

# Hepsera

## 1. NAME OF THE MEDICINAL PRODUCT

Hepsera

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of adefovir dipivoxil.

Excipient(s) with known effect

Each tablet contains 107.4 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.

White to off-white, round, flat-faced tablets with a beveled-edge and debossed with “GS KNU” 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:

- compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis. Initiation of Hepsera treatment should only be considered when the use of an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.
- decompensated liver disease in combination with a second agent without cross-resistance to Hepsera.

### 4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of chronic hepatitis B.

Posology

*Adults*

The recommended dose of Hepsera is 10 mg (one tablet) once daily taken orally with or without food. Higher doses must not be administered.

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.

In patients with decompensated liver disease, adefovir should always be used in combination with a second agent, without cross-resistance to adefovir, to reduce the risk of resistance and to achieve rapid

viral suppression.

Patients should be monitored every six months for hepatitis B biochemical, virological and serological markers.

*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 (see section 4.4).

*Elderly population*

No data are available to support a dose recommendation for patients over the age of 65 years (see section 4.4).

*Patients with renal impairment*

Adefovir is eliminated by renal excretion and adjustments of the dosing interval are required in patients with a creatinine clearance < 50 ml/min or on dialysis. The recommended dosing frequency according to renal function must not be exceeded (see sections 4.4 and 5.2). The proposed dose interval modification is based on extrapolation of limited data in patients with end stage renal disease (ESRD) and may not be optimal.

*Patients with creatinine clearance between 30 and 49 ml/min*

It is recommended to administer adefovir dipivoxil (one 10 mg tablet) every 48 hours in these patients. There are only limited data on the safety and efficacy of this dosing interval adjustment guideline. Therefore, clinical response to treatment and renal function should be closely monitored in these patients (see section 4.4).

*Patients with creatinine clearance < 30 ml/min and dialysis patients*

There are no safety and efficacy data to support the use of adefovir dipivoxil in patients with a creatinine clearance < 30 ml/min or on dialysis. Therefore, use of adefovir dipivoxil is not recommended in these patients and should only be considered if the potential benefits outweigh the potential risks. In that case, the limited data available suggest that for patients with creatinine clearance between 10 and 29 ml/min, adefovir dipivoxil (one 10 mg tablet) may be administered every 72 hours; for haemodialysis patients, adefovir dipivoxil (one 10 mg tablet) may be administered every 7 days following 12 hours continuous dialysis (or 3 dialysis sessions, each of 4 hours duration). These patients should be closely monitored for possible adverse reactions and to ensure efficacy is maintained (see sections 4.4 and 4.8). No dosing interval recommendations are available for other dialysis patients (e.g. ambulatory peritoneal dialysis patients) or non-haemodialysed patients with creatinine clearance less than 10 ml/min.

*Patients with hepatic impairment*

No dose adjustment is required in patients with hepatic impairment (see section 5.2).

*Patients with clinical resistance*

Lamivudine-refractory patients and patients harbouring HBV with evidence of resistance to lamivudine (mutations at rtL180M, rtA181T and/or rtM204I/V) should not be treated with adefovir dipivoxil monotherapy in order to reduce the risk of resistance to adefovir. Adefovir may be used in

combination with lamivudine in lamivudine-refractory patients and in patients harbouring HBV with

mutations at rtL180M and/or rtM204I/V. However, for patients harbouring HBV that contains the rtA181T mutation, consideration should be given to alternative treatment regimens due to the risk of reduced susceptibility to adefovir (see section 5.1).

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 1,000 copies/ml at or beyond 1 year of treatment.

*Paediatric population:* Hepsera is not recommended for use in children below the age of 18 years due to limitations of the available data on safety and efficacy (see section 5.1).

#### Method of administration

Hepsera tablets should be taken once daily, orally with or without food.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### 4.4 Special warnings and precautions for use

#### *General*

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

#### *Renal function*

Adefovir is excreted renally, by a combination of glomerular filtration and active tubular secretion. Treatment with adefovir dipivoxil may result in renal impairment. Long-term treatment with adefovir dipivoxil may increase the risk of renal impairment. While the overall risk of renal impairment in patients with adequate renal function is low, this is of special importance in patients both at risk of or having underlying renal dysfunction, and also in 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 adefovir dipivoxil and that renal function (creatinine clearance and serum phosphate) be monitored every four weeks during the first year and then every three months thereafter. In patients at risk for renal impairment, consideration should be given to more frequent monitoring of renal function.

