1. NAME OF THE MEDICINAL PRODUCT

Entevir 0.5 mg film-coated tablets
Entevir 1.0 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Entevir 0.5 mg film-coated tablets
Each film-coated tablet contains entecavir monohydrate equivalent to 0.5 mg entecavir.

Entevir 1.0 mg film-coated tablets
Each film-coated tablet contains entecavir monohydrate equivalent to 1 mg entecavir.

Excipients with known effect
Each 0.5 mg film-coated tablet contains approximately 121 mg lactose monohydrate.
Each 1 mg film-coated tablet contains 242 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Entevir 0.5 mg film coated tablets
White to off white triangular-shaped tablets debossed with "0.5" on one side, with the following dimensions median 8.4mm±0.2 mm and thickness 3.7mm±0.3 mm.

Entevir 1.0 mg film coated tablets
Pink triangular-shaped tablets debossed with "1" on one side, with the following dimensions median 10.6mm±0.2 mm and thickness 4.5mm±0.3 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

The following points should be considered when initiating therapy with Entevir:
• This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside-treatment-naïve and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative chronic HBV infection with compensated liver disease.
• Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease (see section 4.4).
• Virologic, biochemical, serologic, and safety data are available for a limited number of adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy (see sections 4.2, 4.4 and 5.1).

Paediatric population
Safety and effectiveness of entecavir in pediatric patients below the age of 16 years have not been established.

4.2 Posology and method of administration

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

Posology

Compensated liver disease

Nucleoside naïve patients: the recommended dose in adults and adolescents 16 years of age and older is 0.5 mg once daily, with or without food.

Lamivudine-refractory patients (i.e. with evidence of viraemia while on lamivudine or the presence of lamivudine resistance [LVDr] mutations) (see sections 4.4 and 5.1): the recommended dose in adults is 1 mg once daily, which must be taken on an empty stomach (at least 2 hours before and more than 2 hours after a meal) (see section 5.2).

Decompensated liver disease

The recommended dose for adult patients with decompensated liver disease is 1 mg once daily, which must be taken on an empty stomach (at least 2 hours before and more than 2 hours after a meal) (see section 5.2). For patients with lamivudine-refractory hepatitis B, see sections 4.4 and 5.1.

Duration of therapy
The optimal duration of treatment is unknown. Treatment discontinuation may be considered as follows:

- In HBeAg positive adult patients, treatment should be administered at least until 12 months after achieving HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection on two consecutive serum samples at least 3-6 months apart) or until HBs seroconversion or there is loss of efficacy (see section 4.4).
- In HBeAg negative adult patients, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

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

Elderly: no dosage adjustment based on age is required. The dose should be adjusted according to the patient's renal function (see dosage recommendations in renal impairment and section 5.2).

Gender and race: no dosage adjustment based on gender or race is required.

Renal impairment: the clearance of entecavir decreases with decreasing creatinine clearance (see section 5.2). Dose adjustment is recommended for patients with creatinine clearance < 50 ml/min, including those on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A reduction of the daily dose using entecavir oral solution, as detailed in the table, is recommended. As an alternative, in case the oral solution is not available, the dose can be adjusted by increasing the dosage interval, also shown in the table. If appropriate dose adjustment cannot be achieved with Entevir, entecavir oral solution may be checked for its availability.
The proposed dose modifications are based on extrapolation of limited data, and their safety and effectiveness have not been clinically evaluated. Therefore, virological response should be closely monitored.

Creatinine clearance (ml/min)	**Entevir dosage***	
	Nucleoside naïve patients	**Lamivudine-refractory or decompensated liver disease**
≥ 50	0.5 mg once daily	1 mg once daily

30 – <50	0.25 mg once daily* OR 0.5 mg every 48 hours	0.5 mg once daily OR 1 mg every 48 hours
10 – <30	0.15 mg once daily* OR 0.5 mg every 72 hours	0.3 mg once daily* OR 1 mg every 72 hours
< 10 Haemodialysis** or CAPD	0.05 mg once daily* OR 0.5 mg every 7 days	0.1 mg once daily* OR 01 mg every 7 days

* for doses < 0.5 mg entecavir, entecavir oral solution is recommended. Do not split tablets.
** on haemodialysis days, administer entecavir after haemodialysis.

