SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Hepsera. For information on changes after approvalplease refer to module 8B

1. Chemical, pharmaceutical and biological aspects

Composition

Hepsera is presented as an immediate release tablet containing 10 mg of adefovir dipivoxil, as active substance.
The other ingredients in this formulation are commonly used in tablets
Hepsera is supplied in high-density polyethylene bottle (HDPE), with silica gel desiccant canisters or sachets, and polyester fiber packing material. The closure system consists of a child-resistant polypropylene screw cap lined with an induction activated aluminium foil liner.

Active substance

Adefovir dipivoxil is an ester prodrug of the nucleotide analogue, adefovir. A structural modification of the parent drug has been carried out in order to increase the lipophilicity and to enhance the oral bioavailability of adefovir.
The active substance is a white to off-white crystalline powder. It is soluble in ethanol, sparingly soluble in 0.1N HCl and very slightly soluble in water adjusted to pH 7.2 but relatively highly soluble at physiological pH. The active substance does not contain any chiral center and does not exhibit any optical isomerism.
In laboratory studies the anhydrate crystal form has been observed to convert gradually into a dihydrate crystal form when adefovir dipivoxil was exposed to high humidity conditions (75% R.H., 25ºC) over an approximately one-month period. However, the only crystal form produced during the active substance synthesis and utilised in non-clinical and clinical studies has been the anhydrous crystal form. Adefovir dipivoxil undergoes also hydrolysis in aqueous solution and to a smaller degree in the solid state after exposure to humidity and heat for extended periods.

Adefovir dipivoxil is synthetised from commercially available starting materials. Following crytallisation, the product is dried and milled.

Satisfactory specifications and associated methods have been provided for the starting materials, key intermediates, reagents and solvents.

The active substance specification includes tests for appearance, identity, clarity of solution, water content, assay, impurity content (HPLC), organic volatile impurities (GC), heavy metals, particle size and additional tests to confirm that the active substance is in the anhydrous form. Impurity limits in specification are justified by toxicology studies.

The analytical methods used in routine controls are suitably described and validated.

Batch analysis data confirm satisfactory compliance and uniformity with the proposed specification.

Batches have been studied under long-term conditions (5°C – samples packed in sealed polyethylene bags placed into tightly capped HDPE bottles) for up to 36 months and under accelerated conditions (25°C/60% RH and 30°C/60% RH – samples packed in sealed polyethylene bags placed into tightly capped HPDE bottles or unsealed polyethylene bags placed into open HDPE bottles) for 6 months.

Photostability studies were also performed and showed that the active substance is not light sensitive.

The results obtained support the proposed retest period of 2 years under refrigeration at 2-8°C.

Other ingredients

All the excipients comply with the Ph. Eur. requirements.
The only ingredient from animal origin is the lactose monohydrate using milk and calf rennet of bovine origin during its preparation. The manufacturer has provided confirmation that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption and that the calf rennet complies with the public statement EMEA/CPMP/571/02.
The HDPE bottle and the polypropylene cap meet the general Ph. Eur. requirements for plastic primary packaging material. Confirmation has been given that the silica gel desiccant canisters/sachets and the polyester fiber packing material are suitable for contact with food.

Product development and finished product

The product development was mainly based on the active substance properties and so aimed to minimise the exposure of the active substance to moisture.
The tablet formulation is prepared using a conventional wet granulation process and subsequent controlled drying process to reduce the water content of the granules. The effect of environmental moisture on the drug product has also been minimised by adding silica gel as a desiccant to the immediate packaging bottle and also by using a bottle with sufficient wall thickness and an aluminium foil induction seal.All the excipients selected are commonly used in tablet formulations. The function of each excipient and the rationale for its use has been satisfactorily described.

The formulation used in the clinical studies and the commercial formulations are similar, the only difference being the dimension and the shape of the tablets. Therefore, no bioequivalence study has been performed.

A bioequivalence study has been performed to assess the effect of food on the bioavailability and pharmacokinetic of the intended commercial formulation. The results demonstrate that the absorption of adefovir dipivoxil is unaffected when taken with food.

The method of manufacture can be divided into 5 operations: compounding, granulation/drying, milling, final blending (in two steps: extragranular excipients then lubricant), and compression.

Validation data have been provided on six primary stability batches and also on 3 full-scale batches prepared using three different active substance lots sourced from the two suppliers. These validation data together with the results obtained during process and formulation optimisation studies showed the robustness of the formulation and that the identified critical parameters are under control. Based on these results, satisfactory in-process controls have been established.
The product specification includes tests for appearance, identity, assay, water content, impurity content, content uniformity (Ph. Eur.), dissolution, hardness (Ph. Eur.) and microbial limit (Ph. Eur.). Batch analysis data presented include data for 3 full-scale batches of the finished product manufactured at the intended manufacturing site, comply with the specifications and confirm the robustness and reproducibility of the manufacturing process.

Stability of the Product

Long term and accelerated stability studies were conducted on six primary stability batches. 36 months data are available for one batch, 24 months for another and 18 months for the four other batches under long term conditions (25ºC/60% R.H – packaging intended for commercialisation). Studies under accelerated conditions (40ºC/75% R.H. – packaging intended for commercialisation) have been performed over a 6-months duration. Additional long-term stability studies have been conducted at the intermediate condition of 30ºC/70% R.H. for a 18-month period. A photostability study has also been performed.
The results presented support the proposed shelf life and storage conditions defined in the Summary of Product Characteristics.

2. Toxico-pharmacological aspects

Pharmacodynamics

Mechanism of action

Because adefovir is not well absorbed from the intestine, the prodrug was developed as it was shown *in vitro* that adefovir dipivoxil enters cells more efficiently than the parent compound, and is rapidly converted into adefovir.

Adefovir is actively transported into cells where it is converted by adenylate kinase to the active metabolite adefovir diphosphate through two phosphorylation reactions.
Adefovir diphosphate inhibits hepatitis B virus (HBV) polymerase activity by competing with dATP for incorporation into viral DNA. Adefovir diphosphate lacks a 3´-hydroxyl group and therefore causes premature termination of DNA synthesis after incorporation into the DNA chain. Adefovir diphosphate is a potent inhibitor of HBV DNA polymerase; with a K_i value (inhibition constant) equivalent to 0.1 µM. Adefovir diphosphate shows specificity for HBV polymerase with a K_i value 10-700 fold higher than for mammalian DNA polymerases.
The half-life of adefovir diphosphate was 16-18 hours in T-lymphocytic MT-4 cells. The half-life of adefovir dipivoxil was 30 hours in quiescent human peripheral blood mononuclear cells (PBMCs) and 12 hours in PHA-stimulated PBMCs. *In vivo* intracellular half-life of adefovir diphosphate in PBMCs was approximately 36 hours after a single subcutaneous dose of ^{14}C-labeled adefovir to macaques.

- *In vitro* studies

Adefovir demonstrated antiviral activity against human HBV, duck HBV (DHBV) and woodchuck HBV (WHV) in cells culture models. Concentrations leading to 50 % inhibition of viral replication (IC_{50}) ranged from 0.2 to 1.2 µM in two different HBV DNA transfected hepatoma cell lines.

In different cells types, the cytotoxic concentrations of adefovir ranged from 80 to 500 µM, which revealed a low cytoxicity potential.

Adefovir showed additive or synergistic anti-DHBV activity in combination with lamivudine and penciclovir at several molar ratios. There was no antagonism between these three compounds.

Adefovir diphosphate was active against lamivudine and famciclovir resistant HBV polymerases with the Ki values increasing by less than 2.3 fold compared with the wild type. In addition, mutations associated with hepatitis B immunoglobulin escape did not reduce sensitivity to adefovir in cell culture.

As other nucleotide analogues, adefovir has a nephrotoxic potential. Adefovir was less inhibitory on the growth of human renal proximal tubule epithelial cells (concentration of 50 % cytotoxicity, $CC_{50,}$ 495 µM) than cidofovir (CC_{50} 260 µM) but more than tenofovir, which did not inhibit cell growth at the tested dose (CC_{50}> 2 mM). This cytotoxicity appeared to be linked to the expression of the human renal organic anion transporter 1 (hOAT1) which mediates cellular uptake of these nucleotides thus augmenting the concentration of the compound in cells expressing this transporter. Interference with essential intracellular function(s) rather than a difference in renal transport is responsible for the differential nephrotoxicity of adefovir, cidofovir and tenofovir.

Since nucleoside analogues are associated with mitochondrial toxicity and production of lactic acidosis, the potential effects of adefovir were evaluated in *in vitro* cellular models. At concentrations up to 30 µM, adefovir did not inhibit the synthesis of mitochondrial DNA.

- *In vivo* studies

In vivo animal studies demonstrated the activity of adefovir in the duck model of HBV replication and the activity of adefovir dipivoxil in the woodchuck and mice transgenic models of WHV or HBV

replication. A relapse was seen after cessation of treatment. Although in the duck model adefovir was able to inhibit duck HBV in cells other than hepatocytes, the antiviral activity of adefovir in extra-hepatic cells has not been studied in humans, but the applicant committed to explore this potential effect post-authorisation.

Immunodulatory activity was reported when adefovir or adefovir dipivoxil was administered in mice and rats. It was therefore suggested that through these activities both adefovir and adefovir dipivoxil might indirectly influence the host immune response and contribute to an improvement in liver histology.

- Resistance

Adefovir seems to have a low potential for resistance development due to its close structural relationship with dATP, which limits potential for steric hindrance as mechanism of resistance. In addition, the *in vitro* data suggest that the risk for induction of multi-drug resistance (or cellular resistance) due to changes in host cellular functions would be low in patients receiving adefovir dipivoxil 10 mg daily.

General and safety pharmacology programme

Adefovir dipivoxil had no pharmacological effects on general behaviour in mice at doses up to 100 mg/kg. Piloerection was seen at doses of 30 and 100 mg/kg. However this effect was not considered clinically relevant, which was further supported by the lack of such adverse reaction in the clinical safety database. There was no evidence of effect on the cardiovascular and respiratory functions in dogs receiving intraduodenal doses of adefovir dipivoxil up to 12 mg/kg. Adefovir dipivoxil caused decreased urine volume, electrolyte excretion and decreased gastric emptying in rats at doses of 30 mg/kg.

Pharmacokinetics

The pharmacokinetics profiles of adefovir and adefovir dipivoxil have been investigated in several species (mice, rats and cynomolgus monkeys). Adefovir dipivoxil was administered orally, which is the intended route of administration in humans. Two validated assays were used to determine plasma concentrations of adefovir: HPLC method with humans.
fluororescence derivatisation used in early studies including toxicokinetics (limit of quantification 60 ng/ml) and HPLC-mass spectrometry (limit of quantification 5 ng/ml).

