarate) or tenofovir disoproxil fumarate-containing products including TRUVADA[®] (emtricitabine/tenofovir disoproxil fumarate combination tablet), ATRIPLA[®] (efavirenz/emtricitabine/tenofovir disoproxil fumarate combination tablet), COMPLERA[®] (rilpivirine/emtricitabine/tenofovir disoproxil fumarate combination tablet), and STRIBILD[®] (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate).

HEPSERA should not be administered concurrently with products containing tenofovir alafenamide (VEMLIDY[®] [tenofovir alafenamide], DESCOVY[®] [emtricitabine/tenofovir alafenamide], GENVOYA[®] [elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide], ODEFSEY[®] [emtricitabine/rilpivirine/tenofovir alafenamide], Symtuza[®] [darunavir/cobicistat/emtricitabine/tenofovir alafenamide] or BIKTARVY[®] [bictegravir/emtricitabine/tenofovir alafenamide]).

Patients should be advised that therapy of chronic hepatitis B with HEPSERA has not been proven to reduce the risk of transmission of hepatitis B virus to others through sexual contact or blood contamination and therefore, appropriate precautions should still be taken.

Exacerbations of Hepatitis after Discontinuation of Treatment

Severe acute exacerbation of hepatitis has been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with HEPSERA. Patients who discontinue HEPSERA should be monitored at repeated intervals 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.

Nephrotoxicity

Chronic administration of HEPSEARA (10 mg once daily) may result in nephrotoxicity.

Nephrotoxicity characterized by a delayed onset of gradual increases in serum creatinine and decreases in serum phosphorus was historically shown to be the treatment-limiting toxicity of adefovir dipivoxil therapy at substantially higher doses in HIV-infected patients (60 mg and 120 mg daily) and in chronic hepatitis B patients (30 mg daily). 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 are at risk for nephrotoxicity (see **ADVERSE REACTIONS**). It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with HEPSEARA.

It is important to monitor renal function in all patients before and during treatment with HEPSEARA, particularly for those with pre-existing or other risks for renal impairment. There is limited safety and efficacy data in patients with renal impairment. HEPSEARA is not recommended for these patients unless the potential benefit outweighs the potential risk. Patients with renal impairment at baseline or during treatment may require dose adjustment (see **DOSAGE AND ADMINISTRATION**). The risks and benefits of HEPSEARA treatment should be carefully evaluated prior to discontinuing HEPSEARA in a patient with treatment-emergent nephrotoxicity.

HIV Resistance

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

Lactic Acidosis/Severe Hepatomegaly with Steatosis

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

A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside

analogous 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 HEPSEARA 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).

Duration of Treatment

The optimal duration of treatment with HEPSEARA has not been established. The relationship between treatment with HEPSEARA and long-term outcomes such as hepatocellular carcinoma or decompensated cirrhosis is not known.

HBV Resistance

Long-term use of adefovir dipivoxil may result in emergence of HBV resistance. Resistance to adefovir dipivoxil can result in viral load rebound which may result in exacerbation of hepatitis B and, particularly in the setting of diminished hepatic function, lead to liver decompensation and possible fatal outcome. In order to reduce the risk of resistance, serum HBV virus level should be monitored during adefovir dipivoxil treatment and a change of treatment should be considered if serum HBV DNA remains above 1000 copies/mL after 48 weeks of treatment.

Special Populations

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. HEPSEARA should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus (**see TOXICOLOGY, Pregnancy**). For patients who are on HEPSEARA and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of HEPSEARA.

Pregnancy Registry

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

Labor and Delivery

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

Nursing Women

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

Pediatrics

Safety and efficacy of HEPSERA in pediatric patients have not been established.

Geriatrics

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, since they have a greater frequency of decreased renal or cardiac function due to concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Experience in Patients 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. The most common treatment related adverse events in patients receiving HEPSERA were asthenia, headache, and abdominal pain.

In addition to specific adverse events described under the **WARNINGS AND PRECAUTIONS** section, all treatment-related clinical adverse events that occurred in 3% or greater of HEPSERA-treated patients compared with placebo are listed in Table 1. Patients who received HEPSERA up to 240 weeks in Study 438 reported adverse reactions similar in nature and severity to those reported in the first 48 weeks.

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

| | HEPSERA N=294 | Placebo N=228 |
|------------------------|--------------------------|--------------------------|
| Body as a Whole | | |
| Asthenia | 13% | 14% |
| Headache | 9% | 10% |
| Abdominal pain | 9% | 11% |
| Digestive | | |
| Nausea | 5% | 8% |
| Flatulence | 4% | 4% |
| Diarrhea | 3% | 4% |
| Dyspepsia | 3% | 2% |

In addition, the following selected adverse events were reported in less than 3% of patients treated with HEPSERA:

BODY AS A WHOLE: back pain, chest pain

DIGESTIVE: anorexia

HEMATOLOGIC AND LYMPHATIC: anemia, thrombocytopenia

METABOLIC AND NUTRITIONAL: weight loss

RESPIRATORY: pharyngitis

SKIN AND APPENDAGES: rash

Laboratory Abnormalities

Laboratory abnormalities observed in these studies occurred with similar frequency in the HEPSERA and placebo treated groups with the exception of hepatic transaminase elevations which occurred more frequently in the placebo group. Increased liver transaminases were the most common post-treatment laboratory abnormality in the HEPSERA treated group (**see WARNINGS**). In addition, increased creatinine was identified as an adverse reaction with extended open-label treatment.

A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 2.