Hepatic impairment: no dose adjustment is required in patients with hepatic impairment.

Method of administration

Oral use.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Renal impairment: dosage adjustment is recommended for patients with renal impairment (see section 4.2). The proposed dose modifications are based on extrapolation of limited data, and their safety and effectiveness have not been clinically evaluated. Therefore, virological response should be closely monitored.

Severe Acute Exacerbations of hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir [see Undesirable Effects (4.8)]. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Patients with decompensated liver disease: a higher rate of serious hepatic adverse events (regardless of causality) has been observed in patients with decompensated liver disease, in particular in those with Child-Turcotte-Pugh (CTP) class C disease, compared with rates in patients with compensated liver function. Also, patients with decompensated liver disease may be at higher risk for lactic acidosis and for specific renal adverse events such as hepatorenal syndrome. Therefore, clinical and laboratory parameters should be closely monitored in this patient population (see also sections 4.8 and 5.1).

Lactic acidosis and severe hepatomegaly with steatosis: occurrences of lactic acidosis (in the absence of hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues, including entecavir, alone or in combination with antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Lactic acidosis with entecavir use has also been reported in association with hepatic decompensation, other serious medical conditions, or drug exposures. Caution should be exercised when prescribing nucleoside analogues to any patient with hepatomegaly, hepatitis or other known risk factors for liver disease. Patients with decompensated liver disease may be at higher risk for lactic acidosis. Cases have also been reported in patients with no known risk factors. Treatment with nucleoside analogues should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). Benign digestive symptoms, such as nausea, vomiting and abdominal pain, might be indicative of lactic acidosis development. Severe cases, sometimes with fatal outcome, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate.

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

Resistance and specific precaution for lamivudine-refractory patients: mutations in the HBV polymerase that encode lamivudine-resistance substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with entecavir associated resistance (ETVr). In a small percentage of lamivudine-refractory patients, ETVr substitutions at residues rtT184, rtS202 or rtM250 were present at baseline. Patients with lamivudine-resistant HBV are at higher risk of developing subsequent entecavir resistance than patients without lamivudine resistance. The cumulative probability of emerging genotypic entecavir resistance after 1, 2, 3, 4 and 5 years treatment in the lamivudine-refractory studies was 6%, 15%, 36%, 47% and 51%, respectively. Virological response should be frequently monitored in the lamivudine-refractory population and appropriate resistance testing should be performed. In patients with a suboptimal virological response after 24 weeks of treatment with entecavir, a modification of treatment should be considered (see sections 4.5 and 5.1). When starting therapy in patients with a documented history of lamivudine-resistant HBV, combination use of entecavir plus a second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy.

Pre-existing lamivudine-resistant HBV is associated with an increased risk for subsequent entecavir resistance regardless of the degree of liver disease; in patients with decompensated liver disease, virologic breakthrough may be associated with serious clinical complications of the underlying liver disease. Therefore, in patients with both decompensated liver disease and lamivudine-resistant HBV, combination use of entecavir plus a second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy.

Human immunodeficiency virus (HIV)/HBV co-infected patients not receiving concomitant antiretroviral therapy: entecavir has not been evaluated in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment. Emergence of HIV resistance has been observed when entecavir was used to treat chronic hepatitis B infection in patients with HIV infection not receiving highly active antiretroviral therapy (HAART) (see section 5.1). Therefore, therapy with entecavir should not be used for HIV/HBV co-infected patients who are not receiving HAART. Entecavir has not been studied as a treatment for HIV infection and is not recommended for this use.