In patients who develop renal insufficiency and have advanced liver disease or cirrhosis, dosing interval adjustment of adefovir or switch to an alternative therapy for hepatitis B infection should be considered. Treatment cessation for chronic hepatitis B in these patients is not recommended.

#### *Patients with creatinine clearance between 30 and 49 ml/min*

The dosing interval of adefovir dipivoxil should be adjusted in these patients (see section 4.2). In addition, renal function should be closely monitored with a frequency tailored to the individual patient's medical condition.

#### *Patients with creatinine clearance < 30 ml/min and dialysis patients*

Adefovir dipivoxil is not recommended in patients with a creatinine clearance of < 30 ml/min or on dialysis. Administration of adefovir dipivoxil in these patients should only be considered if the potential benefits outweigh the potential risks. If treatment with adefovir dipivoxil is considered essential, then the dosing interval should be adjusted (see section 4.2). These patients should be closely monitored for possible adverse reactions and to ensure efficacy is maintained.

*Patients receiving medicinal products that may affect renal function*

Adefovir dipivoxil should not be administered concurrently with tenofovir disoproxil fumarate (Viread).

Caution is advised in patients receiving other medicinal products that may affect renal function or are excreted renally (e.g. cyclosporin and tacrolimus, intravenous aminoglycosides, amphotericin B, foscarnet, pentamidine, vancomycin, or medicinal products which are secreted by the same renal transporter, human Organic Anion Transporter 1 (hOAT1), such as cidofovir). Co-administration of 10 mg adefovir dipivoxil with medicinal products in these patients may lead to an increase in serum concentrations of either adefovir or a co-administered medicinal product. The renal function of these patients should be closely monitored with a frequency tailored to the individual patient's medical condition.

For renal safety in patients pre- and post-transplantation with lamivudine-resistant HBV, see section 4.8.

*Hepatic function*

Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation (see section 4.8).

Patients with advanced liver disease or cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation which may be fatal. In these patients, including patients with decompensated liver disease, treatment cessation is not recommended and these patients should be monitored closely during therapy.

In the event of these patients developing renal insufficiency, see above *Renal function*.

If treatment cessation is necessary, patients should be closely monitored for several months after stopping treatment as exacerbations of hepatitis have occurred after discontinuation of 10 mg adefovir dipivoxil. 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 adefovir dipivoxil were not accompanied by clinical and laboratory changes associated with liver decompensation. Patients should be closely monitored after stopping treatment. Most post-treatment exacerbations of hepatitis were seen within 12 weeks of discontinuation of 10 mg adefovir dipivoxil.

*Lactic acidosis and severe hepatomegaly with steatosis*

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 hepatitis C or D*

There are no data on the efficacy of adefovir dipivoxil in patients co-infected with hepatitis C or hepatitis D.

#### *Co-infection with HIV*

Limited data are available on the safety and efficacy of 10 mg adefovir dipivoxil in patients with chronic hepatitis B, co-infected with HIV. To date there is no evidence that daily dosing with 10 mg adefovir dipivoxil results in emergence of adefovir-associated resistance mutations in the HIV reverse transcriptase. Nonetheless, there is a potential risk of selection of HIV strains resistant to adefovir with possible cross-resistance to other antiviral medicinal products.

As far as possible, treatment of hepatitis B by adefovir dipivoxil in an HIV co-infected patient should be reserved for patients whose HIV RNA is controlled. Treatment with 10 mg adefovir dipivoxil has not been shown to be effective against HIV replication and therefore should not be used to control HIV infection.

#### *Elderly*

The clinical experience in patients > 65 years of age is very limited. Caution should be exercised when prescribing adefovir dipivoxil 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 concomitant use of other medicinal products in the elderly.

#### *Resistance*

Resistance to adefovir dipivoxil (see section 5.1) 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. Virological response should be closely monitored in patients treated with adefovir dipivoxil, with HBV DNA measured every 3 months. If viral rebound occurs, resistance testing should be performed. In case of emergence of resistance, treatment should be modified.