Table 2. 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 ($> 5 \times$ ULN) | 20% | 41% |
| Hematuria ($\geq 3+$) | 11% | 10% |
| AST ($> 5 \times$ ULN) | 8% | 23% |
| CK ($> 4 \times$ ULN) | 7% | 7% |
| Amylase ($> 2 \times$ ULN) | 4% | 4% |
| Glycosuria ($\geq 3+$) | 1% | 3% |

No patients with adequate renal function treated with Hepsara developed a serum creatinine increase $\geq 44 \mu\text{mol/L}$ ($\geq 0.5 \text{ mg/dL}$) from baseline by Week 48. By Week 96, 10% and 2% of HEPSERA-treated patients, by Kaplan-Meier estimate, had increases in serum creatinine $\geq 27 \mu\text{mol/L}$ ($\geq 0.3 \text{ mg/dL}$) and $\geq 44 \mu\text{mol/L}$ from baseline, respectively (no placebo-controlled results were available for comparison beyond Week 48). Of the 29 of 492 patients with elevations in serum creatinine $\geq 27 \mu\text{mol/L}$ from baseline, 20 out of 29 resolved on continued treatment ($\leq 18 \mu\text{mol/L}$ or $\leq 0.2 \text{ mg/dL}$), 8 of 29 remained unchanged and 1 of 29 resolved on discontinuing treatment. 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 in Study 438 continued on HEPSERA for a median duration of 226 weeks ($n=125$); 4/125 patients (3%) had elevations in serum creatinine $\geq 44 \mu\text{mol/L}$ from baseline which resolved in 1 patient who permanently discontinued treatment and remained stable in 3 patients who continued treatment. In Study 437, 65 patients continued HEPSERA for a median duration of 234 weeks. Six patients had a confirmed increase of $\geq 44 \mu\text{mol/L}$ ($\geq 0.5 \text{ mg/dL}$) from baseline with 2 patients discontinuing from the study due to the elevated serum creatinine concentration. (see **Laboratory Abnormalities – Special Risk Patients**).

Experience in Pre- and Post-liver Transplantation Patients with Lamivudine-Resistant HBV

Pre- ($N = 226$) and post-liver transplantation patients ($N = 241$) with chronic hepatitis B and clinical evidence of lamivudine-resistant hepatitis B virus were treated in an open-label study with HEPSERA for up to 203 weeks, with a median time on treatment of 51 and 99 weeks, respectively.

The most common treatment-related adverse events reported in pre- and post-liver transplantation patients treated with HEPSERA with a 2% frequency or higher are shown in Table 3.

Table 3. Treatment-Related Adverse Events Reported in $\geq 2\%$ of Pre- or Post-liver Transplantation Patients

| | Pre-liver Transplantation N=226 | Post-liver Transplantation N=241 |
|----------------------------------|---------------------------------------|--|
| Body as a Whole | | |
| Asthenia | 4% | 6% |
| Abdominal pain | 2% | 5% |
| Headache | < 1% | 4% |
| Digestive | | |
| Nausea | 1% | 5% |
| Vomiting | 1% | 3% |
| Diarrhea | 2% | 4% |
| Jaundice | < 1% | 2% |
| Metabolic and Nutritional | | |
| ALT increase | 1% | 4% |
| AST increase | 1% | 3% |
| Hyperkalemia | 0% | 2% |
| Hypophosphatemia | 2% | 2% |
| Liver function tests abnormal | 1% | 2% |
| Musculoskeletal | | |
| Myalgia | 0% | 3% |
| Skin and Appendages | | |
| Pruritus | 1% | 5% |
| Rash | 1% | 2% |
| Urogenital | | |
| Abnormal kidney function | 1% | 3% |
| Creatinine increase | 2% | 12% |
| Renal failure | 1% | 2% |

Fever, flatulence, hepatic failure, cough increase, pharyngitis and sinusitis occurred in less than 2% of patients.

Laboratory Abnormalities – Special Risk Patients

Pre- (N = 226) and post-liver transplantation patients (N = 241) with chronic hepatitis B and clinical evidence of lamivudine-resistant hepatitis B virus were treated in an open-label study with HEPSERA for up to 203 weeks, with a median time on treatment of 51 and 99 weeks, respectively. Changes in renal function occurred in pre- and post-liver transplantation patients with risk factors for renal dysfunction, including concomitant use of cyclosporine and tacrolimus, renal insufficiency at baseline, hypertension, diabetes, and on-study transplantation. Increases in serum creatinine ≥ 44 $\mu\text{mol/L}$ (≥ 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 ≥ 44 $\mu\text{mol/L}$ 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 ≥ 44 $\mu\text{mol/L}$ from baseline resolved (≤ 27 $\mu\text{mol/L}$ or ≤ 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. Among patients who were assessed for serum phosphorus, values < 0.65 mmol/L were observed in 3/186 (1.6%) of pre-liver transplantation patients and in 6/208 (2.9%) 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.

Post Market Adverse Drug Reactions

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.

Metabolism and Nutrition Disorders: hypophosphatemia

Gastrointestinal Disorders: pancreatitis

Musculoskeletal System and Connective Tissue Disorders: Osteomalacia (manifested as bone pain and which may contribute to fractures) and myopathy, both associated with proximal renal tubulopathy.

Renal and Urinary Disorders: renal failure, Fanconi syndrome, proximal renal tubulopathy

DRUG INTERACTIONS

Since adefovir is eliminated by the kidney, coadministration of HEPSERA (adefovir dipivoxil) with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either adefovir and/or renally eliminated coadministered drugs. HEPSERA should not be administered concurrently with products containing

tenofovir disoproxil fumarate or tenofovir alafenamide (see **WARNINGS AND PRECAUTIONS, General**).

At concentrations substantially higher (>4000 fold) than those observed in vivo, adefovir did not inhibit any of the following human CYP450 isoforms, CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. 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.

HEPSERA has been evaluated in healthy volunteers in combination with lamivudine, trimethoprim/sulfamethoxazole, acetaminophen and ibuprofen and in post-liver transplantation patients in combination with tacrolimus.

The pharmacokinetics of lamivudine, trimethoprim/sulfamethoxazole, acetaminophen, tacrolimus, and ibuprofen were unaltered when coadministered with HEPSEARA.

The pharmacokinetics of adefovir were unaltered when HEPSEARA was coadministered with lamivudine, acetaminophen, tacrolimus, and trimethoprim/ sulfamethoxazole. When HEPSEARA was coadministered with ibuprofen (800 mg TID) increases in adefovir C_{max} (33%), AUC (23%) and urinary recovery were observed. This increase appears to be due to higher relative oral bioavailability, not a reduction in renal clearance of adefovir. This increase was not considered to be of a sufficient magnitude to warrant a change in dosing of HEPSEARA.

DOSAGE AND ADMINISTRATION

The recommended dose of HEPSEARA (adefovir dipivoxil) in chronic hepatitis B patients with adequate renal function is 10 mg, once daily, taken orally, without regard to food. The optimal duration of treatment is unknown (see **WARNINGS, Exacerbation of Hepatitis after Discontinuation of Treatment**). Therapy should be initiated and monitored by a physician experienced in the management of chronic hepatitis B.