Absorption and distribution

Following oral administration, adefovir dipivoxil was rapidly absorbed in all three species and converted to adefovir, with Tmax values reached within 0.25 to 1.5 hours post-dose. Plasma concentrations declined in a biphasic manner. The oral bioavailability ranged between 34 and 47 % in rats and between 21 and 35 % in monkeys.
Repeated doses administration resulted in pharmacokinetics parameters similar to those obtained after single dose administration. The pharmacokinetics of adefovir seemed linear. Cmax and AUC were almost proportional to the dose and there was no sign of accumulation. Adefovir displayed similar pharmacokinetics in pregnant and non-pregnant rats.

Following oral administration of adefovir dipivoxil in rats and monkeys, adefovir distributed extensively with the highest amounts found in gastrointestinal tissues, liver and kidney.
The protein binding of adefovir was not evaluated in animals but was found to be very low in human plasma and serum (less < 4 %).

Metabolism and elimination

The biological stability of adefovir dipivoxil was studied *in vitro* in plasma and tissue homogenates from rats and humans. It was rapidly converted to the intermediate adefovir-monoester and then

adefovir through cleavage of the phosphoester linkages by non-specific esterases. The half-life of conversion of adefovir dipivoxil to adefovir monopivoxil was 50 min in rat intestinal wash and 3 min in human plasma, indicating that the prodrug would be sufficiently stable in the intestines to allow time for oral absorption. The half-life of the monoester itself was not determined but is presumed to be relatively short.
No other metabolites than adefovir have been detected in radiolabelling studies in rats and monkeys.
Adefovir did not inhibit P450 enzymes up to the highest tested concentration of 300 µM. Adefovir dipivoxil inhibited CYP3A4 activity at a concentration of 19 and 83 µM using midazolam and testosterone as substrates, respectively. As it is rapidly degraded to adefovir, this slight inhibition of CYP3A4 can be considered without clinical relevance. The other P450 enzymes were not inhibited by adefovir dipivoxil.

After intravenous administration of adefovir, it was mainly excreted as unchanged in the urine of all animal species tested (85 % in rats and 75 % in monkeys excreted as unchanged).

Toxicology

Toxicological studies have been studied in mice, rats, guinea pigs, woodchucks, rabbits and monkeys, where adefovir dipivoxil was administered orally as per the proposed therapeutic route of administration. In addition the toxicology of adefovir was evaluated in mice, rabbits and monkeys using intravenous, subcutaneous or intramuscular route of administration. Definitive toxicology and toxicokinetics studies were conducted in accordance to Good Laboratory Practices.

Single dose toxicity

Adefovir and adefovir dipivoxil showed a low acute toxicity. After a single dose of adefovir administered intravenously or subcutaneously, the minimum lethal doses were > 500 mg/kg in mice, 500 mg/kg in rats and 150 mg/kg in monkeys. Clinical signs were mainly a decreased activity in mice and rats. There was no death after oral administration of adefovir dipivoxil up to 225 mg/kg in rats or monkeys. The no observable effect level (NOEL) was 75 mg/kg in both species.

Repeated dose toxicity

The toxicity of adefovir was evaluated in rats and monkeys, which received intravenous or subcutaneous administrations for up to 4 weeks. The primary target organs were the kidney, bone marrow and the skin. Dermal reactions characterised by hair loss, exfoliation and scabbing of the fore and hid limbs and/or ventral thoracic area and microscopically by epidermal hyperkeratosis and/or suppurative inflammation were observed in monkeys following intravenous (25 mg/kg/day) and subcutaneous administration (20 mg/kg/day). Although these effects were only seen after parenteral administration and the safety margin was large, the mechanism behind these lesions at a non injection site is unknown.
The toxicity of adefovir dipivoxil administered orally was evaluated in mice (up to 13 weeks), in rats (up to 26 weeks) and cynomolgus monkeys (up to 52 weeks). The target organs were the kidney, gastrointestinal tract, liver, lymphoid and haematopoietic system.

Nephrotoxicity was the dose-limiting toxicity in rats and monkeys and the no observable adverse effect levels (NOAEL) in these species were respectively 2 mg/kg (extrapolated to be 1.5 times the human exposure for 10 mg dose) and 1 mg/kg (exposure less than human exposure for 10 mg dose). The incidence and severity of renal tubular nephropathy were related to dose and duration of treatment. Nephrotoxicity was characterised by renal tubular nephropathy with elevation of urea, creatinine, glucosuria, and proteinuria. Kidney weights were also augmented. Histology revealed renal tubular karyomegaly, tubular dilatation and individual tubular epithelial cell necrosis. Tubular karyomegaly was considered as a morphological change without any consequences. As already mentioned in the pharmacodynamic part of this document, *in vitro* experiments suggested that the hOAT1, which transports adefovir, could play a role in adefovir nephrotoxicity. In view of the low safety margins with regard to renal toxicity, appropriate monitoring measures of renal function of

patients treated have been included in the Summary of Product Characteristics as further discussed in the clinical part of this document.

Dose-related hyperplastic, degenerative and inflammatory changes of the gastric epithelium were seen in monkeys (≥ 8 mg/kg/day in the 4-week study). In the 13-week study in this species, changes in faecal consistency and vomitus were seen especially in the 25 mg/kg/day group. There was no such changes in the longer-term studies (52-week with doses up to 5 mg/kg equivalent to the human exposure), which suggested that this effect is probably linked to local irritation, and therefore did not raise any concern for the clinical use of adefovir dipivoxil.

Liver changes such as hepatocellular karyo/cytomegaly and individual cell necrosis were only observed in mice with doses of 10 mg/kg/day adefovir dipivoxil and above. In the monkeys studies, liver transaminases were increased 2-3 fold at doses of 5 to 25 mg/kg/day, which correspond to a systemic exposure approximately 3 to 27 times the human exposure. The increase in liver transaminases without histological changes was reversed after treatment cessation. On the background of these data and human clinical data demonstrating decreases in serum transaminases with adefovir dipivoxil treatment, effects on the liver do not appear to be a concern for its clinical use.

In the 13-week study in mice, bone marrow toxicity was noted at 10-100 mg/kg/day (systemic exposures 11 to 76 times human exposure). In the intravenous and subcutaneous studies, lymphoid depletion of the spleen, thymus and lymph nodes and hypocellularity of the bone marrow were seen in rats with doses ≥ 20 mg/kg/day and monkeys with doses ≥ 20 mg/kg/day (at 250 times the human exposure). This toxicity at high doses is expected for nucleotide analogues. As the safety margins are large, there is no reason for concern in humans.

Dose dependent increases in serum total creatinine phosphokinase activities were observed in monkeys administered adefovir dipivoxil at doses ≥ 5 mg/kg/day for 4, 13 or 52 weeks. These increases were readily reversible following a recovery period. In addition animals were not lethargic and histology of skeletal muscle was negative. Based on these data and *in vitro* data, which revealed that adefovir dipivoxil only has a low potential for mitochondrial toxicity, there was no evidence for mitochondrial toxicity, which was confirmed in clinical studies.

In the subchronic and chronic toxicity studies in monkeys, free and total serum carnitine were reduced in a dose and duration dependent manner with no apparent clinical or histological related toxicity. Carnitine levels slightly increased during the recovery period.

Reproduction toxicity

Adefovir dipivoxil did not affect the fertility and general reproduction performance of the male and female rats at doses up to 30 mg/kg.

In rats, adefovir given intravenously resulted in embryotoxicity (increased number of resorption and the percentage of resorbed conceptuses per litter), increased incidence of foetal malformations (e.g. anasarca, depressed eye bulge, umbilical hernia, and kinked tail) and other common variations (e.g. supernumerary ribs) but only at doses resulting in maternal toxicity (20 mg/kg/day).

When adefovir dipivoxil was administered orally at a dosage up to 35 mg/kg in rats, neither embryotoxic nor teratogenic effects were observed. NOEL for teratogenicity was above 35 mg/kg, providing a systemic exposure of approximately 23 times that achieved in humans at the recommended clinical dose. The maternal and foetal NOAEL was 10 mg/kg. In rabbit, no effect was seen on embryo-foetal development and the NOEL for maternal and foetal toxicity was 20 mg/kg/day, providing a systemic exposure of approximately 40 times that achieved in humans at the recommended clinical dose.
Developmental toxicity was noted in the pre- and post-natal development study in rats (reduction of F1 pup weights at weaning and an increase in F1 pup deaths) but only with doses of adefovir dipivoxil resulting in maternal toxicity (40 mg/kg dose).

In all studies, adverse effects were only seen at very high doses and clear NOELs were determined with maternal systemic exposures many times higher than the human clinical exposure. It is expected that the foetal exposure obtained in these studies would also be very high. Adefovir dipivoxil should therefore not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus as mentioned in the Summary of Product Characteristics.

Genotoxicity

In vitro, adefovir was negative in the bacterial mutation assay using single doses up to 5000 µg/plate with/without metabolic activation. Adefovir was however positive in the chromosome aberration assay in human peripheral blood lymphocytes with dose-related elevations in the frequency of chromosomal aberrations seen at 25 and 50 µg/ml without metabolic activation.
Adefovir dipivoxil was positive in the mouse lymphoma assay (mutation frequencies were increased at 12.5 and 25 µg/ml with or without metabolic activation) but negative in the *in vivo* mouse micronucleus assay using doses up to 2000 mg/kg. The profile of adefovir and adefovir dipivoxil is similar to nucleoside analogues in that it induces chromosomal aberrations (but not point mutations) *in vitro* but is not genetoxic *in vivo*.

Carcinogenicity

The carcinogenic potential of adefovir dipivoxil was evaluated in mice using doses up to 10 mg/kg and rats using doses up to 5 mg/kg by oral gavage using standard protocols. No carcinogenic effects of adefovir dipivoxil have been evidenced. Animals were exposed to the highest possible dose despite the absence of body weight gain reduction and the low multiple of human exposure obtained at these doses (10 mg/kg corresponding to approximately 8 times the human exposure and 5 mg/kg corresponding to approximately 4 times the human exposure).

Local tolerance

Adefovir dipivoxil was a moderate skin and eye irritant in rabbits but did not provoke dermal sensitisation in guinea-pigs.

Impurities

There was no unexpected toxicity when adefovir was enriched with impurities and/or organic volatile impurities.

Pivalic acid
Pivalic acid is a product of the *in vivo* metabolism of adefovir dipivoxil to adefovir, which is renally excreted after being conjugated with serum free carnitine. As mentioned above the carnitine depletion observed in monkeys is of no apparent consequences.

Formaldehyde
Formaldehyde is released during hydrolysis of the pivaloyloxymethyl promoiety but the estimated daily exposure to formaldehyde at the clinical therapeutic dose of adefovir dipivoxil does not raise any concern.

Environmental risk assessment

The assessment of the environmental risk did not suggest any significant risk to the environment related to the use of adefovir dipivoxil.