Hepsera contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

#### *Excipients*

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

### **4.5 Interaction with other medicinal products and other forms of interaction**

The potential for CYP450 mediated interactions involving adefovir with other medicinal products is low, based on the results of *in vitro* experiments in which adefovir did not influence any of the common CYP isoforms known to be involved in human drug metabolism and based on the known elimination pathway of adefovir. A clinical study in liver-transplant patients has shown that no pharmacokinetic interaction occurs when adefovir dipivoxil 10 mg once daily is administered concomitantly with tacrolimus, an immunosuppressant which is predominantly metabolised via the CYP450 system. A pharmacokinetic interaction between adefovir and the immunosuppressant, cyclosporin, is also considered unlikely as cyclosporin shares the same metabolic pathway as tacrolimus. Nevertheless, given that tacrolimus and cyclosporin can affect renal function, close monitoring is recommended when either of these agents is coadministered with adefovir dipivoxil (see section 4.4).

Concomitant administration of 10 mg adefovir dipivoxil and 100 mg lamivudine did not alter the pharmacokinetic profile of either medicinal product.

Adefovir is excreted renally, by a combination of glomerular filtration and active tubular secretion. Co-administration of 10 mg adefovir dipivoxil with other medicinal products that are eliminated by

tubular secretion or alter tubular function may increase serum concentrations of either adefovir or the co-administered medicinal product (see section 4.4).

Due to the high pharmacokinetic variability of pegylated interferon, no definitive conclusion can be drawn regarding the effect of adefovir and pegylated interferon co-administration on the pharmacokinetic profile of either medicinal product. Even though a pharmacokinetic interaction is unlikely given the two products are eliminated via different pathways, caution is recommended if both products are co-administered.

#### Paediatric population

Interaction studies have only been performed in adults.

### **4.6 Fertility, pregnancy and lactation**

The use of adefovir dipivoxil must be accompanied by the use of effective contraception.

#### Pregnancy

There are no or limited data on the use of adefovir dipivoxil in pregnant women.

Studies in animals administered adefovir intravenously at toxic doses have shown reproductive toxicity (see section 5.3). Studies in orally dosed animals do not indicate teratogenic or foetotoxic effects.

Adefovir dipivoxil is not recommended during pregnancy and in women of childbearing potential not using contraception. Adefovir dipivoxil 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 adefovir dipivoxil 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.

#### Breast-feeding

It is unknown whether adefovir dipivoxil is excreted in human milk. A risk to the newborns/infants cannot be excluded. It is recommended that mothers being treated with adefovir dipivoxil do not breast-feed their infants.

#### Fertility

No human data on the effect of adefovir dipivoxil on fertility are available. Animal studies do not indicate harmful effects of adefovir dipivoxil on male and female fertility.

### **4.7 Effects on ability to drive and use machines**

Hepsera is expected to have no or negligible influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed.

### **4.8 Undesirable effects**

#### Summary of the safety profile

In patients with compensated liver disease, the most frequently reported adverse reactions during 48 weeks of adefovir dipivoxil therapy were asthenia (13 %), headache (9 %), abdominal pain (9 %) and nausea (5 %).

In patients with decompensated liver disease, the most frequently reported adverse reactions during up to 203 weeks of adefovir dipivoxil therapy were increased creatinine (7 %) and asthenia (5 %).

### Tabulated summary of adverse reactions

Assessment of adverse reactions is based on experience from post-marketing surveillance and from three pivotal clinical studies in patients with chronic hepatitis B:

- two placebo-controlled studies in which 522 patients with chronic hepatitis B and compensated liver disease received double-blind treatment with 10 mg adefovir dipivoxil (n=294) or placebo (n=228) for 48 weeks.
- an open-label study in which pre- (n=226) and post-liver transplantation patients (n=241) with lamivudine-resistant HBV were treated with 10 mg adefovir dipivoxil once daily, for up to 203 weeks (median 51 and 99 weeks, respectively).

The adverse reactions considered at least possibly related to treatment are listed below, by body system organ class, and frequency (see Table 1). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ) or not known (identified through post-marketing safety surveillance and the frequency cannot be estimated from the available data).