Discontinuation of HEPSEARA treatment and a change in treatment should be considered in case of evidence of ineffectiveness or efficacy loss.

Dosage Adjustment in Renal Impairment

Adefovir is eliminated by renal excretion, therefore adjustments in the dosing interval of HEPSEARA are required in patients with creatinine clearance < 50 mL/min.

The dosing frequency according to renal function must not exceed the recommended scheduled based on a pharmacokinetic study (see Table 4). Clinical response to treatment and renal function should be closely monitored in these patients.

Table 4. Dosing Interval Adjustments of HEPSERA in Patients with Renal Impairment

| | Creatinine Clearance (mL/min)* | | | |
|--------------------------------------|--------------------------------|----------------------|----------------------|---------------------------------------|
| | ≥ 50 | 30–49 | 10–29 | Hemodialysis Patients |
| Recommended Dose and Dosing Interval | 10 mg every 24 hours | 10 mg every 48 hours | 10 mg every 72 hours | 10 mg every 7 days following dialysis |

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

Hepatic Impairment

No dose adjustment is required in patients with hepatic impairment (see **ACTIONS and CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Missed Dose

If a patient misses a dose at the regularly scheduled time, but then remembers it that same day, the patient should take the missed dose immediately. The next dose should be taken at the regularly scheduled time the following day. The patient should not take two doses of HEPSERA at once to make up for missing a dose.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

If overdose occurs, activated charcoal may be used to remove unabsorbed drug. The patient should be monitored for evidence of toxicity, and standard supportive treatment should be applied as necessary.

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

Daily doses of adefovir dipivoxil 500 mg for 2 weeks and 250 mg for 12 weeks have been associated with gastrointestinal side effects (also, see **WARNINGS and PRECAUTIONS, NEPHROTOXICITY**).

ACTIONS AND CLINICAL PHARMACOLOGY

HEPSERA is an oral prodrug of adefovir, a nucleoside phosphonate analog of adenosine monophosphate, which is actively transported into mammalian cells where it is converted into the active metabolite, adefovir diphosphate, by host enzymes. Adefovir diphosphate has an intracellular half-life of 12 to 36 hours in activated and resting lymphocytes. Adefovir diphosphate inhibits viral polymerases by direct binding competition with the natural

substrate (deoxyadenosine triphosphate) and, after incorporation into viral DNA, results in DNA chain termination. The inhibition constant (K_i) for adefovir diphosphate for recombinant HBV DNA polymerase was 0.1 μM . Adefovir diphosphate selectively inhibits HBV DNA polymerases at concentrations 12-, 700-, and 10-fold lower than those needed to inhibit human DNA polymerases α , β , and γ , respectively.

Adefovir has in vitro antiviral activity against hepadnaviruses. The in vitro IC_{50} (concentration of drug which inhibits viral replication by 50%) of adefovir against wild-type HBV varied from 0.2 μM to 1.2 μM in human hepatic cell lines (0.2–1.2 μM in HB611, and 0.7–1.2 μM in HepG2 hepatoma cell lines).

Pharmacokinetics

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

Absorption

Adefovir dipivoxil is a dipivaloyloxymethyl ester prodrug of the active ingredient adefovir. The oral bioavailability of adefovir is approximately 59%.

Following oral administration of a single dose of HEPSEARA to chronic hepatitis B patients, the median (range) peak serum concentration (C_{max}) was achieved after 1.75 hrs (0.58–4.00). C_{max} and area under the curve (AUC) values were 16.70 (9.66–30.56) ng/mL and 204 (110–356) ng•h/mL, respectively. The median (range) oral clearance of adefovir was 304.90 (173.07–490.62) mL/hr/kg. Plasma adefovir concentrations declined in a biexponential manner with a median terminal elimination half-life of 7.22 hours (4.72–10.70 hours).

The pharmacokinetics of adefovir in subjects with adequate renal function were not affected following 10 mg once daily dose of HEPSEARA over 7 days. The effect of long term once daily administration of HEPSEARA on adefovir pharmacokinetics has not been studied.

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.

Metabolism

Following oral administration, HEPSEARA 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 HEPSEARA.

Excretion

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**). Coadministration of HEPSERA with other drugs that are eliminated by, or alter tubular secretion may increase serum concentrations of either adefovir or the administered drug.

Effects of Food on Oral Absorption

HEPSERA may be taken without regard to food. Adefovir exposure was unaffected when HEPSERA was administered with food (~1000 kcal high-fat meal).

Special Populations and Conditions

Pediatrics and Geriatrics

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

Gender

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

Race

No definitive studies have been performed. Results from two pharmacokinetic studies in healthy Chinese volunteers (N = 12 in single dose study and N = 20 in 7-day multiple dose study) reported similar pharmacokinetic results to historical data from various studies in healthy and chronic hepatitis B Caucasian volunteers and patients.

Renal Impairment

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

In Table 5, the pharmacokinetics of adefovir in patients with varying degrees of renal impairment without chronic hepatitis B are described.

Table 5. Pharmacokinetic Parameters (Median) of Adefovir in Patients with Varying Degrees of Renal Function

| Renal Function Group | Unimpaired N=7 | Mild N=8 | Moderate N=7 | Severe N=10 | ESRD N=8 |
|--|-------------------|-------------|-----------------|----------------|-------------|
| Baseline creatinine clearance (mL/min) | > 80 | 50–80 | 30–49 | < 30 | NA* |
| C _{max} (ng/mL) | 18.7 | 21.7 | 27.1 | 53.7 | 56.7 |
| AUC _{0-∞} (ng•hr/mL) | 200 | 281 | 466 | 1300 | NA |
| CL/F (mL/min) | 454 | 324 | 195 | 70 | NA |
| CL _{renal} (mL/min) | 211 | 149 | 86 | 35 | NA |

* NA = Not applicable

Hepatic Impairment

The pharmacokinetics of adefovir have been studied in patients with hepatic impairment without chronic hepatitis B. There were no substantial alterations in adefovir pharmacokinetics in patients with moderate and severe hepatic impairment compared to unimpaired patients. No change in dosing is required in patients with hepatic impairment.