3. Clinical aspects

The clinical development programme for adefovir dipivoxil enrolled a wide range of patients to support the use of adefovir dipivoxil in adult patients with chronic hepatitis B. The programme, which includes more than 1,000 patients, consists of:

- 5 pharmacokinetics studies
- 3 Phase II studies to evaluate the anti-HBV activity of adefovir dipivoxil and to define the dose as well as an extension phase study
- 2 pivotal placebo-controlled clinical studies in patients with chronic hepatitis B (HBeAg positive and HBeAg negative, respectively) and compensated liver disease
- 1 open-label study in patients with chronic hepatitis B failing lamivudine therapy who have received a liver transplantation or who are waiting for a transplantation.
- 3 supportive studies in patients with lamivudine-resistant chronic hepatitis B infection, including studies in patients with compensated/decompensated liver disease, and in patients co-infected with HIV.

Adefovir dipivoxil was originally developed for the treatment of HIV infection using higher doses (60 mg and 120 mg daily) but the programme was discontinued since the limited benefit of the compound did not outweigh its significant nephrotoxicity reported with higher doses. Pertinent safety data from the HIV programme have however been submitted in this current application.

All the studies were conducted in accordance with the agreed international ethical principles and Good Clinical Practices.

Clinical pharmacology

Pharmacodynamics

Mechanism of action

As already mentioned in section 3.3 of this document (Part III: pharmaco-toxicological aspects) adefovir dipivoxil undergoes a rapid enzymatic hydrolysis by non-specific esterases yielding adefovir (10 mg adefovir dipivoxil is equivalent to 5.448 mg adefovir). The site of hydrolysis has not been fully identified, but is supposed to take place both in the gut lumen and throughout the absorptive pathway. Adefovir is then rapidly converted through two phosphorylation reactions in the hepatocyte cytosol to the active intracellular metabolite adefovir diphosphate which is a potent competitive inhibitor of HBV polymerase and acts as a chain terminator of HBV DNA replication. Adefovir dipivoxil showed potent *in vitro* and *in vivo* anti-HBV activity.

Hepatitis B virus covalently closed circular (ccc) DNA is a critical intracellular replicative intermediate that appears responsible for viral persistence during chronic infection and antiviral therapy. Preliminary data originated from one phase 3 study (437) showed that adefovir dipivoxil decreased the intracellular pool of ccc DNA by 86% after 48 weeks of therapy. However it has to be further evaluated whether the cccDNA determination could be an indicator of sustained response and could help in defining treatment duration. The applicant committed to provide further data post-authorisation to address this issue.

As observed in animals, preliminary data obtained in a subgroup of patients from study 437 showed that adefovir exerts also an immunomodulatory effect via interferon gamma. The enhanced HBV specific T-cell reactivity to HBV was more observed in adefovir-treated patients compared to placebo.

Dynamic studies

Three studies were conducted in patients with chronic hepatitis B to confirm the *in vitro* anti-HBV activity and to identify the recommended dose for clinical use. Adefovir is converted intracellularly by adenylate kinases to the active metabolite adefovir diphosphate, which exhibits an intracellular half-

life of 12 to 36 hours in lymphocytes supporting the once daily dose regimen. An overview of these studies is presented in table 1.

Table 1 Phase I/II pharmacodynamic/dose ranging studies				
Study	**General Design**	**Patient Population**	**Pts analysed**	**Dose/ Duration**
404	Double-blind, randomised, placebo-controlled, dose escalation	Chronic hepatitis B, elevated ALT, HBeAg positive.	Initial: 20 Maintenance: 15	Initial: ADV 125 mg, 250 and 500 mg for 4 weeks or placebo (dose escalation stopped) Maintenance: ADV 60 or 120 mg for 24 weeks
412 (initial)	Randomised, double-blind, placebo-controlled, dose escalation	Chronic hepatitis B, elevated ALT. Cohort 1: HBeAg positive Cohort 2: HBeAg negative (presumed precore mutant)	Cohort 1 53 Cohort 2 10	ADV 5, 30 and 60 mg or placebo for 12 weeks ADV 30 mg or placebo for 12 weeks
413 (initial)	Randomised, double-blind, placebo-controlled, dose escalation	Chronic HBV infection, normal ALT (< 1.2 x ULN), HBeAg positive	14	ADV 30 mg for 12 weeks (dose escalation stopped)

In addition to these three studies, a 52-week extension phase using a daily dose of 30 mg adefovir dipivoxil was planned for HBeAg positive patients after completion of their participation to the initial phase of either study 412 or 413 and after completing a 24-week off-treatment follow-up period. Similarly HBeAg negative chronic hepatitis B patients could be enrolled in the extension phase to maintain suppression of HBV replication. While participating in this extension phase all patients enrolled had their daily dose of adefovir dipivoxil reduced to 10 mg as a consequence of emergence of mild reversible nephrotoxicity associated with the use of doses above 30 mg daily for more than 20 weeks. At that time the majority of patients enrolled had been treated for 30 weeks.

Endpoints

In all these studies, the primary efficacy endpoint was change in serum $\log_{10}$ HBV DNA concentration from baseline. Secondary efficacy endpoints included the rate of conversion of HBV serological markers (studies 412 and 413) and change in serum ALT from baseline (study 413). The safety endpoints were frequency and severity of adverse reactions, change in laboratory values and vital signs as well as need for dose modification and treatment discontinuations.

Results

All the oral doses of adefovir dipivoxil tested (5, 30, 60 and 125 mg daily) were associated with a rapid (within one week) reduction in serum HBV DNA levels compared to placebo. This effect was sustained during initial treatment periods for up to 12 weeks, but HBV DNA levels returned to baseline when treatment was discontinued.
In study 412, treatment with 30 and 60 mg resulted in similar degrees of suppression of viral load whereas the effect of 5 mg daily was less pronounced although still significant compared to placebo. The median serum HBV DNA change from baseline at week 12 was -0.02 $\log_{10}$ copies/ml in the placebo group, compared with -1.82 $\log_{10}$ copies/ml in the 5 mg group, -3.78 $\log_{10}$ copies/ml in the 30 mg group, and -3.34 $\log_{10}$ copies/ml in the 60 mg group ($p< 0.001$).
A similar antiviral response was seen in the HBeAg negative cohort. At week 12, the median serum HBV DNA change from baseline was -3.59 $\log_{10}$ copies/ml in the adefovir dipivoxil 30 mg group (n=8) compared with -0.28 $\log_{10}$ copies/ml in the placebo group ($p = 0.037$) (n=2). A plateau dose/effect was therefore evidenced, with the 30 mg and 60 mg doses being similar in potency.
In the 52 weeks extension study, treatment with adefovir dipivoxil was associated with a sustained suppression of serum HBV DNA concentrations similar to those observed during short-term treatment. The median time weighted average change from baseline in HBV DNA (n = 38) was - 3.40 $\log_{10}$ copies/ml at week 24, -3.45 $\log_{10}$ copies/ml at week 48 and - 3.40 $\log_{10}$ copies/ml up to

week 76 ($p < 0.001$ for all time points compared to baseline). Serum HBV DNA concentrations became undetectable in 22 of 38 patients (58 %) by week 48 and in 24 of 38 patients (63 %) by week 96 (Amplicor assay with lower limit of quantification < 400 copies/ml). Seroconversion occurred in 6 of the 28 patients (21 %) who were anti-HBe negative at baseline of the extension phase (disappearance of HBeAg and emergence of anti-HBe with sustained suppression of HBV DNA). The number of patients with normalization of ALT concentrations increased over the course of treatment from 4 of 39 patients (10 %) at baseline to 19 of 30 patients (63 %) at week 48.
The results of these studies were considered for the dose selection as further discussed in the section "dose ranging studies" below.

Pharmacokinetics

The pharmacokinetic profile of adefovir following oral administration of 10 mg adefovir dipivoxil has been determined in the following 5 studies:

- Study 412: Single and multiple pharmacokinetics in patients with chronic hepatitis B
- Study 473: Pharmacokinetics in non-HBV volunteers with renal impairment
- Study 474: Pharmacokinetics in non-HBV volunteers with hepatic impairment
- Study 475: Drug interaction in normal volunteers
- Study 476: Food interaction in normal volunteers

In addition, the applicant submitted supportive pharmacokinetics data generated from the previously conducted clinical programme in HIV-infected patients. This refers mainly to data from studies using higher doses of intravenous adefovir (1.0 or 3.0 mg/kg/day) for the estimation of the oral bioavailability and data from a 60 mg oral dose of adefovir dipivoxil for the estimation of the dose proportionality.

The tablets used in the studies and the ones intended for marketing differed only slightly in shape and therefore were considered identical. The analytical methods used for the assay of adefovir in serum, plasma and urine have been adequately validated.

Absorption and distribution

Adefovir dipivoxil is rapidly absorbed. Following oral administration of single dose of 10 mg adefovir dipivoxil in fasted patients with chronic hepatitis B (target population) adefovir rapidly reached maximum concentrations (C_{max}) at median time of 1.75 hours (0.58 h – 4h). Median C_{max} and $AUC_{0-\infty}$ values were 16.70 ng/ml (9.66 – 30.56 ng/ml) and 204.40 ng.h/ml (109.75 - 356.05 ng.h/ml) respectively. In non-HBV subjects comparable results were obtained, with time to reach maximum plasma adefovir concentrations occurring approximately 0.76 to 1.25 hours post-dose.

Data from the previous HIV clinical programme suggested an apparent dose proportionality over the dose range of 10 mg and 60 mg.

The absolute oral bioavailability was estimated at 59 %, however this value should be taken with caution as it has been calculated using historical intravenous data generated from studies in HIV-infected patients where higher doses of adefovir were used.

Pharmacokinetics parameters were not affected by concomitant intake of a high-fat meal. The prolonged T_{max} (approximately 2 hours delay) was considered without clinical relevance in chronic dosing and is caused by delayed gastric emptying. Adefovir dipivoxil can therefore be taken with or without food as recommended in the Summary of Product Characteristics.

The distribution of adefovir has not been studied in humans, but preclinical data showed that adefovir distributed to most tissues with highest concentrations found in intestinal tissues, kidney and liver. The volume of distribution at steady state (Vss) following intravenous administration of adefovir of 1 and 3 mg/kg/day in HIV infected patients was 392 ± 75 ml/kg and 352 ± 9 ml/kg respectively. *In vitro* binding to plasma protein was very low (< 4 %) over a concentration range of 0.1 to 25 mg/ml.

The pharmacokinetics profile of adefovir was similar after multiple administrations.
The inter and intra variability has not been specifically evaluated, however individual data from various studies seem to indicate that the inter variability is moderate (approximately 30 %).

Metabolism and elimination

Apart from the enzymatic hydrolysis of adefovir dipivoxil to adefovir during the absorption, no other metabolic pathways have been identified in humans. Adefovir is not a substrate of the cytochrome P450.