**Table 1: Tabulated summary of adverse reactions associated with adefovir dipivoxil based on clinical study and post-marketing experience**

Frequency	Adefovir dipivoxil
<i>Nervous system disorders:</i>	
Common:	Headache
<i>Gastrointestinal disorders:</i>	
Common:	Diarrhoea, vomiting, abdominal pain, dyspepsia, nausea, flatulence
Not known:	Pancreatitis
<i>Skin and subcutaneous tissue disorders:</i>	
Common:	Rash, pruritus
<i>Musculoskeletal and connective tissue disorders:</i>	
Not known:	Osteomalacia (manifested as bone pain and infrequently contributing to fractures) and myopathy, both associated with proximal renal tubulopathy
<i>Renal and urinary disorders:</i>	
Very common:	Increases in creatinine
Common:	Renal failure, abnormal renal function, hypophosphatemia
Uncommon:	Proximal renal tubulopathy (including Fanconi syndrome)
<i>General disorders and administration site conditions:</i>	
Very common:	Asthenia

### Description of selected adverse reactions

#### *Exacerbation of hepatitis*

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment with 10 mg adefovir dipivoxil (see section 4.4).

#### *Long-term safety data in patients with compensated disease*

In a long-term safety study of 125 HBeAg negative patients with compensated liver disease, the adverse event profile was overall unchanged after a median exposure of 226 weeks. 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 a long-term safety study of 65 HBeAg positive patients with compensated liver disease (after a median exposure of 234 weeks), 6 patients (9 %) 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. Patients with a confirmed increase in creatinine of  $\geq 0.3$  mg/dl by week 48 were at a statistically significant higher risk of a subsequent confirmed increase in creatinine of



≥ 0.5 mg/dl. Hypophosphatemia and a decrease in carnitine concentrations were reported each in 3 % of patients on extended treatment.

Based on post-marketing data, long-term treatment with adefovir dipivoxil may lead to progressive alteration of renal function resulting in renal impairment (see section 4.4).

#### *Safety in patients with decompensated disease*

Renal toxicity is an important feature of the safety profile of adefovir dipivoxil in patients with decompensated liver disease. In clinical studies of wait-listed and post-liver transplantation patients, four percent (19/467) of patients discontinued treatment with adefovir dipivoxil due to renal adverse events.

#### Paediatric population

Because of insufficient data on safety and efficacy, Hepsera should not be used in children under the age of 18 years (see Sections 4.2 and 5.1).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

Additionally, you should also report to GSK Israel ([il.safety@gsk.com](mailto:il.safety@gsk.com)).

## **4.9 Overdose**

Administration of 500 mg adefovir dipivoxil daily for 2 weeks and 250 mg daily for 12 weeks has been associated with the gastrointestinal disorders listed above and anorexia.

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 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**

Pharmacotherapeutic group: Nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF08.

#### Mechanism of action

Adefovir dipivoxil 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.

#### Pharmacodynamic effects

Adefovir diphosphate selectively inhibits HBV DNA polymerases at concentrations 12-, 700-, and 10-fold lower than those needed to inhibit human DNA polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ , respectively. Adefovir diphosphate has an intracellular half-life of 12 to 36 hours in activated and resting lymphocytes.

Adefovir is active against hepadnaviruses *in vitro*, including all common forms of lamivudine-resistant HBV (rtL180M, rtM204I, rtM204V, rtL180M/rtM204V), famciclovir-associated mutations (rtV173L,

rtP177L, rtL180M, rtT184S or rtV207I) and hepatitis B immunoglobulin escape mutations (rtT128N and rtW153Q), and in *in vivo* animal models of hepadnavirus replication.

#### Clinical efficacy and safety

The demonstration of the benefit of adefovir dipivoxil is based on histological, virological, biochemical, and serological responses in adults with:

- HBeAg positive and HBeAg negative chronic hepatitis B with compensated liver disease.
- lamivudine-resistant HBV with either compensated or decompensated liver disease, including patients pre- and post-liver transplantation or co-infected with HIV. In the majority of these studies adefovir dipivoxil 10 mg was added to ongoing lamivudine treatment in patients failing lamivudine therapy.

In these clinical studies patients had active viral replication (HBV DNA  $\geq 100,000$  copies/ml) and elevated ALT levels ( $\geq 1.2 \times$  Upper Limit of Normal (ULN)).