STORAGE AND STABILITY

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

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

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

HEPSERA (adefovir dipivoxil) is available as tablets. Each tablet contains 10 mg of adefovir dipivoxil. HEPSERA are white, flat-faced tablets debossed with “10” and “GILEAD” on one side and the stylized figure of a liver on the other side. Each bottle contains 30 tablets and desiccant (silica gel), and is closed with a child-resistant closure. The tablets also include the following inactive ingredients: pregelatinized starch, croscarmellose sodium, lactose monohydrate, talc and magnesium stearate.

PART II. SCIENTIFIC INFORMATION

CLINICAL TRIALS

Study Demographics and Trial Design

HBeAg-Positive Chronic Hepatitis B

Study 437 was a randomized, double-blind, placebo-controlled, 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, 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 as measured by Roche Amplicor polymerase chain reaction (PCR) assay (LLOQ=1000 copies/mL), and a median ALT of 2.3 times the upper limit of normal. The median age of patients was 33 years, 74% were male, 59% were Asian, 36% were Caucasian, and 24% had prior interferon- α treatment, 2% had prior lamivudine treatment.

Presumed Precore Mutant (HBeAg-negative/anti-HBe-positive/ HBV DNA positive) Chronic Hepatitis B

Study 438 was a randomized (2:1), double-blind, placebo-controlled, two-arm study in patients with presumed precore mutant chronic hepatitis B. Patients were serum HBsAg-positive for a minimum of 6 months, HBeAg-negative at screening and anti-HBe-positive. At baseline, patients had a median total Knodell HAI score of 10, a median serum HBV DNA level of 7.08 log₁₀ copies/mL as measured by the Roche Amplicor polymerase chain (PCR) reaction assay (LLOQ=1000 copies/mL), and a median ALT of 2.3 times the upper limit of normal. The median age of patients was 46 years, 83% were male, 66% were Caucasian and 30% were Asian, and 41% had prior interferon- α treatment, 8% had prior lamivudine, 8% had prior famciclovir.

Table 6. Studies 437 and 438 Trial Design

| Study No. | Trial Design | Dosage, Duration and Route of Administration | Study Subjects | Median Age | Gender |
|-----------|---|---|---|------------|----------|
| GS-98-437 | Double-Blind Randomized Placebo-Controlled | Arm 1: 10 mg adefovir dipivoxil Arm 2: placebo 48 weeks duration | HBeAg-Positive Chronic Hepatitis. Arm 1 n=171 Arm 2= 167. | 33 years | 74% male |
| GS-98-438 | Double-Blind Randomized Placebo-Controlled | First 48 Weeks: Arm 1: 10 mg adefovir dipivoxil Arm 2: placebo Second 48 Weeks: Arm 1 Re-randomized to adefovir dipivoxil or placebo (2:1 ratio) Arm 2 switched to adefovir dipivoxil 10 mg Weeks 49-96 All patients completing DB phase and on adefovir dipivoxil in year 2 were eligible for up to 144 week long term FU period | Presumed Pre-Core Mutant Patients. First 48 weeks: Arm 1 n=123 Arm 2 n=61. Second 48 weeks: Adefovir dipivoxil to placebo n=40. Adefovir dipivoxil to adefovir dipivoxil n=79. Placebo to adefovir dipivoxil n=60. Long term adefovir dipivoxil n=125 | 46 years | 83% male |

Study Results

The primary efficacy endpoint in both studies was histological improvement defined as ≥ 2 point decrease in the Knodell necro-inflammatory score with no worsening of the Knodell fibrosis score at Week 48; results of which are shown in Table 7. Post-baseline missing or unassessable biopsies were considered as treatment failures. Histological improvement was observed more frequently in patients treated with HEPSERA than in those treated with placebo after 48 weeks of treatment (see Table 7). In Study 437, 53% of HEPSERA-treated patients had histological improvement compared to 25% of placebo-treated patients at Week 48. In Study 438, 64% of HEPSERA-treated patients had histological improvement compared to 33% of placebo-treated patients at Week 48.

Table 7. Histological Improvement at Week 48*

| | Study 437 | | Study 438 | |
|-------------------------------------|------------------|------------------|------------------|-----------------|
| | HEPSERA N=168 | Placebo N=161 | HEPSERA N=121 | Placebo N=57 |
| Improvement** | 53% | 25%† | 64% | 33%†† |
| No improvement | 36% | 65%† | 29% | 63%†† |
| Missing/ unassessable data*** | 11% | 9%† | 7% | 4%†† |

† p < 0.0001 ††p = 0.0002

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

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

*** Post-baseline missing/unassessable biopsies were considered as treatment failures.

Table 8 illustrates the changes in Ishak Fibrosis Score by treatment group.

Table 8. Changes in Ishak Fibrosis Score at Week 48

| Number of Adequate Biopsy Pairs* | Study 437 | | Study 438 | |
|--|------------------|------------------|------------------|-----------------|
| | HEPSERA N=150 | Placebo N=146 | HEPSERA N=112 | Placebo N=55 |
| Ishak Fibrosis Score | | | | |
| Improved** | 35% | 19% | 34% | 15% |
| Unchanged | 54% | 59% | 62% | 49% |
| Worsened** | 11% | 22% | 4% | 36% |

* Denominator is the number of patients with adequate biopsy at baseline and at Week 48, patients with missing biopsy information excluded.

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

At Week 48, improvement was seen with respect to median change in serum HBV DNA (\log_{10} copies/mL), normalization of ALT, and HBeAg loss and seroconversion as compared to placebo in patients receiving HEPSEARA (Table 9).

