HEPSERA™
(adefovir dipivoxil)

1. NAME OF THE MEDICINAL PRODUCT

Adefovir dipivoxil

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet for oral use contains 10 mg adefovir dipivoxil. For excipients, see 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

HEPSERA tablets, 10 mg are white to off-white, round, flat-faced tablets with a beveled edge and debossed on one side, and blank on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Reductions in viral replication and improvements in liver function have also been demonstrated in supportive studies in a limited number of chronic hepatitis B patients with genotypic evidence of lamivudine-resistance, including patients with compensated or decompensated liver disease and patients co-infected with HIV (see section 4.4 Special Warnings and Special Precautions for Use).

4.2 Posology and Method of Administration

Adults (18-65 years):

The recommended dose of *HEPSERA* is 10 mg (one tablet) once daily taken orally with or without food.

The indication has been obtained primarily based on clinical trials of 48 weeks duration. The optimum duration of treatment is unknown.

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

Children and adolescents (< 18 years):

The safety and efficacy of *HEPSERA* in patients under the age of 18 years have not been established (see section 4.4 Special Warnings and Special Precautions for use).

Elderly (> 65 years):

The safety and efficacy of adevovir dipivoxil in patients over the age of 65 years have not been established (see section 4.4 Special Warnings and Special Precautions for use). Caution should be exercised when prescribing *HEPSERA* to the elderly, keeping in mind the greater frequency of

decreased renal or cardiac function in these patients and the increase in concomitant diseases or use of other medicinal products concomitantly in the elderly.

Renal impairment

Adefovir is eliminated by renal excretion, therefore adjustments of the dosing interval are required in patients with renal dysfunction. No adjustment of the dosing interval is required in patients with a creatinine clearance ≥ 50 mL/min. Adjustments of the dosing interval are required in patients with a creatinine clearance < 50 mL/min, as detailed in Table 1. The recommended dosing frequency according to renal function must not be exceeded (see sections 4.4 Special Warnings and Special Precautions for use and 5.2 Pharmacokinetics, Special Patient Populations). Although patients with renal impairment were included in a pharmacokinetic study, the safety and effectiveness of these dosing interval guidelines have not been clinically evaluated. Therefore, clinical response to treatment should be closely monitored in these patients. Patients with creatinine clearance below 10ml/min have not been studied.

Table 1: Dosing recommendations in patients with renal impairment

	Creatinine Clearance (ml/min)		Haemodialysis Patients*
	30- 49	10- 29	
Recommended Dose and Dosing Interval	10 mg every 48 hours	10 mg every 72 hours	10 mg every 7 days following dialysis

*dosing recommendation derived in study where high flux dialysis was conducted three times a week.

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment (see section 5.2 Pharmacokinetics, Special Patient Populations, Hepatic Impairment).

Treatment discontinuation may be considered as follows:

In HBeAg positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or there is loss of efficacy (see section 4.4). Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.

In HBeAg negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

In patients with decompensated liver disease or cirrhosis, treatment cessation is not recommended.

4.3 Contra-indications

HEPSERA is contra-indicated in patients with known hypersensitivity to adefovir, adefovir dipivoxil or to any of the excipients in *HEPSERA* tablets.

4.4 Special Warnings and Special Precautions for Use

Doses higher than those recommended must not be administered.

Renal function

Treatment with *HEPSERA* 10mg may result in renal impairment. While the overall risk of renal impairment in patients with adequate renal function is low, this is of special importance in patients at risk of or having underlying renal dysfunction and patients receiving medicinal products that may affect renal function. 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*. In patients at risk for, or with a history of, renal dysfunction, routine monitoring for changes in both serum creatinine and serum phosphate is recommended.

As adefovir is eliminated by renal excretion, the dose should be adjusted in patients with a creatinine clearance of <50 mL/minute (see section 4.2 Posology and Method of Administration). Patients with end-stage renal disease (ESRD) managed with forms of dialysis other than haemodialysis, e.g. ambulatory peritoneal dialysis, have not been studied.

Elevations in serum creatinine and/or decreases in serum phosphate have been observed in clinical studies when *HEPSERA* was administered at doses three to twelve times higher than the recommended dose of 10 mg for the treatment of chronic hepatitis B.

In post-liver transplantation patients, changes in serum creatinine were observed. These changes were generally mild and were observed in patients with multiple risk factors for changes in renal function (see section on Undesirable Effects).