HIV/HBV co-infected patients receiving concomitant antiretroviral therapy: Before initiating entecavir therapy, HIV antibody testing should be offered to all patients. Entecavir has not been studied as a treatment for HIV infection and is not recommended for this use. Entecavir has been studied in 68 adults with HIV/HBV co-infection receiving a lamivudine-containing HAART regimen (see section 5.1). No data are available on the efficacy of entecavir in HBeAg-negative patients co-infected with HIV. There are limited data on patients co-infected with HIV who have low CD4 cell counts (< 200 cells/mm^3).

General: patients should be advised that therapy with entecavir has not been proven to reduce the risk of transmission of HBV and therefore appropriate precautions should still be taken.

Lactose: this medicinal product contains approximately 121 mg of lactose monohydrate in each 0.5 mg daily dose or 242 mg of lactose monohydrate in each 1 mg daily dose.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Since entecavir is predominantly eliminated by the kidney (see section 5.2), coadministration with medicinal products that reduce renal function or compete for active tubular secretion may increase serum concentrations of either medicinal product. Apart from lamivudine, adefovir dipivoxil and tenofovir disoproxil fumarate, the effects of coadministration of entecavir with medicinal products that are excreted renally or affect renal function have not been evaluated. Patients should be monitored closely for adverse reactions when entecavir is coadministered with such medicinal products.

No pharmacokinetic interactions between entecavir and lamivudine, adefovir or tenofovir were observed.

Entecavir is not a substrate, an inducer or an inhibitor of cytochrome P450 (CYP450) enzymes (see section 5.2). Therefore CYP450 mediated drug interactions are unlikely to occur with entecavir.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential: given that the potential risks to the developing foetus are unknown, women of childbearing potential should use effective contraception.

Pregnancy: there are no adequate data from the use of entecavir in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Entevir should not be used during pregnancy unless clearly necessary. There are no data on the effect of entecavir on transmission of HBV from mother to newborn infant.
Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV.

Breastfeeding: it is unknown whether entecavir is excreted in human milk. Available toxicological data in animals have shown excretion of entecavir in milk (for details see section 5.3). A risk to the infants cannot be excluded. Therefore, a decision should be made to discontinue nursing or to discontinue Entevir taking into consideration the importance of continued hepatitis B therapy to the mother and the known benefits of breastfeeding.

Fertility: toxicology studies in animals administered entecavir have shown no evidence of impaired fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Dizziness, fatigue and somnolence are common side effects which may impair the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile
In clinical studies in patients with compensated liver disease, the most common adverse reactions of any severity with at least a possible relation to entecavir were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%). Exacerbations of hepatitis during and after discontinuation of entecavir therapy have also been reported (see section 4.4 and *c. Description of selected adverse reactions*).

b. Tabulated list of adverse reactions
Assessment of adverse reactions is based on experience from postmarketing surveillance and four clinical studies in which 1,720 patients with chronic hepatitis B infection and compensated liver disease received double-blind treatment with entecavir (n = 862) or lamivudine (n = 858) for up to 107 weeks (see section 5.1). In these studies, the safety profiles, including laboratory abnormalities, were comparable for entecavir 0.5 mg daily (679 nucleoside-naive HBeAg positive or negative patients treated for a median of 53 weeks), entecavir 1 mg daily (183 lamivudine-refractory patients treated for a median of 69 weeks), and lamivudine.

Adverse reactions considered at least possibly related to treatment with entecavir are listed by body system organ class. Frequency is defined as very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$);

uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders:	rare: anaphylactoid reaction
Psychiatric disorders:	common: insomnia
Nervous system disorders:	common: headache, dizziness, somnolence
Gastrointestinal disorders:	common: vomiting, diarrhoea, nausea, dyspepsia
Hepatobiliary disorders	common: increased transaminases
Skin and subcutaneous tissue disorders:	uncommon: rash, alopecia
General disorders and administration site conditions:	common: fatigue

Cases of lactic acidosis have been reported, often in association with hepatic decompensation, other serious medical conditions or drug exposures (see section 4.4).