Adefovir is excreted renally as unchanged. After a single oral dose of 10 mg adefovir dipivoxil urinary recovery of adefovir over 24 hours was 41.9 % in chronic HBV-patients. The median renal clearance (Cl_{renal}) of adefovir was 163.67 ml/min/kg (range: 36.66-231.89), which is greater than glomerular filtration rate. This indicates a substantial contribution of tubular secretion to the excretion of adefovir in humans and preclinical studies showed that a human organic anion transporter (hOAT1) played an essential role in the active secretion.
Plasma concentration declined in a bi-exponential manner with a median terminal elimination half-life of 7.22 hours (range 4.72-10.70) after single dose and 7.14 hours (range 4.22 – 17.43) after multiple doses.

Special populations

The pharmacokinetic of adefovir was not influenced by gender, race (but data mainly obtained in Caucasians), weight, age or HBV infection status.
The pharmacokinetic profile of adefovir has not been evaluated in children nor in patients older than 65 years of age. The use of adefovir dipivoxil cannot be recommended in these patients as mentioned in the Summary of Product Characteristics.

A single oral dose pharmacokinetic study showed greater AUC and $T_{1/2}$ values in non-HBV infected patients with moderate or severe hepatic dysfunction defined by Child-Pugh-Turcotte classification compared to subjects with normal hepatic impairment but these differences were not statistically significant. No dose adjustment is therefore recommended in these patients as mentioned in the Summary of Product Characteristics.

The influence of renal function on adefovir pharmacokinetic was evaluated in a single dose study (10 mg) in non-HBV infected patients with different degree of renal impairment including end-stage renal disease requiring dialysis. The following results were obtained:

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)**
C_{max} (ng/ml)	17.8 ± 3.2	22.4 ± 4.0	28.5 ± 8.6	51.6 ± 10.3
AUC -∞ (ng.hr/ml)	201 ± 40.8	266 ± 55.7	455 ± 176	1240 ± 629
CL/F (ml/min)	469 ± 99.0	356 ± 85.6	237 ± 118	91.7 ± 513
CL_{renal} (ml/min)	231 ± 48.9	148 ± 39.3	83.9 ± 27.5	37.0 ± 18.4

In haemodialysed subjects, high flux haemodialysis was shown to efficiently removed adefovir. The median fraction of the administered dose removed over 4 hour was approximately 35 %.
Based on these data, dose interval modification are proposed based on extrapolation of limited data in patients with end stage renal disease (ESRD) and may not be optimal. The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients as mentioned in the Summary of Product Characteristics. There are no data in subjects with creatinine clearance below 10 ml/min and patients with end stage renal disease not managed with haemodialysis and therefore the use of adefovir dipivoxil in such patients should be closely monitored as recommended in the Summary of Product Characteristics.
The applicant committed to conduct a clinical study to further gather dosing guidelines for renal impairment in patients with chronic hepatitis B and varying degree of chronic renal impairment, the results of which will be submitted post-authorisation.

Interaction studies

Since adefovir is not metabolised by CYP450 and did not inhibit *in vitro* CYP450, the likelihood of interactions with medicinal products metabolised using these isoenzymes is therefore very limited.
No pharmacokinetics interaction was observed when adefovir was co-administered with lamivudine, acetaminophen, and trimethoprim/sulfamethoxazole, substances undergoing tubular secretion. By contrast, increases in adefovir Cmax (33%) and AUC (23%) were noted in combination with ibuprofen, but these increases were not considered to be clinically relevant. In the absence of data with compounds known to affect renal function, including nephrotoxic substances (e.g. aminoglycosides, cyclosporin) a warning has been included in the Summary of Product Characteristics to closely monitor patients in case of co-administration. In addition the applicant committed to conduct further interaction studies, the results of which will be submitted post-authorisation.
Supportive data generated in the previous HIV development programme using doses 6 and more than 12 fold the dose proposed for the treatment of hepatitis B did not reveal any clinically relevant interactions with a range of protease inhibitors, nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors.

Clinical efficacy

The efficacy of the 10 mg daily dose of adefovir dipivoxil was assessed in 2 main placebo-controlled studies in treatment-naïve and treatment experienced chronic hepatitis B patients without lamivudine-resistant HBV:

- study 437 performed in HBeAg positive patients
- study 438 performed in pre-core mutant HBeAg negative HBV patients

In addition, the efficacy of adefovir dipivoxil has been evaluated in chronic hepatitis B patients with lamivudine-resistant HBV:

- a main open label study in patients who have received a liver transplantation or are wait-listed for transplantation (study 435)
- an active controlled study of the combination of adefovir dipivoxil and lamivudine versus adefovir dipivoxil or lamivudine alone in patients with compensated (HBeAg positive) liver disease (study 461).
- An open label study in HIV co-infected patients with compensated liver disease (study 460i**)** where adefovir dipivoxil was added to lamivudine.
- An open-label study evaluating the addition of adefovir dipivoxil to lamivudine in patients with decompensated liver disease (Stratum B) and a comparative study evaluating the combination of adefovir dipivoxil added to lamivudine or lamivudine alone (Stratum A) in patients with compensated liver disease (study 465).

An overview of the studies is displayed in table 2:

Table 2

Study	Type of Study	Treat. arms	Duration	Noof Patients reported Enrolled (ITT)	Primary efficacy criterion	Study Design
437 *Year 1 completed* *Blinded year 2 discontinued* *open-label phase pts enrolled into studies 480/481 or 437 long-term safety and efficacy (LTSE)*	**HBeAg positive** chronic hepatitis B ALT > 1.2 – 10 x ULN HBV DNA : $\geq 10^6$ copies/ml	year1: *ADV 10 mg *ADV 30 mg *Placebo year 2: ADV 10 mg	96 weeks + 24 weeks follow-up Year 1 only (72 weeks reported)	Year 1: *ADV 30 mg = 173 (173) *ADV 10 mg= 172 (171) *Placebo = 170 (167) **Total 515** Year 2: 459 re-randomised. 435 received : 1 correct assignment *138 placebo→ADV10 + 85 ADV10 → ADV10 *70 ADV10 → placebo + 142 ADV30 → placebo	Histology at 48 weeks : Improvement defined as $\geq$ 2 point reduction in the necroinflammatory component of the Knodel HAI score with no concomitant worsening in fibrosis	Randomised, double-blind, multicentre, placebo-controlled Further randomisation of placebo and ADV 10 mg arms to daily administration of 250 mg L-carnitine or placebo. All 30 mg patients received 250 mg L-carnitine
438 *Year 1 completed* *Year 2 on-going* *On completion, pts enrolled into 480 or 438 LTSE*	**HBeAg negative** (presumed precore mutant) chronic hepatitis B, HBV DNA+ ALT >1.5-15 x ULN HBV DNA : 10^5 copies/ml	*ADV 10 mg *Placebo	96 weeks treatment (72 weeks reported)	Year 1 : **Total 185 (184)** *ADV 10 mg = 123 (123) *Placebo=62 (61) *year 2 (n=180): *60 placebo→ADV10; 80 ADV10 →ADV10; *40 ADV10 → placebo	Histology at 48 weeks: Improvement defined as $\geq$ 2 point reduction in the necroinflammatory component of the Knodel HAI score with no concomitant worsening in fibrosis	Randomised, double-blind, multicentre, placebo-controlled
435 *On-going*	Chronic hepatitis B, pre (cohorts B /post (cohorts A) orthotopic liver transplantation (OLT) /YMDD mutants	ADV 10mg	48 weeks median treatment 56 weeks for post-tansplantation median treatment 19 weeks for patients pre-transplant	Cohort A =196; Cohort B = 128 Cohort 1: Patients with adequate renal, hepatic, and haematologic function and no prior adefovir use. Cohort 2: Patients previously enrolled in compassionate use study 451i in which they received open-label adefovir. Cohort 3: Patients with renal, hepatic, and/or haematologic dysfunction.	DAVG24 (cohorts 1A and 3A only)	Open-label, multicentre
461	**HBeAg positive** chronic hepatitis B/ **compensated** liver disease/ **YMDD** mutants ALT >1.2 ULN HBV DNA >10^6copies/ml	ADV 10 mg Lamivudine (LAM) 100 mg ADV10 + LAM 100 in combination	48 weeks Planned. (48 weeks data reported)	ADV10 : 20 LAM 100mg : 20 ADV10 + LAM100 : 19 **Total:n=58** (59 enrolled)	DAVG16	Randomised, double-blind, multicentre, active-controlled
460i	Chronic hepatitis B patients co-infected with **HIV** /**YMDD** mutants	ADV 10 mg (in addition to ongoing LAM (150 mg bid)	2 years (72 weeks reported)	N=35	Serum HBV DNA and normalisation ALT	Open-label, single centre, safety study

Study	Type of Study	Treat. arms	Duration	Noof Patients reported Enrolled (ITT)	Primary efficacy criterion	Study Design
465	Chronic hepatitis B/ **YMDD** mutants **Stratum A** : **HBeAg positive** and **compensated** liver disease **Stratum B** : **HBeAg positive or negative** / **decompensated**	Stratum A: ADV 10 mg in addition to ongoing LAM 100 mg Placebo in addition to ongoing LAM 100 mg Stratum B ADV 10 mg and LAM 100 mg (both open-label)	52 weeks planned + open 52-week extension (52-week reported)	N=141 Stratum B : N=40 (39 only reported as efficacy population) (Stratum A, N=95)	HBV DNA response.	Stratum A: randomised, double-blind, placebo controlled Stratum B: randomised open-label

The lack of active comparator in the 2 main studies is justified by the fact that lamivudine was not an approved therapy for the treatment of chronic hepatitis B when study 437 was initiated. Moreover, even if lamivudine had become available when study 438 started, the activity of lamivudine is limited in the targeted pre-core mutant population and it was of particular interest to compare the performance of adefovir in HBeAg positive and negative patients by using the same study design. In addition, in view of the targeted population, interferon alpha was not considered as an optimal comparator.

Dose response studies and main clinical studies

Dose ranging studies

As already presented, the results from the dynamic studies showed that the antiviral efficacy as assessed by the decrease of HBV DNA reached a plateau at 30 mg daily dose. Results from study 412 clearly indicated the need to select a dose between 5 mg and 30 mg in order to optimise the therapeutic effectiveness without increasing the risk of nephrotoxicity. The efficacy of adefovir dipivoxil 10 mg was demonstrated in the dynamic studies although no patients received this dose without previous treatment with a higher dose. Adefovir dipivoxil 10 mg was chosen as a lower dose to evaluate based on mathematical modelling of viral kinetic data collected in study 412, which showed that the efficacy of the 30 mg daily dose was slightly superior to 10 mg, although the difference is small. Based on these data, both 30 mg and 10 mg were chosen to be investigated in the first main study 437. The efficacy of 10 mg dose was confirmed in the main studies, although in study 437 the 30 mg dose provided higher efficacy, evidenced most in terms of viral load reduction (results further presented in the main studies section). Safety analysis showed nevertheless that the 30 mg daily dose was associated with mild nephrotoxicity, which was reversible upon discontinuation, whereas adefovir dipivoxil was not nephrotoxic at the 10 mg daily dose.
These data, the anticipated long-term treatment and efficacy/safety data from the main clinical studies support the recommendation of the 10 mg daily dose.