HEPSERA has not been evaluated in patients receiving nephrotoxic medicinal products or medicinal products which are secreted by the same renal transporter, human Organic Anion Transporter 1 (hOAT1).

Care should be taken with co-administration of 10 mg *HEPSERA* and medicinal products that are eliminated by active tubular secretion, as this may lead to an increase in serum concentrations of either adefovir or the co-administered medicinal product due to competition for this elimination pathway (see section on Interaction with Other Medicinal Products and Other Forms of Interaction).

Hepatic function

Patients with advanced liver disease or cirrhosis should be monitored closely during the initiation of therapy.

Patients should be closely monitored for several months after stopping treatment as exacerbations of hepatitis have occurred after discontinuation of 10 mg *HEPSERA*. These exacerbations occurred in the absence of HBeAg seroconversion and presented as serum ALT elevations and increases in serum HBV DNA. Elevations in serum ALT that occurred in patients with compensated liver function treated with 10 mg Hepsera were not accompanied by clinical or laboratory changes associated with liver decompensation. Most events appear to have been self-limited. Patients with advanced liver disease or cirrhosis may be at higher risk for hepatic decompensation and severe exacerbations of hepatitis, including fatalities, have been reported.

Occurrences of lactic acidosis (in the absence of hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues. As adefovir is structurally related to nucleoside analogues, this risk cannot be excluded. Treatment with nucleoside analogues should be discontinued when rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology occur. Benign digestive symptoms, such as

nausea, vomiting and abdominal pain, might be indicative of lactic acidosis development. Severe cases, sometimes with fatal outcome, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate. Caution should be exercised when prescribing nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease. These patients should be followed closely.

To differentiate between elevations in transaminases due to response to treatment and increases potentially related to lactic acidosis, physicians should ensure that changes in ALT are associated with improvements in other laboratory markers of chronic hepatitis B.

Co-infection with HIV

Treatment with 10 mg *HEPSERA* has not been shown to be effective against HIV replication. Patients co-infected with HIV should have their HIV RNA controlled (< 400 copies/ml) with proven antiretroviral therapy before treatment with *HEPSERA* 10 mg for HBV infection.

For HIV co-infected patients not requiring anti-retroviral therapy, there is a risk of HIV mutation when using adefovir alone for treating chronic hepatitis B.

Other

Safety and efficacy in children and adolescent patients (under the age of 18 years), and elderly patients over 65 years of age have not been established.

Patients should be advised that therapy with *HEPSERA* has not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore appropriate precautions should still be taken.

Pivalic acid, a product of the *in vivo* metabolism of *HEPSERA* to adefovir, conjugates with free carnitine with subsequent renal excretion. Therefore *HEPSERA* should be administered with care to patients with known carnitine deficiency (congenital). The clinical significance of binding with carnitine is unknown. There are no data on the concurrent administration of *HEPSERA* and agents which may reduce carnitine levels such as valproic acid, or other compounds liberating pivalic acid. In clinical studies of *HEPSERA* 10 mg daily for treatment of patients with chronic HBV, changes in serum carnitine levels were similar between *HEPSERA* and placebo-treated patients. Therefore, patients do not require routine L-carnitine supplementation or monitoring of serum carnitine levels when treated with *HEPSERA* 10 mg daily.

HEPSERA should not be administered concurrently with tenofovir DF or tenofovir DF- containing products including Truvada (emtricitabine/ tenofovir DF combination tablet) and Atripla (efavirenz/ emtricitabine/ tenofovir DF combination tablet)

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Adefovir is excreted renally, by a combination of glomerular filtration and active tubular secretion (see section on Pharmacological Properties, Pharmacodynamic Properties). Apart from ibuprofen, lamivudine, paracetamol, trimethoprim/sulphamethoxazole and tenofovir DF, the effect of co-administration of 10 mg *HEPSERA* with medicinal products that are excreted renally or other drugs known to affect renal function have not been evaluated.

Co-administration of 10 mg *HEPSERA* with other medicinal products that are eliminated by tubular secretion or alter tubular secretion may increase serum concentrations of either adefovir or the co-administered medicinal product (see section on Special Warnings and Special Precautions for use).

Adefovir did not alter the pharmacokinetics of trimethoprim/sulphamethoxazole, paracetamol, ibuprofen and lamivudine.