#### *Experience in patients with compensated liver disease*

In two placebo-controlled studies (total n=522) in HBeAg positive or in HBeAg negative chronic hepatitis B patients with compensated liver disease, significantly more patients ( $p < 0.001$ ) in the 10 mg adefovir dipivoxil groups (53 and 64 %, respectively) had histological improvement from baseline at week 48 than in the placebo groups (25 and 33 %). Improvement was defined as a reduction from baseline of two points or more in the Knodell necro-inflammatory score with no concurrent worsening in the Knodell fibrosis score. Histological improvement was seen regardless of baseline demographic and hepatitis B characteristics, including prior interferon-alpha therapy. High baseline ALT levels ( $\geq 2 \times$  ULN) and Knodell Histology Activity Index (HAI) scores ( $\geq 10$ ) and low HBV DNA ( $< 7.6 \log_{10}$  copies/ml) were associated with greater histological improvement. Blinded, ranked assessments of both necro-inflammatory activity and fibrosis at baseline and week 48, demonstrated that patients treated with 10 mg adefovir dipivoxil had improved necro-inflammatory and fibrosis scores relative to placebo-treated patients.

Assessment of the change in fibrosis after 48 weeks treatment using the Knodell scores confirms that patients treated with adefovir dipivoxil 10 mg had more regression and less progression of fibrosis than patients treated with placebo.

In the two studies mentioned above, treatment with 10 mg adefovir dipivoxil was associated with significant reductions in serum HBV DNA (3.52 and 3.91  $\log_{10}$  copies/ml, respectively, *versus* 0.55 and 1.35  $\log_{10}$  copies/ml), increased proportion of patients with normalisation of ALT (48 and 72 % *versus* 16 and 29 %) or increased proportion of patients with serum HBV DNA below the limits of quantification ( $< 400$  copies/ml Roche Amplicor Monitor PCR assay) (21 and 51 % *versus* 0 %) when compared with placebo. In the study in HBeAg positive patients, HBeAg seroconversion (12 %) and HBeAg loss (24 %) was observed significantly more frequently in patients receiving 10 mg adefovir dipivoxil than in patients receiving placebo (6 % and 11 %, respectively) after 48 weeks of treatment.

In the HBeAg positive study, treatment beyond 48 weeks resulted in further reductions in serum HBV DNA levels and increases in the proportion of patients with ALT normalisation, HBeAg loss and seroconversion.

In the HBeAg negative study patients on adefovir dipivoxil (0-48 weeks) were re-randomised in a blinded-manner to continue on adefovir dipivoxil or receive placebo for an additional 48 weeks. At week 96, patients continuing on adefovir dipivoxil 10 mg had sustained suppression of serum HBV with maintenance of the reduction seen at week 48. In over two thirds of patients suppression of serum HBV DNA was associated with normalisation of ALT levels. In most patients who stopped treatment with adefovir dipivoxil, serum HBV DNA and ALT levels returned towards baseline.

Treatment with adefovir dipivoxil resulted in improvement in the liver fibrosis from baseline to 96 weeks therapy when analysed using the Ishak score (median change:  $\Delta = -1$ ). No differences in the median fibrosis score were seen between groups using the Knodell fibrosis score.

Patients who completed the first 96 weeks of the HBeAg negative study and received adefovir dipivoxil treatment during weeks 49 to 96, were offered the opportunity to receive open-label treatment with adefovir dipivoxil from study week 97 through to week 240. Serum HBV DNA levels remained undetectable and ALT levels normalised in approximately two thirds of patients following treatment with adefovir dipivoxil for up to 240 weeks. Clinically and statistically significant improvement in fibrosis was seen in the changes in Ishak scores from the start of adefovir dipivoxil treatment to the end of the study (week 240) (median change:  $\Delta = -1$ ). By the end of the study, 7 of 12 patients (58 %) with bridging fibrosis or cirrhosis at baseline, had an improved Ishak fibrosis score of  $\geq 2$  points. Five patients achieved and maintained HBsAg seroconversion (HBsAg negative/HBsAb positive).

#### *Experience in patients pre- and post-liver transplantation with lamivudine-resistant HBV*

In a clinical study in 394 chronic hepatitis B patients with lamivudine-resistant HBV (pre-liver transplantation (n=186) and post-liver transplantation (n=208)), treatment with 10 mg adefovir dipivoxil resulted in a median reduction in serum HBV DNA of 4.1 and 4.2 log<sub>10</sub> copies/ml, respectively, at week 48. In the pre-liver transplantation and post-liver transplantation cohorts 77 of 109 (71 %) patients and 64 of 159 (40 %) patients, respectively, achieved undetectable HBV DNA levels at week 48 (< 1,000 copies/ml Roche Amplicor Monitor PCR assay). Treatment with 10 mg adefovir dipivoxil showed similar efficacy regardless of the patterns of lamivudine-resistant HBV DNA polymerase mutations at baseline. Improvements or stabilisation were seen in Child-Pugh-Turcotte score. Normalisation of ALT, albumin, bilirubin and prothrombin time was seen at week 48 in 51-85 % of the patients.