Treatment beyond 48 weeks: continued treatment with entecavir for a median duration of 96 weeks did not reveal any new safety signals.

c. Description of selected adverse reactions

Laboratory test abnormalities: frequencies of selected treatment-emergent laboratory abnormalities reported during therapy in four clinical trials of entecavir compared with lamivudine are tabulated below.

Selected Treatment-Emergent Laboratory Abnormalities Reported in Four Entecavir Clinical Trials

	Nucleoside-Naïve		**Lamivudine-Refractory**	
Test	**Entecavir 0.5 mg n=679**	**Lamivudine 100 mg n=668**	**Entecavir 1 mg n=183**	**Lamivudine 100 mg n=190**
Any Grade 3-4 laboratory abnormality	35%	36%	37%	45%
ALT >10 X ULN and >2 X baseline	2%	4%	2%	11%
ALT >5.0 X ULN	11%	16%	12%	24%
Albumin <2.5 g/dL	<1%	<1%	0	2%
Total bilirubin >2.5 X ULN	2%	2%	3%	2%
Lipase 2.1 X ULN	7%	6%	7%	7%
Creatinine >3.0 X ULN	0	0	0	0
Confirmed creatinine increase 0.5 mg/dL	1%	1%	2%	1%
Hyperglycemia, fasting >250 mg/dL	2%	1%	3%	1%
Glycosuria	4%	3%	4%	6%
Hematuria	9%	10%	9%	6%
Platelets <50,000/mm	<1%	<1%	<1%	<1%

Exacerbations during treatment: in studies with nucleoside naive patients, on treatment ALT elevations > 10 times ULN and > 2 times baseline occurred in 2% of entecavir treated patients vs 4% of lamivudine treated patients. In studies with lamivudine-refractory patients, on treatment ALT elevations > 10 times ULN and > 2 times baseline occurred in 2% of entecavir treated patients vs 11% of lamivudine treated patients. Among entecavir-treated patients, on-treatment ALT elevations had a median time to onset of 4-5 weeks, generally resolved with continued treatment, and, in a majority of cases, were associated with a ≥ 2 $\log_{10}$/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment.

Exacerbations after discontinuation of treatment: acute exacerbations (> 10 times ULN and > 2 times reference [minimum of baseline or last end-of-dosing measurement]) of hepatitis have been reported in patients who have discontinued anti-hepatitis B virus therapy, including therapy with entecavir (see section 4.4).

Subjects with ALT Elevations >10 X ULN and >2 X Reference*

	Entecavir	**Lamivudine**
Nucleoside-naïve		
• HBeAg-positive	4/174 (2%)	13/147 (9%)
• HBeAg-negative	24/302 (8%)	30/270 (11%)
Lamivudine-refractory	6/52 (12%)	0/16

*Reference is the minimum of the baseline or last measurement at end of dosing. Median time to off-treatment exacerbation was 23 weeks for Entecavir-treated subjects and 10 weeks for lamivudine-treated subjects.

In the clinical trials entecavir treatment was discontinued if patients achieved a prespecified response. If treatment is discontinued without regard to treatment response, the rate of post-treatment ALT flares could be higher. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

d. Other special populations

Experience in patients with compensated liver disease: The safety profiles of entecavir and lamivudine were comparable in these studies. The most common adverse reactions of any severity (≥3%) with at least a possible relation to study drug for entecavir-treated subjects were headache, fatigue, dizziness, and nausea. The most common adverse reactions among lamivudine-treated subjects were headache, fatigue, and dizziness. One percent of ENTECAVIR-treated subjects in these four studies compared with 4% of lamivudine-treated subjects discontinued for adverse events or abnormal laboratory test results. Clinical adverse reactions of moderate-severe intensity and considered at least possibly related to treatment occurring during therapy in four clinical studies in which entecavir was compared with lamivudine are presented in Table below.