The pharmacokinetics of adefovir were unaltered when 10 mg adefovir dipivoxil was co-administered with tenofovir DF.

Concomitant administration of 10 mg *HEPSERA* and 800 mg ibuprofen 3 times daily resulted in increases in AUC and Cmax of adefovir of 23% and 33% respectively. These increases are considered to be due to higher bioavailability rather than a reduction in renal clearance of adefovir. The clinical significance of this increase in adefovir exposure is unknown and no dose adjustment is recommended.

Based on the results of *in vitro* experiments and the known elimination pathway of adefovir, the potential for CYP450 mediated interactions involving adefovir with other medicinal products is low.

Co-administration of 10 mg *HEPSERA* and 100 mg lamivudine did not alter the pharmacokinetic profile of either medicinal product.

4.6 Use During Pregnancy and Lactation

Fertility
Studies in animals have shown no effects on male or female fertility (see section on Pre-clinical Safety Data).

Pregnancy
There are no adequate data on the use of *HEPSERA* in pregnant women.

Studies in animals with intravenously administered adefovir have shown reproductive toxicity (see section 5.3 Pre-clinical Safety Data). Studies of *HEPSERA* in orally dosed animals do not indicate teratogenic or fetotoxic effects.

HEPSERA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

There are no data on the effect of *HEPSERA* on transmission of HBV from mother to infant. Therefore, the standard recommended procedures for immunisation of infants should be followed to prevent neonatal acquisition of HBV.

Given that the potential risks to developing human foetuses are unknown, women of child-bearing potential treated with *HEPSERA* must use effective contraception.

Lactation

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

4.7 Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *HEPSERA* on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be predicted from the pharmacology of the drug.

4.8 Undesirable Effects

Frequencies are defined as very common (>1/10), common (>1/100 and <1/10), and uncommon (>1/1000 and <1/100).

Clinical Trial Data:

Adults with compensated liver disease

Assessment of adverse reactions is based on two studies in which 522 patients with chronic hepatitis B and compensated liver disease received double-blind treatment with 10 mg *HEPSERA* (n=294) or placebo (n=228) for 48 weeks.

The 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 absolute frequency. Adverse reactions in the 10 mg *HEPSERA* and placebo-treated groups occurred with similar frequency.

Laboratory abnormalities observed in these studies occurred with similar frequency in the 10 mg *HEPSERA* and placebo-treated groups with the exception of hepatic transaminase elevations which occurred more frequently in the placebo-treated group (see Hepatobiliary disorders).

Gastrointestinal disorders:

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

General disorders and administrative site conditions:

Very common: asthenia

Nervous system disorders:

Common: headache

Renal and urinary disorders:

Uncommon: increase in serum creatinine

Increased creatinine was identified as an adverse reaction with extended open-label treatment in two studies.

In 125 HbeAg negative patients (up to 226 weeks duration), the adverse event profile was overall unchanged. No clinically significant changes in renal function were observed. However, mild to moderate increases in serum creatinine concentrations, hypophosphatemia and a decrease in carnitine concentrations were reported in 3%, 4% and 6% of patients, respectively, on 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.

Hepatobiliary disorders:

Common: post-treatment elevations of ALT

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment with 10 mg *HEPSERA*. In patients followed for up to 6 months after discontinuation of treatment, post-treatment elevations in ALT were observed at a higher incidence in patients who had received 10 mg *HEPSERA* than in patients who had received placebo. These post-treatment ALT flares were self-limiting in nature and were not associated with clinical or laboratory evidence of decompensated liver disease.

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 *HEPSERA* once daily for up to 203 weeks with a median time on treatment of 51 and 99 weeks respectively. The adverse reactions considered at least possibly related to treatment were:

Gastrointestinal disorders:

Common: abdominal pain, nausea, vomiting, diarrhoea

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Metabolism and nutrition disorders:

Common: hypophosphotemia

General disorders and administration site conditions:

Common: asthenia

Nervous system disorders:

Common: headache

Renal and urinary disorders:

Very common: increases in creatinine

Common: renal failure, abnormal renal function

Changes in renal function occurred in waitlisted 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. Four percent (19/467) of patients discontinued treatment with adefovir dipivoxil due to renal adverse events.