Table 9. Change in Serum HBV DNA, ALT Normalization, HBeAg Loss and Seroconversion at Week 48

| | Study 437 | | Study 438 | |
|--|------------------|------------------|------------------|-----------------|
| | HEPSERA N=171 | Placebo N=167 | HEPSERA N=123 | Placebo N=61 |
| Median change in serum HBV DNA from baseline (log ₁₀ copies/mL) | -3.52 | -0.55 | -3.91 | -1.35 |
| HBV DNA < 1000 copies/mL** | 28% | 0% | 64% | 3% |
| ALT normalization | 48% | 16% | 72% | 29% |
| HBeAg loss | 24% | 11% | NA* | NA* |
| HBeAg seroconversion | 12% | 6% | NA* | NA* |

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

** Lower limit of quantification of the experimental Roche Amplicor™ polymerase chain reaction assay.

Genotypic and Phenotypic Analyses of HEPSEARA

Resistance surveillance by genotypic analysis at baseline and Week 48 was performed in all HEPSEARA treated patients with detectable serum HBV DNA (using the experimental Roche Amplicor PCR assay) in Study 437 (N = 215) and 438 (N = 56). During the study period, 48 weeks, no HBV DNA polymerase mutations were associated with decreased susceptibility to adefovir in cell culture and enzymatic assays (IC₅₀ and K_i values were within 0.6- to 3.6-fold of wild-type) (see **MICROBIOLOGY for resistance surveillance beyond 48 weeks**).

Treatment Beyond 48 Weeks

In Study 438, patients who received HEPSEARA during the first 48 weeks were re-randomized in a blinded manner to either continue on HEPSEARA or receive placebo for an additional 48 weeks. Patients who continued on HEPSEARA for an additional 48 weeks (N = 79) maintained suppression of serum HBV DNA levels (median HBV DNA change from baseline -3.47 log₁₀ copies/mL; 71% < 1000 copies/mL) and have had sustained reductions in ALT levels (73% < ULN) similar to the results at 48 weeks (see Table 9). In contrast, patients who discontinued HEPSEARA (switched to placebo for additional 48 weeks; N = 40) had serum HBV DNA levels return towards baseline (median HBV DNA change from baseline -1.09 log₁₀ copies/mL; 8% < 1000 copies/mL) and ALT levels rebounded (32% < ULN) in the majority of patients.

Patients who received placebo during the first 48 weeks and HEPSEARA during the second 48 weeks and patients who received HEPSEARA during the first and second 48 weeks continued on HEPSEARA 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. Following treatment with HEPSEARA for 144, 192, and 240 weeks, 53 of 69 (77%), 51 of 65 (78%) and 37 of 55 (67%) patients in the 240-week cohort, respectively, had undetectable HBV DNA levels and 43 of 64 (67%), 44 of 59 (75%) and 38 of 55 (69%) patients had ALT

normalization; 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. 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 (58%) patients 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. 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+).

Pre- and Post-Liver Transplantation Patients

HEPSERA was also evaluated in an open-label, uncontrolled study of 467 chronic hepatitis B patients pre- (N = 226) and post- (N = 241) liver transplantation with clinical evidence of lamivudine-resistant HBV (Study 435). At baseline, 60% of pre-liver transplantation patients were classified as Child-Pugh-Turcotte score of Class B or C. The median baseline HBV DNA as measured by the Roche Amplicor polymerase chain reaction assay (LLOQ=1000 copies/mL) was 7.4 and 8.2 log₁₀ copies/mL, and the median baseline ALT was 1.8 and 2.0 times the upper limit of normal in pre- and post-liver transplantation patients, respectively. Results of this study are displayed in Table 10. Treatment with HEPSERA resulted in a similar reduction in serum HBV DNA regardless of the patterns of lamivudine-resistant HBV DNA polymerase mutations at baseline.

Table 10. Efficacy in Pre- and Post-Liver Transplantation Patients at Week 48*

| Efficacy Parameter | Pre-liver Transplantation N=(226) | Post-liver Transplantation (N=241) |
|--|--|---|
| Median change in HBV DNA from baseline (log ₁₀ copies/mL) | -4.1 (n=117) | -4.2 (n=164) |
| **Proportion with undetectable HBV DNA (< 1000 copies/mL) | 71% (77 of 109) | 40% (64 of 159) |
| Stable or improved Child-Pugh-Turcotte score | 96%** (86 of 90) | 93% (107 of 115) |
| Normalization of: *** | | |
| ALT | 74% (61 of 82) | 51% (56 of 110) |
| Albumin | 80% (43 of 54) | 81% (21 of 26) |
| Bilirubin | 58% (38 of 66) | 76% (29 of 38) |
| Prothrombin time | 85% (39 of 46) | 56% (5 of 9) |

*Centrally assessed population defined as all patients with a baseline and at least one post-baseline HBV DNA result where the analysis was performed by the central laboratory.

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

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

Treatment Beyond 48 Weeks:

In the pre-liver transplantation cohort, 25 of 33 (76%) patients achieved undetectable HBV DNA levels (< 1000 copies/mL), and 16 of 19 (84%) patients had ALT normalization at 96 weeks. In the post-liver transplantation cohort, 61 of 94 (65%) and 35 of 45 (78%) of patients achieved undetectable HBV DNA levels (< 1000 copies/mL) and 46 of 66 (70%) and 15 of 26 (58%) patients had ALT normalization at 96 and 144 weeks, respectively.

Patients with Lamivudine Resistant HBV and Compensated Liver Disease

In Study 461, a double-blind, active-controlled study in 59 chronic hepatitis B patients with clinical evidence of lamivudine-resistant hepatitis B virus, patients were randomized to receive either HEPSERA monotherapy or HEPSERA in combination with lamivudine 100 mg or lamivudine alone. At Week 48, the median decrease in serum HBV DNA from baseline was 4.04 log₁₀ copies/mL in the HEPSERA 10 mg arm and 3.59 log₁₀ copies/mL in patients treated with HEPSERA in combination with lamivudine. The median decrease in

serum HBV DNA from baseline in the lamivudine arm alone was 0. ALT normalized in 47% of patients treated with HEPSERA, in 53% of patients treated with HEPSERA in combination with lamivudine, and 5% of patients treated with lamivudine alone. The changes in serum HBV DNA over time are summarized in Table 11 below.