Clinical Adverse Reactions of Moderate-Severe Intensity (Grades 2-4) Reported in Four Entecavir Clinical Trials				
	Nucleoside-Naive		Lamivudine-Refractory	
Body System/ Adverse Reaction	**Entecavir 0.5 mg n=679**	**Lamivudine 100 mg n=668**	**Entecavir 1 mg n=183**	**Lamivudine 100 mg n=190**
Any Grade 2-4 adverse reaction	15%	18%	22%	23%
Gastrointestinal				
Diarrhea	<1%	0	1%	0
Dyspepsia	<1%	<1%	1%	0
Nausea	<1%	<1%	<1%	2%

Vomiting	<1%	<1%	<1%	0
General				
Fatigue	1%	1%	3%	3%
Nervous System				
Headache	2%	2%	4%	1%
Dizziness	<1%	<1%	0	1%
Somnolence	<1%	<1%	0	0
Psychiatric				
Insomnia	<1%	<1%	0	<1%

Experience in patients with decompensated liver disease: the safety profile of entecavir in patients with decompensated liver disease was assessed in a randomized open-label comparative study in which patients received treatment with entecavir 1 mg/day (n = 102) or adefovir dipivoxil 10 mg/day (n = 89) (study 048).The most common treatment-emergent adverse events from entecavir treatment of any severity, regardless of causality, occurring through week 48 were peripheral edema (16%), ascites (15%), pyrexia (14%), hepatic encephalopathy (10%), and upper respiratory infection (10%). Clinical adverse reactions observed include blood bicarbonate decreased (2%) and renal failure (<1%). 18% subjects on entecavir treatment and 20% subjects on adefovir dipivoxil treatment died during the first 48 weeks of therapy. Majority of deaths (11 in the entecavir group and 16 in the adefovir dipivoxil group) were due to liver-related causes such as hepatic failure, hepatic encephalopathy, hepatorenal syndrome, and upper gastrointestinal hemorrhage. The rate of hepatocellular carcinoma (HCC) through Week 48 was 6% for entecavir treatment and 8% for adefovir dipivoxil treatment arm. 5% of subjects in either treatment arm discontinued therapy due to an adverse event through Week 48. No subject in either treatment arm experienced an on-treatment hepatic flare (ALT >2 X baseline and >10 X ULN) through Week 48. 11% subjects on entecavir treatment and 13% subjects on adefovir dipivoxil treatment had a confirmed increase in serum creatinine of 0.5 mg/dL through Week 48.

Experience in patients co-infected with HIV: the safety profile of entecavir in HIV/HBV co-infected subjects was similar to that of placebo through 24 weeks of blinded treatment and similar to that seen in non-HIV infected subjects.

Liver Transplant Recipients
Among 65 subjects receiving Entecavir in an open-label, post-liver transplant trial, the frequency and nature of adverse events were consistent with those expected in patients who have received a liver transplant and the known safety profile of entecavir. No subjects had HBV DNA values ≥50 IU/mL while receiving entecavir (plus hepatitis B immune globulin). All 61 evaluable subjects lost HBsAg post-transplant; 2 of these subjects experienced recurrence of measurable HBsAg without recurrence of HBV viremia. If Entecavir treatment is determined to be necessary for a liver transplant recipient who has received or is receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus, renal function must be carefully monitored both before and during treatment with entecavir.

Postmarketing Experience
The following adverse reactions have been voluntarily reported during postmarketing use of entecavir. These reports cannot be used to reliably estimate their frequency or establish a causal relationship to entecavir exposure:
Immune system disorders: anaphylactoid reaction.
Metabolism and nutrition disorders: lactic acidosis.
Hepatobiliary disorders: increased transaminases.
Skin and subcutaneous tissue disorders: alopecia, rash.