Post-marketing Data

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

Musculoskeletal and connective tissue disorders:

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

Metabolism and nutrition disorders:

Hypophosphotemia

Gastrointestinal disorders:

Pancreatitis

Renal and Urinary disorders:

Fanconi syndrome, proximal renal tubulopathy

4.9 Overdose

Symptoms and Signs

Daily doses of adefovir, 25-50 times greater (250 mg and 500 mg daily) than those recommended for the treatment of chronic HBV infection, administered for 14 days to HIV positive subjects, have been associated with mild to moderate gastrointestinal effects.

Treatment

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; the median weight-corrected haemodialysis clearance of adefovir is 104 mL/min. The elimination of adefovir by peritoneal dialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action:

HEPSERA is an oral prodrug of adefovir, an acyclic nucleotide phosphonate analogue of adenosine monophosphate, which is actively transported into mammalian cells where it is converted by host enzymes to adefovir diphosphate. Adefovir diphosphate inhibits viral polymerases by competing for direct binding with the natural substrate (deoxyadenosine triphosphate) and, after incorporation into viral DNA, causes DNA chain termination. 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 diphosphate has an intracellular half-life of 12 to 36 hours in activated and resting lymphocytes.

Pharmacodynamic effects:

Adefovir is active against hepadnaviruses *in vitro*, including all common forms of lamivudine-resistant HBV (L528M, M552I, M552V, L528M/M552V), famciclovir-associated mutations (V521L, P525L, L528M, T532S or V555I) and hepatitis B immunoglobulin escape mutations (T476N and W501Q), and in *in vivo* animal models of HBV.

Two mutations (rtN236T and rtA181V) in the HBV reverse transcriptase domain have been shown to be associated with resistance to adefovir.

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.

In vitro, the rtN236T mutation conferred a 2- to 3-fold reduced susceptibility to lamivudine and the rtA181V mutation conferred a 1- to 14-fold reduced susceptibility to lamivudine.

Resistance to adefovir 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 patients with evidence of lamivudine-resistance (rtL180M, rtA181T, and/ or rtM2041/V) or with prior lamivudine exposure, adefovir dipivoxil should be used in combination with lamivudine and not as adefovir dipivoxil monotherapy in order to reduce the risk of resistance to adefovir.

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.

5.2 Pharmacokinetic Properties

Absorption

HEPSERA is a dipivaloyloxymethyl ester prodrug of the active ingredient adefovir. The oral bioavailability of adefovir from 10 mg *HEPSERA* is 59%. Following oral administration of a single dose of 10 mg *HEPSERA* to chronic hepatitis B patients, the median (range) peak serum concentration (C_{max}) was achieved after 1.75 h (0.58-4.0 h). Median C_{max} and $AUC_{0-\infty}$ values were 16.70 (9.66-30.56) ng/mL and 204.40 (109.75-356.05) ng•h/mL, respectively. Co-administration of 10 mg *HEPSERA* with food did not affect systemic exposure to adefovir.

Distribution

Preclinical studies show that after oral administration of *HEPSERA*, adefovir is distributed to most tissues with the highest concentrations occurring in kidney, liver and intestinal tissues. *In vitro* binding of adefovir to human plasma or human serum proteins is ≤ 4%, respectively over the adefovir concentration range of 0.1 to 25 μg/mL. The volume of distribution at steady-state following *intravenous* administration of 1.0 or 3.0 mg/kg/day is 392 ± 75 and 352 ± 9 mL/kg, respectively.

Metabolism

Following oral administration, *HEPSERA* is rapidly converted to adefovir. At concentrations substantially higher (> 4000 fold) than those observed *in vivo*, adefovir did not inhibit any of the following human CYP450 isoforms: CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A4. 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.

Elimination

Adefovir is excreted renally by a combination of glomerular filtration and active tubular secretion. After repeated administration of 10 mg *HEPSERA*, forty five percent of the dose is recovered as adefovir in the urine over 24 hours. Plasma adefovir concentrations declined in a biexponential manner with a median terminal elimination half-life of 7.22 h (4.72-10.70 h).

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

Special Patient Populations:

Gender:

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

Elderly:

Pharmacokinetic studies have not been conducted in the elderly.

Children:

Pharmacokinetic studies have not been conducted in children.

Ethnicity:

The available data do not appear to indicate any difference in pharmacokinetics with regard to race.