Table 11 Median Change in Serum HBV DNA –Study 461

| | HBV DNA Median Change From Baseline (log ₁₀ copies/mL) | | |
|----------------------------------|---|-------------|-------------------|
| | LAM N=19 | ADV N=19 | ADV + LAM N=20 |
| Baseline Value | 8.2 | 8.4 | 7.9 |
| Change from Baseline to Week: | | | |
| 4 | 0.1 | -1.8 | -1.9 |
| 8 | 0.0 | -2.6 | -2.5 |
| 12 | -0.1 | -2.6 | -2.7 |
| 24 | 0.1 | -3.4 | -3.0 |
| 36 | 0.1 | -3.8 | -3.3 |
| 48 | 0.0 | -4.0 | -3.6 |

Comparative Bioavailability Studies

Comparative bioavailability studies were not conducted. The proposed commercial tablets of adefovir dipivoxil 10 mg are identical in quantitative composition, tablet weight, and volume, having only minor differences in shape to the tablets used in pivotal Phase 3 studies GS-98-437 and GS-98-438. The difference in tablet shape between the clinical tablets (6.35 mm, biconvex) and the proposed commercial tablets (7 mm, flat-faced) did not result in a difference in dissolution behavior in vitro and is not expected to affect the bioavailability of adefovir dipivoxil.

DETAILED PHARMACOLOGY

MICROBIOLOGY

In Vitro Cross-resistance

Preclinical studies: HBV engineered to encode DNA polymerase mutations, including YMDD mutations (rtL180M, rtM204I, rtM204V, rtL180M plus rtM204V plus-rtV173L, rtL180M plus rtM204V,) remains susceptible to adefovir in cell-based assays of HBV replication. Mutations in the HBV DNA polymerase (rtT128N and rtR or rtW153Q) due to immune escape mutations in the overlapping gene for hepatitis B surface antigen, associated with resistance to hepatitis B immune globulin, do not affect susceptibility to adefovir in cell-culture assays of HBV replication. Adefovir also demonstrated in vitro activity against HBV variants with entecavir associated mutations (rtT184G, rtS202I, rtM250V).

HBV variants expressing the adefovir-associated resistance mutation rtN236T showed no change in susceptibility to entecavir in vitro and a 2- to 3-fold decrease in lamivudine susceptibility in vitro. The adefovir-associated resistance mutation rtA181V showed a range of decreased susceptibilities to lamivudine of 1- to 14-fold, and a 12-fold decrease in susceptibility to entecavir in vitro. In patients with either the rtA181V or the rtN236T mutation, a 2 to 6 log reduction in serum HBV DNA was observed when treatment with lamivudine was added to or substituted for treatment with adefovir dipivoxil.

Resistance

Clinical Studies

Monotherapy studies in nucleoside-naïve patients: In HBeAg-positive and HBeAg-negative patients in studies 437 and 438, respectively, no adefovir-associated resistance mutations were observed at Week 48. After median exposures of 135 weeks (range 88–179) and 189 weeks (range 110–235), the incidence of adefovir-associated resistance mutations (rtN236T or rtA181V/T) in HBeAg-positive patients (Study 437) was 3% and 17%, respectively. In HBeAg-negative patients (Study 438), the cumulative probability of adefovir-associated resistance mutations was 3%, 11%, 18 % and 29% at 96, 144, 192 and 244 weeks, respectively. Of the 29 HBe-Ag-negative patients who were treated for up to 240 weeks and developed adefovir-associated resistance mutations, 18 had a confirmed increase of ≥ 1 log₁₀ HBV DNA copies/mL above nadir or never achieved HBV DNA levels below 4 log₁₀ copies/mL while on treatment. In addition, the long term development of resistance to adefovir dipivoxil was significantly higher in patients with serum HBV DNA above 1000 copies/mL after 48 weeks of treatment.

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. Four patients demonstrated the rtN236T mutation after 72 weeks of adefovir dipivoxil therapy. Development of the rtN236T mutation was associated with serum HBV DNA rebound. All 4 patients who developed the rtN236T mutation in their HBV had discontinued lamivudine

therapy before the development of genotypic resistance and all four 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 up to 144 weeks of therapy. (see **DESCRIPTION OF CLINICAL TRIALS**).

In Vitro Studies

Clinical isolates with genotypic changes conferring reduced in vitro susceptibility to nucleoside analog inhibitors for the treatment of HBV infection have been observed. Long-term resistance analyses performed by genotyping samples from all adefovir dipivoxil-treated patients with detectable serum HBV DNA determined that mutations rtN236T and rtA181V contribute to adefovir resistance. In vitro the rtN236T mutation conferred a 4- to 14-fold reduced susceptibility and the rtA181V mutation conferred a 2.5- to 4.2-fold reduced susceptibility to adefovir.

PHARMACEUTICAL INFORMATION

Drug Substance

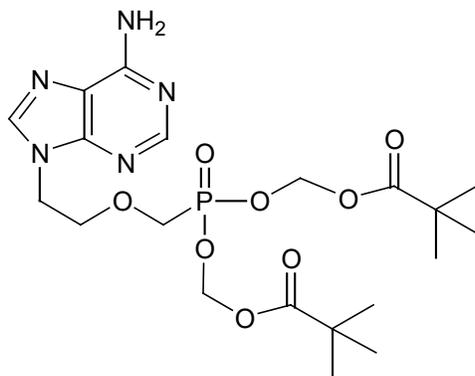
Common Name: Adefovir dipivoxil

Chemical Name:

- (1) 9-[2-[[Bis[(pivaloyloxy)methoxy]phosphiny]methoxy]ethyl]adenine (IUPAC)
- (2) Propionic acid, 2,2-dimethyl-, [[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]-phosphinylidene]bis(oxyethylene) ester (CAS)

Molecular Formula: C₂₀H₃₂N₅O₈P

Structural Formula:



Molecular Weight: 501.48

Physical Form: Adefovir dipivoxil is a white to off-white crystalline powder.

Solubility: Adefovir dipivoxil has an aqueous solubility of 19 mg/mL at pH 2.0 and 0.4 mg/mL at pH 7.2.

Adefovir dipivoxil is a phosphonomethylether prodrug of adefovir, a synthetic nucleotide analog of adenosine 5'-monophosphate. In vivo, adefovir dipivoxil is converted to the parent compound, adefovir, and through two phosphorylation reactions to adefovir diphosphate. Adefovir diphosphate exhibits activity against the hepatitis B virus (HBV) DNA polymerase. Adefovir dipivoxil is a white to off-white crystalline powder with an aqueous solubility of 19 mg/mL at pH 2.0 and 0.4 mg/mL at pH 7.2. It has an octanol/aqueous phosphate buffer (pH 7) partition coefficient (log p) of 1.91.