4.9 Overdose

There is limited experience of entecavir overdose reported in patients. Healthy subjects who received up to 20 mg/day for up to 14 days, and single doses up to 40 mg had no unexpected adverse reactions. If overdose occurs, the patient must be monitored for evidence of toxicity and given standard supportive treatment as necessary. Following a single 1 mg dose of entecavir, a 4-hour hemodialysis session removed approximately 13% of the entecavir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF10

Mechanism of action: entecavir, a guanosine nucleoside analogue with activity against HBV polymerase, is efficiently phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine TP, entecavir-TP functionally inhibits the 3 activities of the viral polymerase: (1) priming of the HBV polymerase, (2) reverse transcription of the negative strand DNA from the pregenomic messenger RNA, and (3) synthesis of the positive strand HBV DNA. The entecavir-TP K_i for HBV DNA polymerase is 0.0012 μM. Entecavir-TP is a weak inhibitor of cellular DNA polymerases α, β, and δ with K_i values of 18 to 40 μM. In addition, high exposures of entecavir had no relevant adverse effects on γ polymerase or mitochondrial DNA synthesis in HepG2 cells (K_i > 160 μM).

Antiviral activity: entecavir inhibited HBV DNA synthesis (50% reduction, EC_{50}) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC_{50} value for entecavir against LVDr HBV (rtL180M and rtM204V) was 0.026 μM (range 0.010-0.059 μM).
Recombinant viruses encoding adefovir-resistant substitutions at either rtN236T or rtA181V remained fully susceptible to entecavir.

An analysis of the inhibitory activity of entecavir against a panel of laboratory and clinical HIV-1 isolates using a variety of cells and assay conditions yielded EC_{50} values ranging from 0.026 to > 10 μM; the lower EC_{50} values were observed when decreased levels of virus were used in the assay.
In cell culture, entecavir selected for an M184I substitution at micromolar concentrations, confirming inhibitory pressure at high entecavir concentrations. HIV variants containing the M184V substitution showed loss of susceptibility to entecavir (see section 4.4).

In HBV combination assays in cell culture, abacavir, didanosine, lamivudine, stavudine, tenofovir or zidovudine were not antagonistic to the anti-HBV activity of entecavir over a wide range of concentrations. In HIV antiviral assays, entecavir at micromolar concentrations was not antagonistic to the anti-HIV activity in cell culture of these six NRTIs or emtricitabine.

Resistance in cell culture: In cell-based assays, 8- to 30-fold reductions in entecavir phenotypic susceptibility were observed for lamivudine-resistant strains. Further reductions (>70-fold) in entecavir phenotypic susceptibility required the presence of amino acid substitutions rtM204I/V with or without rtL180M along with additional substitutions at residues rtT184, rtS202, or rtM250, or a combination of these substitutions with or without an rtI169 substitution in the HBV reverse transcriptase.

Lamivudine-resistant strains harboring rtL180M plus rtM204V in combination with the amino acid substitution rtA181C conferred 16- to 122-fold reductions in entecavir phenotypic susceptibility.

Clinical Studies: the demonstration of benefit is based on histological, virological, biochemical, and serological responses after 48 weeks of treatment in active-controlled clinical trials of 1,633 adults with chronic hepatitis B infection, evidence of viral replication and compensated liver disease. The safety and efficacy of entecavir were also evaluated in an active-controlled clinical trial of 191 HBV-infected patients with decompensated liver disease and in a clinical trial of 68 patients co-infected with HBV and HIV.

In studies in patients with compensated liver disease, histological improvement was defined as a ≥ 2-point decrease in Knodell necro-inflammatory score from baseline with no worsening of the Knodell fibrosis score. Responses for patients with baseline Knodell Fibrosis Scores of 4 (cirrhosis) were comparable to overall responses on all efficacy outcome measures (all patients had compensated liver disease). High baseline Knodell necroinflammatory scores (> 10) were associated with greater histological improvement in nucleoside-naive patients. Baseline ALT levels ≥2 times ULN and baseline HBV DNA ≤9.0 $\log_{10}$ copies/ml were both associated with higher rates of virologic response (Week 48 HBV DNA < 400 copies/ml) in nucleoside-naive HBeAg-positive patients. Regardless of baseline characteristics, the majority of patients showed histological and virological responses to treatment.