Main studies

Studies 437 and 438

1. Description of the studies

These studies were randomised, double-blind, placebo-controlled, multicentre comparing adefovir dipivoxil versus placebo in patients with HBeAg positive (study 437) and HBeAg negative liver compensated HBV infection (study 438) with evidence of HBV replication.

Both studies had the same design to facilitate comparison of data and differed only with regard to inclusion criteria: documented positive HBeAg for study 437 and documented negative HBeAg and positive HBeAb for study 438.

The other main inclusion criteria were for both studies:
- documented chronic hepatitis B (positive serum HBsAg present for 6 months prior to randomisation)
- serum positive HBV DNA at screening (Roche Amplicor PCR assay, lower limit of quantification 400 copies/ml): $> 10^6$ copies/ml for study 437 and $> 10^5$ copies/ml for study 438
- ALT values 1.2 to 10 times the upper limit of the normal range (ULN) (study 437) or 1.5 to 15 ULN (study 438) on at least 2 measurements with 1-month interval, and within 6 months prior to randomisation.
- no co-infection (HIV, HCV and HDV seronegative)

The primary objective of both studies was to compare the efficacy of a 48-week treatment course with adefovir dipivoxil 10 mg versus placebo in the treatment of chronic hepatitis B with compensated liver disease (year 1). The re-assignment of dose groups at the beginning of year 2 allowed all patients to receive at least 1 year of active treatment.

The secondary objectives included:

- Comparison between 48 week efficacy of the 10 and the 30 mg doses (year 1, study 437) and 96 week efficacy (year 1 and 2 treatment with adefovir dipivoxil)
- Assessment of 96-week safety (year 1 and 2 treatment with adefovir dipivoxil).
- Effect of treatment withdrawal (year 1 treatment with adefovir dipivoxil, year 2 placebo)
- Assessment of the need for L-carnitine supplementation (as reductions in serum carnitine levels were observed in the HIV programme using higher doses of adefovir dipivoxil).

2. Primary endpoints/assays

The primary endpoint in both studies was the percentage of responders with liver histological improvement at week 48, as defined by a reduction from baseline of 2 points or more in the Knodell necro-inflammatory score, with no concurrent worsening of the Knodell fibrosis score.
The same independent specialist, blinded both with regard to the treatment and the time when biopsy was performed, evaluated the baseline and week-48 biopsies.

The secondary efficacy endpoints covered a wide range of responses to treatment and included:

- further measurements of the histological response
- criteria for evaluating the virological (e.g decrease in serum HBV DNA)
- criteria for evaluating the biochemical response (e.g ALT normalisation)
- measurement of serological response (e.g HBeAg seroconversion defined by loss of HBeAg and concomitant acquisition of anti-HBeAb in study 437 only).

3. Statistical analysis

Planned sample sizes were calculated on the expected difference in response rates between adefovir dipivoxil 10 mg and placebo arms, based on the primary endpoint, with a 90 % power and using a Fisher exact test at a two-sided $\alpha = 0.05$ level of significance.

For both studies the primary population for analysis was the intent-to-treat (ITT) with missing data = failure. The primary efficacy analysis was a comparison between the adefovir dipivoxil 10 mg and placebo groups (unstratified version of the Cochran-Mantel-Haentszel test). For the analysis of the secondary parameters based on change from baseline, comparisons between adefovir dipivoxil 10 mg and placebo were based on the Wilcoxon rank sum test. For endpoints based on proportions, comparisons on placebo were based on Cochran-Mantel-Haentszel test.

RESULTS

4. Study populations/accountability of patients

The demographic and baseline disease characteristics of patients from studies 437 and 438 (ITT population) are displayed in table 3.

Table 3: Main baseline characteristics / studies 437 and 438 (ITT)		
Characteristic	**Study 437 (N = 511)**	**Study 438 (N = 184)**
HBV Type		
HBeAg+	500	0
HBeAg – (presumed precore mutant)	11 (but HBeAg+ at screening)	184
Age (years)		
Mean ± SD	35 ± 11.3	46 ± 10.0
Median	33	46
Gender		
Male, n (%)	378 (74%)	152 (83%)
Female, n (%)	133 (26%)	32 (17%)
Race		
Caucasian, n (%)	184 (36%)	122 (66%)
Black, n (%)	16 (3%)	6 (3%)
Asian, n (%)	304 (59%)	56 (30%)
Other	7 (1%)	0 (0%)
Knodell HAI Scores		
Total		
Mean ± SD	9.40 ± 3.37	9.38 ± 3.33
Median	10	10
Necro-Inflammatory		
Mean ± SD	7.67 ± 2.82	7.52 ± 2.74
Median	8	7
Fibrosis		
Mean ± SD	1.72 ± 1.09	1.86 ± 1.16
Median	1	
Cirrhosis	**32 (6%)**	**20 (11%)**
HBV DNA (log_{10} copies/ml)		
Mean ± SD	8.20 ± 0.88	6.93 ± 0.89
Median	8.36	7.08
Q1, Q3	7.61, 8.82	6.33, 7.55
ALT (IU/L)		
Mean ± SD	133.77 ± 129.00	145.59 ± 151.54
Median	94	98
Q1, Q3	65, 158	69, 165
> ULN	501 (98%)	175 (95%)
Prior HBV treatments		
Interferon-alfa	123 (**24%**)	76 (**41%**)
Lamivudine	10 (2%)	14 (8%)

In both studies, treatment arms were well balanced with regard to demographic data and other baseline characteristics.

Overall, patients enrolled had active viral replication (HBV DNA ≥ 100,000 copies/ml), moderate elevated ALT (median around 2.3 in each group and each study), and the majority had some levels of fibrosis (F1 through F4 in the Knodell scoring system). Only a minority of patients (171/608, 28 %) in these studies had bridging fibrosis at baseline and only 9 of 494 (2 %) patients in study 437 and 1 of 168 (<1 %) patients in study 438 had a Knodell fibrosis score of 0.

Discontinuation

The percentage of treatment discontinuation before week 48 was low in both studies: 8 % in study 437 (8 % in the placebo group versus 7 % in adefovir 10 mg group and 8 % in adefovir 30 mg group) and 2 % in study 438 (2 % in both groups). The main reasons for discontinuation pertained to occurrence of adverse events (2 % in study 437 and 1 % in study 438) and withdrew consent (3 % in study 437 and 1 % in study 438).

5. Efficacy results

The primary analyses of the study endpoint was performed after 48 weeks of the study and the results are presented in table 4:

Table 4: Primary criterion analysis of studies 437/438 (ITT / 48-week missing/unassessable biopsies = failure)

	Study 437			**Study 438**	
	Placebo (N=167)	**ADV 10 mg (N=171)**	**ADV 30 mg (N=173)**	**Placebo (N=61)**	**ADV 10 mg (N=123)**
n (with baseline biopsy)	161 (100%)	168 (100%)	165 (100%)	57 (100%)	121 (100%)
Histological improvement, n (%) (Ω necro-infl :2 with no worsening of fibrosis)	41 (25%)	89 (53%)	98 (59%)	19 (33%)	77 (64%)
No improvement, n (%) (one or both items missing)	105 (65%)	61 (36%)	47 (28%)	36 (63%)	35 (29%)
48-week missing biopsy, n (%)	14 (9%)	16 (10%)	16 (10%)	2 (4%)	3 (2%)
48-week-unassessable biopsy, n (%)	1 (<1%)	2 (1%)	4 (2%)	0	3 (2%)
Treatment difference, % (95% CI)*		27.5% (17.4%, 37.6%)	33.9% (23.9%, 44.0%)		30.3% (15.4%-45.2%)
p-value**		**<0.001**	**<0.001**		**<0.001**
Improvement rate	24.5%(41/167)	52% (89/171)	56.6% (98/173)	31% (19/57)	63% (77/121)

* Treatment differences and 95 % confidence intervals for the difference in the proportion of patients with improvement relative to placebo

** From general association Cochran-Mantel-Haentszel test

As highlighted in table 4, treatment with adefovir dipivoxil resulted in significant histological improvement, when compared to placebo, both in HBeAg positive and HBeAg negative patients.

The 48-week efficacy results on the secondary endpoints are presented in table 5.

Table 5: 48-week secondary efficacy results of studies 437/438					
	Study 437			**Study 438**	
Efficacy Variable at Week 48	**Placebo (N=167)**	**ADV 10 mg (N=171)**	**ADV 30 mg (N=173)**	**Placebo (N=167)**	**ADV 10 mg (N=171)**
Liver Histology (Knodell Scores), ITT					
Median change from baseline:					
- total HAI score - p-value	0	-3 <0.001	-4 <0.001	1	-4 <0.001
- necro-inflammatory score - p-value	0	-2 <0.001	-3 <0.001	0	-3 <0.001
- fibrosis score - p-value	0	0 0.061	0 0.001	0	0 0.005
Blinded Ranked Assessment					
- n (%) necro-inflammatory improvement - n (%) necro-inflammatory worsening - p-value	59 (41%) 49 (34%)	107 (71%) 20 (13%) <0.001	112 (77%) 15 (10%) <0.001	23 (42%) 28 (51%)	90 (80%) 3 (3%) <0.001
- n (%) with fibrosis improvement - n (%) with fibrosis worsening - p-value	35 (24%) 38 (26%)	62 (41%) 21 (14%) <0.001	78 (54%) 14 (10%) <0.001	14 (25%) 21 (38%)	54 (48%) 5 (4%) <0.001
HBV DNA					
Serum HBV DNA < 400 copies/ml, n (%) p-value	0%	36 (21%) <0.001	67 (39%) <0.001	0	63 (51%) <0.001
Median change (log_{10} copies/ml) p-value	-0.55	-3.52 <0.001	-4.76 <0.001	-1.35	-3.91 <0.001
ALT					
Normalised, % p-value	26 (16%)	81 (48%) <0.001	93 (55%) <0.001	17 (29%)	84 (72%) <0.001
Median change (IU/l) p-value	-17	-51 <0.001	-54 <0.001	-38	-55
% of patients with HBeAg seroconversion p-value	9 (6%)	20 (12%) <0.05	23 (14%) 0.011	NA	NA
% of patients with HBeAg loss only p-value	11%	24% 0.0013	27% 0.0002	NA	NA

* : p-value ADV10 mg versus placebo.

These results show consistency across all tested variables and confirm the efficacy of adefovir dipivoxil 10 mg on histological (inflammation + fibrosis), viral and biochemical responses both in HBeAg positive and negative patients. The antiviral efficacy was dose and time dependent. For instance in study 437, the median change at 24 week from baseline was –2.85 log_{10} copies/ml compared to – 3.52 log_{10} at week 48. Efficacy appears even higher, in terms of histological improvement and of ALT and viral load reduction, in HBeAg negative patients, in whom interferon alpha or lamivudine therapy provided poor results.