In the pre-liver transplantation cohort, 25 of 33 (76 %) patients achieved undetectable HBV DNA levels and 84 % of patients had ALT normalisation 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 at 96 and 144 weeks, respectively, and 70 % and 58 % of patients had ALT normalisation at these study visits. The clinical significance of these findings as they relate to histological improvement is not known.

#### *Experience in patients with compensated liver disease and lamivudine-resistant HBV*

In a double-blind comparative study in chronic hepatitis B patients with lamivudine-resistant HBV (n=58), there was no median reduction in HBV DNA from baseline after 48 weeks of treatment with lamivudine. Forty-eight weeks of treatment with adefovir dipivoxil 10 mg alone or in combination with lamivudine resulted in a similar significant decrease in median serum HBV DNA levels from baseline (4.04 log<sub>10</sub> copies/ml and 3.59 log<sub>10</sub> copies/ml, respectively). The clinical significance of these observed changes in HBV DNA has not been established.

#### *Experience in patients with decompensated liver disease and lamivudine-resistant HBV*

In 40 HBeAg positive or HBeAg negative patients with lamivudine-resistant HBV and decompensated liver disease receiving treatment with 100 mg lamivudine, addition of 10 mg adefovir dipivoxil treatment for 52 weeks resulted in a median reduction in HBV DNA of 4.6 log<sub>10</sub> copies/ml. Improvement in liver function was also seen after one year of therapy.

#### *Experience in patients with HIV co-infection and lamivudine-resistant HBV*

In an open-label investigator study in 35 chronic hepatitis B patients with lamivudine-resistant HBV and co-infected with HIV, continued treatment with 10 mg adefovir dipivoxil resulted in progressive reductions in serum HBV DNA levels and ALT levels throughout the course of treatment up to 144 weeks.

In a second open-label, one-arm study, 10 mg adefovir dipivoxil and pegylated interferon alpha-2a were added to ongoing lamivudine therapy in 18 HIV/HBV co-infected patients with lamivudine-resistant HBV. Patients were all HBeAg positive and had median CD4 cell count of

441 cells/mm<sup>3</sup> (no patient had CD4 count < 200 cells/mm<sup>3</sup>). During therapy, serum HBV DNA levels were significantly lower compared to baseline for up to 48 weeks of treatment while ALT levels declined progressively from week 12. However, on-treatment HBV DNA response was not maintained off-therapy since all the patients had a rebound in HBV DNA after adefovir dipivoxil and pegylated interferon alpha-2a discontinuation. No patients became HBsAg- or HBeAg-negative during the study. Due to the small sample size and the study design, in particular the lack of treatment arms with pegylated interferon alpha-2a monotherapy and with adefovir monotherapy, it is not possible to draw formal conclusions on the best therapeutic management of HIV co-infected patients with lamivudine-resistant HBV.

#### *Clinical resistance in patients receiving adefovir dipivoxil as monotherapy and in combination with lamivudine*

In several clinical studies (HBeAg positive, HBeAg negative, pre- and post-liver transplantation with lamivudine-resistant HBV and lamivudine-resistant HBV co-infected with HIV patients), genotypic analyses were conducted on HBV isolates from 379 of a total of 629 patients, treated with adefovir dipivoxil 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. After 96, 144, 192 and 240 weeks of treatment with adefovir dipivoxil, resistance surveillance was performed for 293, 221, 116 and 64 patients, respectively. Two novel conserved site mutations were identified in the HBV polymerase gene (rtN236T and rtA181V), which conferred clinical resistance to adefovir dipivoxil. The cumulative probabilities of developing these adefovir-associated resistance mutations in all patients treated with adefovir dipivoxil were 0 % at 48 weeks and approximately 2 %, 7 %, 14 % and 25 % after 96, 144, 192 and 240 weeks, respectively.