TOXICOLOGY

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in mice and rats receiving adefovir dipivoxil have been conducted. In mice, at doses of 1, 3, or 10 mg/kg/day, no treatment-related increases in tumor incidence were found at 10 mg/kg/day (systemic exposure was 10 times that achieved in human at a therapeutic dose of 10 mg/day). In rats dosed at 0.5, 1.5, or 5 mg/kg/day, no drug-related increase in tumor incidence was observed. The exposure at the high dose was 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), but was not clastogenic in the in vivo mouse micronucleus assay.

Adefovir was not mutagenic in microbial mutagenicity assays involving *Salmonella typhimurium* (Ames) and *Escherichia coli* in the presence and absence of metabolic activation. Adefovir induced chromosomal aberrations in the in vitro human peripheral blood lymphocyte assay without metabolic activation.

In reproduction toxicology studies, no evidence of impaired fertility was seen in male or female rats at doses up to 30 mg/kg/day.

Pregnancy

Reproduction studies conducted with adefovir dipivoxil administered orally have shown no embryotoxicity or teratogenicity in rats at doses up to 35 mg/kg/day, or in rabbits at 20 mg/kg/day. In a toxicokinetic study in pregnant animals, systemic exposure in rats given 25 mg/kg/day or rabbits given 20 mg/kg/day were approximately 23 and 40 times that in humans at the therapeutic dose.

When adefovir was administered intravenously to pregnant rats at doses associated with notable maternal toxicity (20 mg/kg/day, systemic exposure 38 times human), embryotoxicity and an increased incidence of fetal malformations (anasarca, depressed eye

bulge, umbilical hernia and kinked tail) were observed. No adverse effects on development were seen with adefovir administered intravenously to pregnant rats at 2.5 mg/kg/day (systemic exposure 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 in pregnant women only if the potential benefits outweigh the potential risks to the fetus.

Local Tolerance

Based on studies in laboratory animals, adefovir dipivoxil is a mild skin irritant, but is not an allergic skin sensitizer. Adefovir dipivoxil was a severe ocular irritant (without saline irrigation) in a primary eye irritation study in rabbits, but was a mild ocular irritant with saline irrigation. Therefore, following any ocular exposure, eyes should be rinsed as soon as possible to minimize irritation.

REFERENCES

1. Benhamou, Y., et al., Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *The Lancet*, 2001.vol.358:p.718-723.
2. Marcellin, P., et al., Adefovir Dipivoxil for the Treatment of HBeAg-Positive Chronic Hepatitis B. *The New England Journal of Medicine*, 2003, vol. 348, No. 9, p. 808-816.
3. Hadziyannis, S.J., et al., Adefovir Dipivoxil for the Treatment of Patients with Hepatitis B e Antigen-Negative Chronic Hepatitis B. *The New England Journal of Medicine*, 2003, vol. 348, No. 9, p. 800-807.
4. Westland, C.E., et al., Week 48 Resistance Surveillance in Two Phase 3 Clinical Studies of Adefovir Dipivoxil for Chronic Hepatitis B. *Hepatology*, 2003, vol. 38, No. 1, p. 96-103.
5. Westland, C.E., et al., Hepatitis B Virus Genotypes and Virologic Response in 694 Patients in Phase III Studies of Adefovir Dipivoxil. *Gastroenterology*, 2003, vol. 125, No. 1, p. 107-116.
6. Angus, P., et al., Resistance to Adefovir Dipivoxil Therapy Associated With the Selection of a Novel Mutation in the HBV Polymerase. *Gastroenterology*, 2003, vol. 125, No. 1, p. 292-297.

PART III. CONSUMER INFORMATION

**PrHepsera®
(adefovir dipivoxil tablets)**

This leaflet is Part III of a three-part “Product Monograph” published when HEPSERA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about HEPSERA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- HEPSERA is used to treat adults with continuing (chronic) infection with active hepatitis B virus.

What it does:

- HEPSERA binds to viral DNA to interfere with replication of the virus and helps lower the amount of hepatitis B virus in your body.
- HEPSERA will not cure your chronic hepatitis B.
- HEPSERA may help lower the amount of hepatitis B virus in your body.
- It is not known how long HEPSERA may help your hepatitis. Sometimes viruses change in your body and medications no longer work. This is called drug resistance.
- It is not known if HEPSERA will reduce your chances of getting liver cancer or liver damage (cirrhosis) from chronic hepatitis B.
- HEPSERA does not stop you from spreading hepatitis B to others by sex or sharing needles. It is important to practice safe sex and not to share needles.

When it should not be used:

Together with your doctor, you need to decide whether HEPSERA is right for you.

- Do not take HEPSERA if you are allergic to any of the ingredients in HEPSERA (see **What the nonmedicinal ingredients are**).
- Do not take HEPSERA if you are HIV positive.
- Do not take HEPSERA if you are pregnant or breastfeeding.
- HEPSERA has not been studied in adults over the age of 65 or in persons under 18 years of age.
- Do not take HEPSERA if you are also taking VIREAD® (tenofovir disoproxil fumarate), TRUVADA® (emtricitabine/tenofovir disoproxil fumarate), ATRIPLA® (efavirenz/emtricitabine/tenofovir disoproxil fumarate), COMPLERA® (rilpivirine/emtricitabine/tenofovir disoproxil fumarate) or STRIBILD® (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate).
- Do not take HEPSERA if you are also taking VEMLIDY® (tenofovir alafenamide), DESCOVY® (emtricitabine/tenofovir alafenamide), GENVOYA® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide), ODEFSEY® (emtricitabine/rilpivirine/tenofovir alafenamide), Symtuza® (darunavir/cobicistat/emtricitabine/tenofovir alafenamide) or BIKTARVY® (bictegravir/emtricitabine/tenofovir alafenamide).