It has to be underlined that an improvement in fibrosis, which was not expected due to the relatively short time point for assessing histological effects, was observed in 41 % of patients in the adefovir 10 mg group and 54 % in the adefovir 30 mg group versus 24 % in the placebo group.

A significantly greater percentage of HBeAg positive patients achieved seroconversion in the adefovir groups compared to placebo, for both doses, even if this was not expected, given the relatively short time point when referring to the mechanism of action of "virostatic" drugs. There was no HBsAg seroconversion at week 48.

The results showed the slightly higher level of efficacy of the 30 mg dose over the 10 mg dose on those parameters, although no statistical comparisons were performed. However, as further discussed in the clinical safety section of this report the 30 mg dose, in contrast to the 10 mg dose, led to the emergence of mild nephrotoxicity. The 10 mg dose was thus chosen as the recommended dose for further studies.

Long term efficacy

During the second 48-week period, patients in both studies were re-randomised:

- patients from the placebo (and adefovir dipivoxil 30 mg for study 437) arms re-randomised to adefovir dipivoxil 10 mg
- patients from adefovir dipivoxil 10 mg arm re-randomised to either to placebo or to adefovir dipivoxil 10 mg.

However, study medication was misallocated during year 2 of study 437 in 91 % of re-randomised patients. The blinded phase of the study was therefore terminated and patients could end the follow-up period or receive adefovir dipivoxil 10 mg on an open-label basis.

The applicant submitted supplementary results up to 72 weeks for both studies (table 6).

Table 6: Week 48 and 72 Efficacy Data for Studies 437 and 438

	437 (HBeAg positive) (n= 288)		438 (HBeAg negative) (n=183)	
	Week 48	Week 72	Week 48	Week 72
Median Change HBV DNA (log_{10} copies/ml)	-3.5	-3.8	-3.9	-4.2
HBV DNA < 400 copies/ml[a]	26%	46%	66%	80%
ALT normalisation[a]	67%	75%	76%	81%
HBeAg loss[a]	23%	44%	NA	NA
HBeAg seroconversion[a]	14%	23%	NA	NA

[a] Kaplan-Meier estimates

These data confirmed the virological, biochemical and serological efficacy demonstrated in the 48-week period and show additional benefit from extended treatment duration. At week 72, 23 % of patients' assessable patients (n = 66) versus 14 % at week 48 experienced HBeAg seroconversion.

The applicant committed to submit final results of study 438 (96 weeks) as part of the follow-up measures to be fulfilled post-authorisation.

Ancillary analyses

Although, some 40 – 50 % of the patients failed to respond after 48 weeks of treatment, pooled data from studies 437 and 438 did not identify any predictors of non-response.

Baseline characteristics did not seem to have an impact on the response since statistically significant response rates were observed in all sub-groups of patients even if higher rates for histological improvement was observed in patients with elevated baseline Knodell score (> 10), elevated ALT levels (2 x ULN) and relatively low HBV DNA levels (< 7.6 log_{10} copies/ml). Overall 66 % of patients with higher baseline Knodell score (10-14) experienced histological improvement compared to 2 % with lower baseline Knodell score (2-4). An analysis showed also those patients with lower baseline ALT levels, higher baseline HBV DNA levels and lower Knodell necro-inflammatory scores took longer time to achieve a treatment response. These 3 factors also pertain to the prognostic factors for response to interferon or lamivudine therapy.

Comparable efficacy to the overall population was demonstrated in both the HBeAg positive and negative patients with cirrhosis at baseline, but the number of patients with cirrhosis at baseline was low (19 in the placebo and 26 in adefovir 10 mg, pooled data from studies 437 and 438).

Limited data suggest that there is no relationship between ethnic origin or baseline genotype and treatment response.

The applicant committed to further investigates predictors of response/non-response and optimum treatment duration in future clinical studies, the results of which would be submitted post-authorisation. In the meantime, the following recommendations for treatment discontinuation may be considered and have been included in the Summary of Product Characteristics:

- In HBeAg positive patients, treatment should be administered at least until HBeAg seroconversion (HBeAg and HBV DNA loss with HBeAb detection on 2 consecutive samples at least 3 months apart) or until HBsAg seroconversion or in case of evidence of loss of efficacy.
- In HBeAg negative (pre-core mutant) patients, treatment should be administered at least until HBsAg seroconversion or in case of evidence of loss of efficacy.
- In patients with decompensated liver disease, considering the potential risks associated with treatment discontinuation in these patients, treatment cessation is not recommended.

Study 435

This open-label study evaluated the efficacy of adefovir 10 mg once daily in chronic hepatitis B patients with clinical evidence of lamivudine-resistant HBV, compensated or decompensated liver disease and pre- or post liver transplantation.
Patients were enrolled into one of 3 study cohorts based on renal, hepatic, and haematological functions and whether they had previously received adefovir through a compassionate use programme (study 451i). Each of the 3 cohorts contained patients who had previously received a liver transplant (cohort A) and patients who were wait-listed to receive a transplant (cohort B).
This study is still ongoing but results have been submitted for 196 patients from cohort A (post-transplantation (median treatment duration 56.1 weeks)) and 128 patients from cohort B (pre-transplant (median treatment duration 18.7 weeks)). Results at 48 weeks are presented in table 7:

Table 7: Efficacy in Pre- and Post- Liver Transplantation Patients at Week 48 study 435

fficacy Parameter	**Pre-liver transplantation (Cohort B) (n=128)**	**Post-liver transplantation (Cohort A) (n=196)**
Mean change from baseline serum HBV DNA (log_{10} copies/ml) primary endpoint	-3.8 ± 1.4	-4.3 ± 1.6
Stable or improved Child-Pugh-Turcotte score	92%*	96%
Normalisation** of:		
- ALT	76%	49%
- Albumin	81%	76%
- Bilirubin	50%	75%
- Prothrombin time	83%	20%

* 24 week data
** Patients with abnormal values at baseline

The early statistically significant decrease in viral load (-2.1 log_{10} copies/ml at week 4 for cohorts 1A and 3A, -4.4 and –3.9 at week 8 for the same cohorts, respectively) was confirmed, along with the improvement in liver function as assessed by the Child-Pugh-Turcotte score.

Kaplan-Meier estimates of survival in patients with lamivudine-resistant HBV by week 48 were 93 % and 84 % in patients post-liver transplantation and wait-listed for transplantation, respectively. These 1-year survival rates in study 435 are similar to or better than survival rates reported in the literature in pre- and post-liver transplantation patients with HBV treated with HBIg or lamivudine in patients without resistant HBV mutations and are significantly better than survival rates in patients with no treatment. In a recent retrospective study of 166 chronic hepatitis B patients pre- and post-liver transplantation, Kaplan-Meier estimates of HBV recurrence-free survival rates at 1 year were 75 % in patients treated with lamivudine, 60 % in patients treated with HBIg alone, 94 % in patients treated with lamivudine and HBIg in combination and 45 % in patients with no treatment.

Long-term data with a median of 56 weeks and up to 129 weeks confirmed the antiviral and clinical benefit of adefovir dipivoxil in pre and post-liver transplantation patients resistant to lamivudine who are at high risk for morbidity and mortality.

Supportive studies

Results from 3 supportive studies conducted in lamivudine-resistant chronic hepatitis B infected patients were provided (studies 461, 460i and 465) to evaluate the efficacy in terms of virological response of adefovir dipivoxil either used in substitution or in intensification to lamivudine therapy.

Resistance to lamivudine was defined as failure to lamivudine therapy, as evidenced by genotypic characterisation of YMDD variants. Further information on the design of these studies is displayed in table 2.

Efficacy results

Study 461:

This randomised, double blind, active-controlled study aimed to evaluate the safety and efficacy of adefovir dipivoxil 10 mg with or without lamivudine in patients with compensated liver disease and lamivudine-resistant HBV. Results up to 48 weeks on 58 patients were provided and are displayed below.

Study 461: Serum HBV DNA DAVG at Weeks 16 and 48			
HBV DNA (log_{10} copies/ml)	**LAM (n=19)**	**LAM+ADV* (n=20)**	**ADV* (n=19)**
Median $DAVG_{16}$ (range)	-0.07 (-1.13 to 0.33)	-2.45 (-3.58 to –1.11)	-2.46 (-5.09 to –1.70)
Median $DAVG_{48}$ (range)	0.05 (-1.12 to 0.35)	-2.93 (-4.74 to –2.17)	-3.06 (-5.07 to –1.67)

* $P < 0.001$ (Wilcoxon Rank Sum Test) compared to lamivudine

Based on these results, adefovir alone or in combination with lamivudine resulted in a significant reduction in median serum HBV DNA levels from baseline but the clinical significance of these changes is unknown. No additional benefit is expected when adding adefovir to lamivudine therapy versus substituting, but this finding derives from a limited sample size and cannot lead to reliable conclusions.

Study 460i

This open-label, investigator-initiated (single centre) pilot study evaluated the efficacy of adefovir dipivoxil 10 mg once daily in addition to lamivudine therapy in 35 patients with lamivudine-resistant chronic hepatitis B co-infected with HIV. The mean baseline HBV DNA concentration was 8.64-log10 copies/ml. Median time on lamivudine at randomisation was 42.3 months (9-81 months). At the time of reporting, the median time on adefovir dipivoxil was 72 weeks (68-72 weeks). The addition of adefovir dipivoxil resulted in a significant reductions in serum HBV DNA throughout the course of treatment. The mean change from baseline was -3.40 log_{10} copies/ml at week 24, -4.07 log_{10} copies/ml at week 48 and -4.77 log_{10} copies/ml at week 72. ALT normalisation at week 72 occurred in 25 % of patients.

Study 465:

Preliminary 52-week data have been provided for 46 patients of Stratum B, i.e patients with HBeAg positive or negative with decompensated liver disease who received in an open label manner adefovir dipivoxil 10 mg in addition to lamivudine.
Consistent antiviral response was seen across all patients, with a median reduction in HBV DNA of 4.6-log10 copies/ml after 52 weeks of treatment. Improvement in liver function was also seen after one year of treatment.

Resistance sub-studies

Resistance sub-studies were performed in the frame of the main studies 437 (wild type virus), 438 (presumed pre-core mutant) and in study 435 (pre and post liver transplant patients resistant to lamivudine) and on study 460i (lamivudine resistant HIV co-infected). The methodology used was robust. It consisted of the genotypic analysis of emergence of mutations in HBV reverse transcriptase domain accompanied by in vitro phenotypic analysis of the impact of conserved site mutations on the adefovir susceptibilityand were correlated to serum HBV DNA. No adefovir resistant HBV polmerase mutations were identified in these studies after 48 weeks of adefovir dipivoxil therapy. The risk of selection of HIV strains resistant to adefovir with possible cross-resistance to other antiviral medicinal

products is low but cannot be excluded. The applicant committed to continue prospective surveillance programme for the emergence of resistance.