#### *Clinical resistance in monotherapy studies in nucleoside naïve patients*

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 addition, the long-term (4 to 5 years) development of resistance to adefovir dipivoxil was significantly lower in patients who had serum HBV DNA below the limit of quantification (< 1,000 copies/ml) at week 48 as compared to patients with serum HBV DNA above 1,000 copies/ml at week 48. In HBeAg positive patients, the incidence of adefovir-associated resistance mutations was 3 % (2/65), 17 % (11/65) and 20 % (13/65) after a median duration exposure of 135, 189 and 235 weeks respectively.

#### *Clinical resistance in 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 HBV, no adefovir-associated resistance mutations were observed at week 48. With up to 3 years of exposure, no patients receiving both adefovir dipivoxil and lamivudine developed resistance to adefovir dipivoxil. However, 4 patients who discontinued lamivudine treatment developed the rtN236T mutation while receiving adefovir dipivoxil monotherapy and all experienced serum HBV rebound.

The currently available data both *in vitro* and in patients suggest that HBV expressing the adefovir-associated resistance mutation rtN236T is susceptible to lamivudine. Preliminary clinical data suggest the adefovir-associated resistance mutation rtA181V may confer a reduced susceptibility to lamivudine, and the lamivudine-associated mutation rtA181T may confer a reduced susceptibility to adefovir dipivoxil.

#### Paediatric population

The efficacy and safety of a daily dose of 0.25 mg/kg to 10 mg adefovir dipivoxil in children (aged from 2 to < 18 years) were examined in a double-blind, randomised, placebo-controlled study in 173 paediatric patients (115 on adefovir dipivoxil, 58 on placebo) who had HBeAg positive chronic hepatitis B, serum ALT levels  $\geq 1.5 \times$  upper limit of normal (ULN) and compensated liver disease. At week 48, in children aged 2 to 11 years old, no statistically significant difference was observed in the proportions of patients that achieved the primary endpoint of serum HBV DNA < 1,000 copies/ml and normal ALT levels between the placebo arm and the adefovir dipivoxil arm. In the adolescent

population (n=83) (aged from 12 to < 18 years), significantly more patients treated with adefovir dipivoxil achieved the primary efficacy endpoint and obtained significant reductions in serum HBV DNA (23 %) compared to placebo-treated patients (0 %). However, the proportions of subjects who achieved HBeAg seroconversion at week 48 were similar (11 %) between the placebo arm and the adefovir dipivoxil 10 mg arm in adolescent patients.

Overall, the safety profile of adefovir dipivoxil in children was consistent with the known safety profile in adult patients. However, a signal towards a higher rate of decreased appetite and/or food intake was observed in the adefovir arm as compared to the placebo arm. At week 48 and 96, mean changes from baseline in weight and BMI Z scores tended to decrease in adefovir dipivoxil-treated patients. At week 48, all placebo-treated subjects who did not exhibit HBeAg or HBsAg seroconversion, plus all adefovir dipivoxil-treated subjects, were offered the opportunity to receive open-label adefovir dipivoxil from study week 49 through to week 240. A high rate (30%) of hepatic flares was reported following discontinuation of adefovir dipivoxil during the 3 years open-label phase of the study. Furthermore, for the few patients who remained on drug at week 240 (n=12) BMI Z score was lower than typical for their age and gender. Very few patients developed adefovir-associated mutations up to 5 years; however, the number of patients who remained on drugs above week 96 was limited. Due to their limitations, the clinical data available do not allow to draw definitive conclusions on the benefit/risk ratio of the adefovir treatment in children with chronic hepatitis B (see section 4.2).

## 5.2 Pharmacokinetic properties

Adefovir dipivoxil is a dipivaloyloxymethyl ester prodrug of the active substance adefovir, an acyclic nucleotide analogue which is actively transported into cells where it is converted by host enzymes to adefovir diphosphate.

### Absorption

The oral bioavailability of adefovir from 10 mg adefovir dipivoxil is 59 %. Following oral administration of a single dose of 10 mg adefovir dipivoxil 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. Systemic exposure to adefovir was not affected when 10 mg adefovir dipivoxil was taken with a high fat meal. The  $t_{max}$  was delayed by two hours.

### Distribution

Preclinical studies show that after oral administration of adefovir dipivoxil, 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  $\leq 4$  %, 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  $392 \pm 75$  and  $352 \pm 9$  ml/kg, respectively.