Renal impairment

In patients with moderately or severely impaired renal function or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, $AUC_{0-\infty}$ and $t_{1/2}$ of adefovir were increased. It is recommended that the dosing interval of 10 mg *HEPSERA* is modified in patients with creatinine clearance < 50 mL/min or in patients who already have ESRD and require dialysis (see section 4.2 Posology and Method of Administration).

The mean (+ SD) pharmacokinetic parameters of adefovir following administration of a single dose of 10 mg *HEPSERA* to patients with varying degrees of renal impairment are described in the table below:

Renal Function Group	Un-impaired	Mild	Moderate	Severe
Baseline Creatinine Clearance (mL/min)	> 80 (n=7)	50-80 (n=8)	30-49 (n=7)	10-29 (n=10)
Cmax (ng/ml)	17.8+3.22	22.4+4.04	28.5+8.57	51.6+10.3
$AUC_{0-\infty}$ (ng.h/mL)	201+40.8	266+55.7	455+176	1240+629
CL/F (mL/min)	469+99.0	356+85.6	237+118	91.7+51.3
CL_{renal} (mL/min)	231+48.9	148+39.3	83.9+27.5	37.0+18.4

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

Hepatic impairment

Pharmacokinetic properties were similar in patients with moderate and severe hepatic impairment compared to healthy volunteers (see section 4.2 Posology and Method of Administration).

5.3 Clinical data

Emergence of adefovir resistant HBV during clinical studies:

Monotherapy

In placebo-controlled Phase 3 clinical trials, genotypic and phenotypic analyses were conducted on HBV isolates from 271 patients with HBeAg positive or presumed precore mutant chronic hepatitis B, treated with 10 mg *HEPSERA* for 48 weeks. No HBV DNA polymerase mutations associated with resistance to adefovir were identified when patients were genotyped at baseline and at week 48.

In patients receiving adefovir dipivoxil monotherapy (HbeAg negative study) the cumulative probability of developing adefovir-associated resistance mutations was 0%, 3%, 11%, 18% and 29% at 48, 96, 144, 192 and 240 weeks respectively.

In HbeAg positive patients, the incidence of adefovir-associated resistance mutations was 3% and 17% after a median duration exposure of 135 and 189 weeks respectively.

Studies where *HEPSERA* 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 HBV, no adefovir-associated resistance mutations were observed at week 48.

With up to 3 years of exposure, no patients receiving both *HEPSERA* and lamivudine developed resistance to *HEPSERA*. However, 4 patients who discontinued lamivudine treatment developed the rtN236T mutation while receiving *HEPSERA* monotherapy, and all experienced serum HBV rebound.

5.4 Preclinical Safety Data

The primary dose-limiting toxic effect associated with administration of *HEPSERA* in animals (mice, rats and monkeys) was renal tubular nephropathy characterised by histological alterations and/or increases in blood urea nitrogen and serum creatinine. Nephrotoxicity was observed in animals at systemic exposures at least 3-10 times higher than those achieved in humans at the recommended therapeutic dose of 10 mg/day.

No effects on male or female fertility, or reproductive performance, occurred in rats and there was no embryotoxicity or teratogenicity in rats or rabbits administered *HEPSERA* orally.

When adefovir was administered intravenously to pregnant rats at doses associated with notable maternal toxicity (20 mg/kg/day-systemic exposure approximately 38 times that achieved in humans at the therapeutic dose), 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 at 2.5 mg/kg/day administered intravenously (systemic exposure approximately 12 times that achieved in humans at the therapeutic dose).

HEPSERA 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 at doses up to 2,000 mg/kg.

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 long-term carcinogenicity studies in rats and mice with *HEPSERA*, no treatment-related increase in tumour incidence was found in mice at 10 mg/kg/day or in rats at 5 mg/kg/day (systemic exposures approximately 10 and 4 times those achieved in man at the therapeutic dose of 10 mg/day, respectively).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised starch (gluten free); croscarmellose sodium; lactose monohydrate; talc and magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The expiry date is indicated on the packaging.

6.4 Special Precautions for Storage

Do not store above 25°C.

6.5 Nature and Contents of Container

HEPSERA tablets are supplied in high density polyethylene (HDPE) bottles with a child-resistant closure. Each bottle contains 30 tablets and silica gel desiccant.

6.6 Instructions for Use/Handling

No special requirements.

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