Clinical studies in special populations

Considering the need for therapeutic options in children and the attractive resistance profile of the drug, the Applicant committed to investigate pharmacokinetics, efficacy and safety of adefovir in paediatric patients.

Clinical safety

The safety database derived from the following studies:

- Randomised, placebo-controlled studies 437 and 438 in wild-type and presumed pre-core mutant infected patients with compensated disease
- Four studies of adefovir 10 mg in patients with resistance to lamivudine (YMDD mutated virus)
- Data from phase I/II pharmacokinetic/pharmacodynamic programme (studies 404, 412 and 413) in which patients received doses ranging from 5 to 125 mg adefovir
- An additional safety study 451i in patients with pre/post orthotopic liver transplant

In additional adefovir dipivoxil was previously evaluated over 10,000 HIV-infected patients at doses ranging from 60 to 500 mg. As already mentioned because of the dose limiting nephrotoxicity which developed with doses 6 to 12 fold the recommended dose in the treatment of hepatitis B, the development was interrupted.

Patient exposure

Overall out of 522 patients including in studies 437 and 438, 294 received adefovir dipivoxil 10 mg during 48 weeks and 228 received placebo. With extended therapy, 492 of these 522 patients were treated with 10 mg adefovir dipivoxil for up to 109 weeks, with a median duration of 49 weeks.

In lamivudine resistant patients, the overall estimated exposure to adefovir treatment is 523 for more than 48 weeks, 316 for more than 72 weeks and 79 for more that 96 weeks.

The safety assessment described below focuses mainly on the first 48 weeks of the main randomised, double blind, and placebo-controlled studies 437 and 438. As already mentioned, discontinuation due adverse events in these studies was very limited.
Most of studies in lamivudine-resistant patients were open and conducted in severely impaired patients, which render the interpretation of the results difficult.

Adverse events and serious adverse event/deaths

During the first 48 weeks of pivotal studies, 82 % of patients from the 10 mg arm experienced at least one adverse event compared to 85 % in the placebo and 95 % in the 30 mg arms.
The number of patients with related adverse events was 50 % in the placebo group compared to 45 % in adefovir 10 mg group.
The most frequently related adverse events (> 3 %) reported during the first 48 weeks were as follows (table 9):

Table 9: Comparative incidences vs placebo of most frequent related AE (≥ 1%)/ADV10 mg/combined studies 437 + 438						
Adverse Event	**Placebo (0-48 weeks) (N=228)**		**ADV 10 mg (0-48 weeks) (N=294)**		**All ADV 10 mg (0-96 weeks) (N=492)**	
	n	(%)	n	(%)	N	(%)
No of Patients with Related AEs	115	(50%)	132	(45%)	175	(36%)
Asthenia	33	(14%)	39	(13%)	49	(10%)
Headache	23	(10%)	27	(9%)	38	(8%)
Abdominal pain	24	(11%)	27	(9%)	37	(8%)
Nausea	19	(8%)	16	(5%)	21	(4%)
Flatulence	9	4 %	11	4 %	11	2 %
Diarrhoea	8	4 %	8	3 %	9	2 %
Dyspepsia	5	2 %	9	3 %	9	2 %

The incidence of adverse events was comparable in patients with HBeAg positive and negative.

Results were similar in phase I/II studies and in studies conducted in lamivudine resistant patients.

Safety data from study 437 showed that 30 mg dose of adefovir dipivoxil exhibited a less favourable tolerance profile when compared to the 10 mg daily dose, with a higher incidence of adverse events (95 % versus 87 %), particularly decreases in phosphataemia (6 % versus 1 %).

Serious adverse events and deaths

In studies 437 and 438, 13 patients (4 %) in the adefovir 10 mg group experienced a serious adverse event compared to 12 patients (5 %) in the placebo. There was no single event type which occurred in more than one patient except chest pain which occurred in 2 patients in the adefovir group.

There were no deaths reported in studies 437 and 438 at the cut-off dates, however 3 deaths have been reported afterwards (1 sepsis and liver failure in a patient receiving 30 mg adefovir, 1 cardiac failure in patient receiving adefovir 10 mg and 1 mycosis septicaemia due to immunosuppresant treatment after liver transplantation in patient receiving adefovir 10 mg). The deaths were considered probably related to the underlying disease.

In study 435, serious adverse events and deaths reported in pre-liver and post-liver transplantation were not unexpected in term of incidence or nature given the extreme severe patients population with end-stage disease and given the underlying disease or complications. The serious adverse events related to adefovir accounted for 5 % in cohort A and 4 % in cohort B.

Laboratory findings

During the first 48-week phase of studies 437 and 438, ALT and AST elevations were reported in 1 % and < 1 % in the adefovir dipivoxil 10 mg group versus 5 % and 4 % in the placebo group. Elevations were almost equally distributed among grading sub-classes (grade 1 to 4).
Although liver was a target organ in toxicology studies, ALT elevation of > 5 ULN, > 10 ULN and > 20 ULN occurred more often in the placebo group (24 % versus 14 %, 14 % versus 6 % and 3 % versus < 1%, respectively), and were not accompanied by changes in liver function parameters, which is strongly in favour of viral clearance and not hepatic toxicity related to adefovir dipivoxil.

ALT elevations post treatment withdrawal were observed in both studies 437 and 438, especially during year 2 in the group of patients having switched from adefovir dipivoxil 10 mg (36 elevations > 10 ULN) or adefovir dipivoxil 30 mg to placebo. Peak values generally occurred from 4 to 12 weeks post treatment discontinuation. Preliminary data in patients with decompensated hepatitis (studies 435 and 465) did not evidence any risk of fulminant hepatitis in these patients following treatment withdrawal although follow-up data are limited. As a precautionary measure, a warning that careful monitoring of patients following treatment discontinuation is therefore included in the Summary of Product Characteristics.

Other laboratory abnormalities, including hypophosphataemia occurred in less than 1% patients in each treatment group, with the exception of haematuria (6 % in adefovir dipivoxil 10 mg versus 8 % placebo).

Renal tolerance

The key safety concern was renal toxicity as evidenced by impairment of both glomerular filtration (increase in creatinine levels and decrease in phosphataemia) and tubular secretion (increase in proteinuria and glycosuria), during the development in HIV patients and by nephrotoxicity reported with other nucleotide analogues. It has been characterised using preclinical data in several species. It is primarily manifested by the onset of gradual increases in serum creatinine and decreases in serum phosphorus with a delayed onset generally after 20 weeks or more of therapy. The changes can be accompanied by changes in serum bicarbonate, glycosuria, and proteinuria. In HIV infected patients, the risk for development and maximum severity of renal abnormalities was significantly less in patients treated with adefovir dipivoxil at the dose of 60 mg than at the dose of 120 mg once daily. The incidence appears to be dose dependent while the time of onset appears to be similar and independent of dosage.

During the first 48-week course of placebo-controlled trials, there was no evidence of adefovir dipivoxil 10 mg daily dose-induced renal insufficiency as assessed by comparative changes in serum creatinine and phosphorus levels and by comparative grade distribution of abnormalities versus placebo. There was no evidence of adefovir dipivoxil 10 mg daily dose-induced proximal tubulopathy, as assessed by comparative levels of glycosuria, proteinuria, hypouricaemia and hypokalaemia, and by comparative grade distribution of abnormalities versus placebo.

By contrast study 437 showed a nephrotoxicity in the 30 mg adefovir dipivoxil arm, with a higher incidence versus placebo of:

- ➜ increases in serum creatinine by 5 mg/l (21% in adefovir dipivoxil 30 mg arm versus 1% in 10 mg arm versus 0 % in placebo),
- ➜ decreases in serum phosphorus down to > 20 mg/ml (16% in adefovir dipivoxil 30 mg arm versus 3% in 10 mg arm versus 4 % in placebo),
- ➜ grade 1 creatinine elevation (10% in adefovir dipivoxil 30 mg arm versus 1% in 10 mg arm versus 0% in placebo)
- ➜ grades 1 and 2 proteinuria (35% in adefovir dipivoxil 30 mg arm versus 20% in 10 mg arm versus 17 % placebo).

With the extended treatment, increased in serum creatinine > 0.5 mg/dl from baseline was reported in 2 patients out of 492 (<1 %) treated with 10 mg adefovir dipovoxil. Both increases resolved, in one case with continuation of treatment and in one case following discontinuation of treatment.
At the proposed dose of 10 mg once daily, nephrotoxicity does not appear to be a major problem, however as a precautionary measure a warning has been included in the Summary of Product Characteristics to exercise caution in patients with creatinine clearance below 50 ml/min and in patients receiving medicinal products that may affect renal function. In addition it is recommended to frequently monitor renal function in patients with normal renal function. In addition the applicant committed to further monitor during the post-marketing surveillance.

Carnitine loss

Dose-related reduction in serum carnitine levels was observed in the preclinical studies in monkeys and in clinical studies in HIV-infected patients when adefovir was used at high doses. In study 437, the placebo and adefovir 10 mg arms were further randomised to 250 mg- L-carnitine daily or placebo carnitine. There was no evidence of carnitine loss and therefore L-carnitine supplementation is not necessary.

Mitochondrial toxicity

There was no evidence of mitochondrial toxicity (neuropathy, cardiomyopathy, pancreatitis, lactic acidosis), as assessed by elevations in lactic acid, CPK or amylase. Since adefovir belongs to a class

close to the nucleoside analogues for which mitochodrial toxicity has been reported, adequate warning is included in the Summary of Product Characteristics including guidance on how to differentiate increase ALT levels due to efficacy and those due to lactic acidosis. In addition the applicant committed to further monitor during the post-marketing surveillance.

Safety in special populations

Safety evaluation was performed in a number of subgroups of patients treated with adefovir dipivoxil 10 mg once daily and placebo during the first 48 weeks double blind treatment period of studies 437 and 438. There was no noteworthy interaction between age, race, gender, ALT levels and Knodell score and the incidence or seriousness of adverse events between treatment groups.

The safety of adefovir dipivoxil in children has not been established but the applicant committed to perform clinical studies in this population.
Apart from the exclusion/precaution related to hepatotoxic and nephrotoxic drugs, no clinical relevant drug interactions have been identified in clinical studies.

4. Overall conclusions, benefit/risk assessment and recommendation

Quality

The active substance has been well characterised and documented. The pharmaceutical form selected is adequate taking into account the properties and stability of the active substance. The excipients are commonly used in this kind of formulation and the packaging material is well documented. The manufacturing process for finished product batches is consistent and reproducible. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CPMP opinion there were some outstanding minor quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

Preclinical pharmacology and toxicology

Adefovir dipivoxil presented an antiviral activity both *in vitro* and *in vivo* compatible with a potential clinical use for the treatment of HBV infection. In safety pharmacology studies, adefovir dipivoxil caused a decrease in urine volume and electrolyte excretion and a decrease in gastric emptying in rats. No pharmacological effects were seen on the central nervous system in rats or cardiovascular system in dogs.