### Biotransformation

Following oral administration, adefovir dipivoxil is rapidly converted to adefovir. At concentrations substantially higher (> 4,000-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. The median (min-max) renal clearance of adefovir in subjects with normal renal function ( $Cl_{cr} > 80$  ml/min) is 211 ml/min (172-316 ml/min), approximately twice calculated creatinine clearance (Cockcroft-Gault method). After repeated administration of 10 mg adefovir dipivoxil, 45 % 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 when given as adefovir dipivoxil over the dose range of 10 to 60 mg. Repeated dosing of adefovir dipivoxil 10 mg daily did not influence the pharmacokinetics of adefovir.

### Pharmacokinetic/pharmacodynamic relationship(s)

#### *Gender, age and ethnicity*

The pharmacokinetics of adefovir were similar in male and female patients. Pharmacokinetic studies have not been conducted in the elderly. Pharmacokinetic studies were principally conducted in Caucasian patients. The available data do not appear to indicate any difference in pharmacokinetics with regard to race.

#### *Renal impairment*

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

<b>Renal Function Group</b>	<b>Unimpaired</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
<b>Baseline Creatinine Clearance (ml/min)</b>	<b>&gt; 80 (n=7)</b>	<b>50-80 (n=8)</b>	<b>30-49 (n=7)</b>	<b>10-29 (n=10)</b>
C <sub>max</sub> (ng/ml)	17.8 $\pm$ 3.2	22.4 $\pm$ 4.0	28.5 $\pm$ 8.6	51.6 $\pm$ 10.3
AUC <sub>0-<math>\infty</math></sub> (ng·h/ml)	201 $\pm$ 40.8	266 $\pm$ 55.7	455 $\pm$ 176	1240 $\pm$ 629
CL/F (ml/min)	469 $\pm$ 99.0	356 $\pm$ 85.6	237 $\pm$ 118	91.7 $\pm$ 51.3
CL <sub>renal</sub> (ml/min)	231 $\pm$ 48.9	148 $\pm$ 39.3	83.9 $\pm$ 27.5	37.0 $\pm$ 18.4

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

It is recommended that the dosing interval of 10 mg adefovir dipivoxil is modified in patients with creatinine clearance between 30 and 49 ml/min. Adefovir dipivoxil is not recommended in patients with creatinine clearance of < 30 ml/min or in patients on dialysis (see section 4.2 and 4.4).

#### *Hepatic impairment*

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

#### *Paediatric population*

The pharmacokinetics of adefovir dipivoxil were studied in an efficacy and safety study of a daily dose of 0.25 mg/kg to 10 mg adefovir dipivoxil in children (aged 2 to < 18 years). Pharmacokinetic analysis revealed that adefovir exposure was comparable among 3 age groups, 2 to 6 years (0.3 mg/kg), 7 to 11 years (0.25 mg/kg) and 12 to 17 years (10 mg) and all age groups achieved adefovir exposure in the target range (for efficacy results see section 5.1), which was based on adefovir plasma concentrations in adult patients with chronic hepatitis B with established safety and efficacy profiles.

## **5.3 Preclinical safety data**

The primary dose-limiting toxic effect associated with administration of adefovir dipivoxil 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 adefovir dipivoxil orally.

When adefovir was administered intravenously to pregnant rats at doses associated with notable maternal toxicity (systemic exposure 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 systemic exposures approximately 12 times that achieved in humans at the 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 long-term carcinogenicity studies in rats and mice with adefovir dipivoxil, no treatment-related increase in tumour incidence was found in mice or rats (systemic exposures approximately 10 and 4 times those achieved in humans at the therapeutic dose of 10 mg/day, respectively).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose monohydrate  
Croscarmellose sodium  
Talc  
Pregelatinised starch  
Magnesium stearate

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

The expiry date of the product is indicated on the label and packaging.

Use within 30 days after opening.

### **6.4 Special precautions for storage**

Do not store above 30°C. Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

### **6.5 Nature and contents of container**

Hepsera is supplied in high-density polyethylene (HDPE) bottles with a child-resistant closure. Each bottle contains 30 tablets, silica gel desiccant and fibre packing material.

### **6.6 Special precautions for disposal**

Unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MANUFACTURER.**

PATHEON INC., Mississauga, Canada

**8. LICENSE HOLDER AND IMPORTER**

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

**9. LICENSE NUMBER**

129-97-30889

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