What the medicinal ingredient is:

Adefovir dipivoxil

What the nonmedicinal ingredients are:

Croscarmellose sodium, lactose monohydrate, magnesium stearate, pregelatinized starch, talc

What dosage forms it comes in:

HEPSERA is available as tablets. Each tablet contains 10 mg of adefovir dipivoxil. HEPSERA tablets are white, with “10” and “GILEAD” on one side and a picture of a liver on the other side. Each bottle contains 30 tablets and desiccant (silica gel) to absorb moisture, and closed with a child-resistant closure.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Talk to your doctor before you stop taking HEPSERA.** Some people who take HEPSERA get a very serious hepatitis when they stop taking HEPSERA. This usually happens within 12 weeks after you stop HEPSERA. You will need to have regular blood tests to check for liver function and hepatitis B virus levels if you stop taking HEPSERA.
- **HEPSERA may cause kidney problems.** This can happen to anyone that uses HEPSERA, especially people who already have kidney problems. Your doctor may ask you to have blood tests to check for kidney function while you are taking HEPSERA. Since kidney problems often do not cause symptoms and are often only detected with blood tests, it is important to have all of your blood tests as instructed by your doctor.
- **If you get or have HIV infection (the virus that causes AIDS), and you don't know it, or if your HIV is not being treated while you are taking HEPSERA, HEPSERA may increase the chances of you developing resistance to HIV infection, as HEPSERA may have some anti-HIV activity.** You should talk to your doctor to find out if you should have an HIV test before you start taking HEPSERA and whenever there is a chance that you were exposed to HIV.
- **Some people who have taken nucleotide analog medications like HEPSERA, either alone or in combination with other anti-retroviral drugs, have developed a serious condition called lactic acidosis (build up of acid in the blood).** Lactic acidosis is a medical emergency and must be treated in the hospital. (See **Serious Side Effects, How Often They Happen and What To Do About Them** section for symptoms). **Some people who have taken medications like HEPSERA, have developed serious liver problems** called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). (See **Serious Side Effects, How Often They Happen and What To Do About Them** section for symptoms). You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleotide analog medicines, like HEPSERA, for a long time.

BEFORE you use HEPSERA talk to your doctor or pharmacist if:

- You know that you are pregnant or suspect that you may

IMPORTANT: PLEASE READ

be pregnant, so that you can discuss the risk and benefit of taking HEPSERA. It is not known if HEPSERA can harm your unborn child.

- You are breastfeeding.
- You have kidney problems now or had them before.
- You are taking other medications that affect how your kidneys work.
- You think you may have HIV (the virus that causes AIDS).

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medications you take. Some medications may affect how HEPSERA (adefovir dipivoxil) works, especially medications that affect how your kidneys work. Do not take any other medications while you are taking HEPSERA, until you have checked with your doctor.

PROPER USE OF THIS MEDICATION

Usual dose:

- The usual adult dose is one HEPSERA 10 mg tablet orally (by mouth) once a day.
- Your doctor may prescribe a different dosing schedule if you have problems with your kidneys.
- HEPSERA may be taken with or without food.
- Do not stop taking HEPSERA without consulting your doctor. Your hepatitis may get worse if you stop taking HEPSERA.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss your regular time for taking your dose, but then remember it during that same day, take your missed dose immediately.
- Then, take your next dose at the regularly scheduled time the following day.
- Do not take two doses of HEPSERA at once to make up for missing a dose.
- If you are not sure what to do if you miss taking your medication check with your doctor or pharmacist for further instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of HEPSERA are: weakness, headache, stomach pain, nausea, diarrhea, flatulence (intestinal gas) and indigestion.

The most common side effects of HEPSERA in patients with chronic hepatitis B having a liver transplant are: weakness, stomach pain, headache, nausea, vomiting, diarrhea, rash and itching. Some patients also had undesirable effects on their kidneys, including kidney failure and damage to kidney cells.

Other possible side effects may include: muscle pain, muscle weakness,

bone pain and softening of the bone (which may contribute to fractures), which are associated with kidney problems, and inflammation of the pancreas.

These are not all the possible side effects of HEPSERA. Your doctor, nurse or pharmacist can discuss with you a more complete list of possible side effects with HEPSERA. You should report any new or continuing symptoms to your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptoms / Effect | | Talk with your doctor or pharmacist in all cases |
|--|--|--|
| Rare (approximately 1 in 1,000 patients) | Symptoms: You feel very weak or tired. You have unusual (not normal) muscle pain. You have stomach pain with nausea and vomiting. You feel cold especially in your arms and legs. You feel dizzy or lightheaded. You have a fast or irregular heartbeat. Effect: Lactic acidosis | ✓ ✓ ✓ ✓ ✓ ✓ |
| Very Rare (approximately 1 in 10,000 patients) | Symptoms: Your skin or the white part of your eyes turns yellow (jaundice). Your urine turns dark. Your bowel movements (stools) turn light in color. You don't feel like eating food for several days or longer. You feel sick to your stomach (nausea). You have lower stomach pain. Effect: Severe liver problems called hepatotoxicity with liver enlargement (hepatomegaly) and fat in the liver (steatosis) | ✓ ✓ ✓ ✓ ✓ ✓ |

Lactic acidosis is a medical emergency and must be treated in the hospital. You may be more likely to get lactic acidosis or serious liver problems if you are very overweight (obese) or have been taking nucleotide analog medicines, like HEPSERA, for a long time.

This is not a complete list of side effects. For any unexpected effects while taking HEPSERA, contact your doctor or pharmacist.

HOW TO STORE IT

- HEPSERA should be stored in the original container at room temperature (15–30 °C). It is stable until the expiration date printed on the label.
- Do not keep your medication in places that are too hot or cold.
- Do not keep medication that is out of date or that you no

longer need. Return to pharmacy for proper disposal.

© 2020 Gilead Sciences, Inc.

- Keep HEPSERA and all other medications out of reach of children.

GS087632-030

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at**
www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting form and:**
 - **Fax toll-free to 1-866-678-6789, or**
 - **Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be requested by contacting the sponsor, Gilead Sciences, Inc., at:

1-866-207-4267

This leaflet was prepared by Gilead Sciences, Inc.

Last revised: August 19, 2020

Gilead Sciences, Inc.

Foster City, CA 94404

USA

Gilead Sciences Canada, Inc.

Mississauga, ON L5N 2W3

ATRIPLA®, BIKTARVY®, COMPLERA®, DESCOVY®, GENVOYA®, HEPSERA®, ODEFSEY®, STRIBILD®, TRUVADA®, VEMLIDY® and VIREAD® are trademarks of Gilead Sciences, Inc., or its related companies.

All other marks referenced herein are the property of their respective owners.