The pharmacokinetic profile of adefovir dipivoxil has been adequately characterised in several species. Following oral administration, adefovir dipivoxil is rapidly metabolised via non-specific esterases to adefovir via the monoester. No other metabolites have been observed *in vitro* or *in vivo* and adefovir does not inhibit CYP450 system. Adefovir was excreted unchanged via renal route in all animal species tested.

The toxicological profile of adefovir and adefovir dipivoxil was assessed in several species in a complete battery of tests. The principal target organs of toxicity were the kidney, gastrointestinal tract, liver, and lymphoid tissues (including bone marrow). Nephrotoxicity, characterised by renal tubular nephropathy in all species evaluated, was the primary dose-limiting toxicity in the rats or monkeys. Liver and lymphoid tissues were the most sensitive target organs in mice. The dermal lesions at non injection sites observed in monkeys will be further investigated by the applicant as part of follow-up measures to be fulfilled post-authorisation.

Adefovir dipivoxil had no effects on male or female fertility, or reproductive performance in rats and was neither embryotoxic nor teratogenic in pregnant rabbits. The administration of adefovir intravenously in pregnant rats resulted in embryotoxicity, increased incidence of foetal malformations and common variations, but only at maternally toxic doses. Adefovir dipivoxil should therefore only been used in pregnant women if the potential benefit justifies the risk for the foetus.
In *in vitro* genetic toxicity studies, adefovir was negative in the bacterial mutation assay and positive in the chromosome aberration assay in human peripheral blood lymphocytes. Adefovir dipivoxil was positive in the mouse lymphoma assay and negative in the *in vivo* mouse micronucleus assay. Adefovir dipivoxil was not carcinogenic in the mouse or rat studies. The profile of adefovir and adefovir dipivoxil in genetic toxicity and carcinogenicity is therefore similar to nucleoside analogues in that it induces chromosomal aberrations (but not point mutations) *in vitro* but is not genetoxic or carcinogenic in *in vivo* models.

Clinical efficacy

The pharmacokinetics profile of adefovir dipivoxil was adequately defined in healthy volunteers and patients with HBV infection. After oral administration, adefovir dipivoxil undergoes a rapid hydrolysis yielding adefovir during and following absorption process in the gastrointestinal tract. Oral bioavailability of 10 mg adefovir dipivoxil is estimated at 59 % and is unaffected by food, which supports the use of adefovir dipivoxil either with or without food. Of interest the metabolism of adefovir dipivoxil did not interfere with the CYP450 system, which limits the potential for pharmacokinetic interactions. No relevant interaction was shown with antiretroviral medicinal products. Adefovir is eliminated unchanged by the kidneys via tubular secretion. Substances undergoing tubular secretion such as lamivudine did not alter the pharmacokinetics profile. Preclinical studies showed that the human renal organic anion transporter 1 (hOAT1) presumably played an essential role in the active tubular secretion. No interaction studies have been performed with substances known to share the transporter and therefore a warning has been included in the Summary of Product Characteristics. In addition the applicant committed to provide post-authorisation results of further interaction studies, including nephrotoxic substances. Based on limited data dose interval adjustments are recommended in patients with moderate and severe renal impairment and in patients with en stage renal disease requiring haemodialysis as reflected in the Summary of Product Characteristics. As these recommendations may not be optimal the applicant committed to complete dosing guidance by providing post-authorisation further data in HBV infected patients affected with various degree of renal impairment. No dosage modifications are required in patients with hepatic impairment. The pharmacokinetic profile of adefovir dipivoxil has not yet been evaluated in children.

Adefovir diphosphate exhibits a long intracellular half-life (12 to 36 hours in lymphocytes) justifying once daily dosage regimen. Adefovir dipivoxil was shown to be effective in phase II studies. In these studies, the dose of 10 mg once daily provided an acceptable level of efficacy and did not induce any nephrotoxicity compared to the 30 mg dose and therefore was selected as the dose in the main clinical studies. The choice of the dose was further substantiated by a dose-modelling curve. The results of the main studies confirm that this dose exhibits an adequate benefit/risk ratio. However, since the 30 mg exhibited a higher response especially in term of reduction in serum HBV DNA (approximately 1 $\log_{10}$copies/ml), the applicant committed to further investigate, as a post approval commitment, whether an intermediate dose (20 mg) could provide a better efficacy profile than the recommended 10 mg dose with an acceptable safety profile. In addition other pharmacodynamic outstanding issues were identified which will be resolved as follow-up measures to be fulfilled post-authorisation.
The clinical benefit of adefovir dipivoxil is mainly based on the results of two main randomised, double-blind, placebo-controlled studies in non lamivudine-resistant HBeAg positive and negative HBV infected patients, the majority of these patients had fibrosis at baseline. Data up to 48 weeks showed that adefovir dipivoxil induced a statistically significant improvement in liver histology, a suitable primary endpoint allowing direct assessment of both responses to treatment and disease structural progression. In HBeAg positive patients, a highly statistically significant ($p<0.001$) 2 points improvement in the Knodell necro-inflammatory score, with no concurrent worsening of fibrosis, was observed in 53% of patients in the adefovir dipivoxil 10 mg arm versus 25% in the placebo group. The corresponding results in HBeAg negative patients were 64% in adefovir dipivoxil arm versus 33% in the placebo arm. Histological improvement was seen regardless of baseline demographic and hepatitis

B characteristics, including prior interferon-alpha therapy. Assessment of the change in fibrosis after 48 weeks treatment using the Knodell fibrosis scores confirmed that patients treated with adefovir dipivoxil 10 mg had more regression and less progression of fibrosis than patients treated with placebo. In addition, for both studies 48-week data showed a statistically significant decrease in viral load (3.52 and 3.91 log_{10} copies/ml in the adefovir dipivoxil arms versus 0.55 and 1.35 log_{10} copies/ml in placebo arm) and increased proportion of patients with normalisation of ALT (48 and 72 % in the adefovir dipivoxil arm versus 16 and 29 % in placebo arm). 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. Baseline characteristics did not seem to have an impact on the response since statistically significant response rates were observed in all sub-groups of patients even if higher rates for histological improvement was observed in patients with elevated baseline Knodell score (> 10), elevated ALT levels (2 x ULN) and relatively low HBV DNA levels (< 7.6 log_{10} copies/ml).

72 weeks efficacy data (open label follow-up) confirm the virological, biochemical, and serological efficacy demonstrated by 48-week data and show additional benefit from extended treatment duration, in particular 23 % patients of the 288 evaluable patients of study 437 (n = 66) versus 14 % at week 48 experienced HBeAg seroconversion.

In addition the clinical benefit of adefovir dipivoxil was shown in lamivudine resistant HBV infected patients:

- In a clinical study in 324 chronic hepatitis B patients with lamivudine-resistant HBV (pre-liver transplantation (n=128) and post-liver transplantation (n=196)), treatment with 10 mg adefovir dipivoxil resulted in a median reduction in serum HBV DNA of 4.1 and 4.3-log10 copies/ml respectively, at week 48.
- In a double blind, comparative study patients with compensated liver disease and lamivudine-resistant HBV (n=58), 48 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_{10} copies/ml and 3.59 log_{10} copies/ml, respectively).
- 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_{10} copies/ml. Improvement in liver function was also seen after one year of therapy.
- In an open-label investigator study in 35 chronic hepatitis B patients with lamivudine-resistant HBV and co-infected with HIV, treatment with 10 mg adefovir dipivoxil resulted in reduction in serum HBV DNA levels throughout the course of treatment up to 72 weeks (median reduction in HBV DNA from baseline at 72 weeks of 4.77 log_{10} copies/ml). Further data in HBV-HIV co-infected patients will be provided.

Clinical outstanding issues were identified which will be resolved as follow-up measures to be fulfilled post-authorisation such as long term efficacy data, long term data on the rate of sustained response, the efficacy of combination therapy and the optimal use of adefovir dipivoxil in lamivudine resistant patients either as on add-on therapy to lamivudine or as substitution. In addition the optimal treatment duration and the predictors for response/non response will be further investigated.

The genotypic and phenotypic data derived from the clinical studies did not show any mutation induced resistance associated with the use of adefovir dipivoxil but the applicant committed to continue the ongoing prospective surveillance programme for the emergence of resistance.

The clinical benefit in children and adolescents is currently unknown but the applicant presented a paediatric programme, the results of which will be submitted post-authorisation.

Safety

Overall adefovir dipivoxil at the dose of 10 mg once daily was well tolerated in over 1,000 patients treated up to 109 weeks. The undesirable effects reported related mainly to headache, asthenia and gastro-intestinal effects. The safety profile was similar in all different types of HBV infected patients evaluated in the clinical studies (HBeAg positive, negative, resistant to lamivudine and HIV co-infected). From the previous clinical development in HIV nephrotoxicity and carnitine loss were identified as potential toxicities with adefovir dipivoxil but in the clinical studies, at the dose of 10 mg there was no evidence for these toxicities. Close monitoring of patients is however recommended. Although liver was identified in the toxicological studies as a target organ, there was no evidence for liver toxicity in the clinical studies. As adefovir dipivoxil belongs to a class close to nucleoside analogues for which mitochondrial toxicity has been reported, a warning has been included in the Summary of Product Characteristics. The applicant committed to provide long term safety data, with particular focus on mitochondrial toxicity and renal toxicity.

Benefit/risk assessment

The clinical development is comprehensive with the assessment of the efficacy and safety of adefovir dipivoxil in several sub-populations of patients which chronic hepatitis B such as treatment naïve and lamivudine resistant HBV infected patients, including patients identified as difficult to treat (i.e. pre-core mutant, transplanted patients, decompensated and HIV co-infected patients). Overall the efficacy was consistent whatever the type of response (histological, virological biochemical, serological or clinical) the disease subtype (HBeAg positive, negative compensated or not) and the virus subtype (wild type or YMDD mutants associated with lamivudine resistance).

The population included in studies 437 and 438 had evidence of active viral replication (e.g HBV DNA ≥ 100,000 copies/ml) and elevated serum ALT (e.g ≥ 1.2 ULN) and the superiority of adefovir dipivoxil versus placebo was demonstrated regardless of baseline characteristic. However in view of the remaining questions on long term data, particularly with respect to sustained response, the risk of delayed emergence of resistance, and the duration of treatment, the CPMP was of the opinion that treatment with adefovir dipivoxil should be restricted to patients strictly requiring to be treated without delay, the goal of therapy being to hasten progression from stage 2, where fibrosis develops to stage 3 (HBeAg seroconversion).

In addition although results are very encouraging in lamivudine resistant patients, they need to be completed to further substantiate the efficacy of adefovir dipivoxil in these patients in order to make recommendations on the optimal therapeutic management (adefovir to be used in substitution or intensification of lamivudine therapy).

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Hepsera in the treatment of patients with chronic hepatitis B at the dose of 10 mg daily was favourable and therefore recommended the granting of the marketing authorisation in the following indication:

"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
- decompensated liver disease."