Experience in nucleoside-naive patients with compensated liver disease:
Results at 48 weeks of randomised, double blind studies comparing entecavir (ETV) to lamivudine (LVD) in HBeAg positive (022) and HBeAg negative (027) patients are presented in the table.

Histologic Improvement and Change in Ishak Fibrosis Score at Week 48:

	Nucleoside Naive			
	HBeAg Positive (study 022)		HBeAg Negative (study 027)	
	ETV 0.5 mg once daily	LVD 100 mg once daily	ETV 0.5 mg once daily	LVD 100 mg once daily
n	314[a]	314[a]	296[a]	287[a]
Histological improvement[b]	72%*	62%	70%*	61%
Ishak fibrosis score improvement	39%	35%	36%	38%
Ishak fibrosis score worsening	8%	10%	12%	15%

Selected Virologic, Biochemical, and Serologic Endpoints at Week 48:

	Nucleoside Naive			
	HBeAg Positive (study 022)		HBeAg Negative (study 027)	
	ETV 0.5 mg once daily	LVD 100 mg once daily	ETV 0.5 mg once daily	LVD 100 mg once daily
n	354	355	325	313
HBV DNA undetectable (< 300 copies/ml by PCR)[c]	67%*	36%	90%*	72%
Viral load reduction ($\log_{10}$ copies/ml)[c] from baseline	- 6.86*	-5.39	-5.04*	-4.53
ALT normalisation (≤ 1 times ULN)	68%*	60%	78%*	71%
HBeAg Seroconversion	21%	18%	NA	NA

*p value vs lamivudine < 0.05
[a] patients with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥ 2)
[b] a primary endpoint
[c] Roche Cobas Amplicor PCR assay (LLOQ = 300 copies/ml)

Experience in lamivudine-refractory patients with compensated liver disease:
In a randomised, double-blind study in HBeAg positive lamivudine-refractory patients (026), with 85% of patients presenting LVDr mutations at baseline, patients receiving lamivudine at study entry either switched to entecavir 1 mg once daily, with neither a washout nor an overlap period (n = 141), or continued on lamivudine 100 mg once daily (n = 145). Results at 48 weeks are presented in the table.

Histologic Improvement and Change in Ishak Fibrosis Score at Week 48:

	Lamivudine-refractory	
	HBeAg positive (study 026)	
	ETV 1.0 mg once daily	LVD 100 mg once daily
n	124[a]	116[a]
Histological improvement[b]	55%*	28%
Ishak fibrosis score improvement	34%*	16%
Ishak fibrosis score worsening	11%	26%

Selected Virologic, Biochemical, and Serologic Endpoints at Week 48:

	Lamivudine-refractory	
	HBeAg positive (study 026)	
	ETV 1.0 mg once daily	LVD 100 mg once daily
n	141	145
HBV DNA undetectable (< 300 copies/ml by PCR)[c]	19%*	1%
Viral load reduction (log_{10} copies/ml)[c] from baseline	-5.11*	-0.48
ALT normalisation (≤ 1 times ULN)	61%*	15%
HBeAg Seroconversion	8%	3%

*p value vs lamivudine < 0.05
[a] patients with evaluable baseline histology (baseline Knodell Necroinflammatory Score ≥ 2)
[b] a primary endpoint.
[c] Roche Cobas Amplicor PCR assay (LLOQ = 300 copies/ml)

Results beyond 48 weeks of treatment:
Treatment was discontinued when prespecified response criteria were met either at 48 weeks or during the second year of treatment. Response criteria were HBV virological suppression (HBV DNA < 0.7 MEq/ml by bDNA) and loss of HBeAg (in HBeAg positive patients) or ALT < 1.25 times ULN (in HBeAg negative patients). Patients in response were followed for an additional 24 weeks off-treatment. Patients who met virologic but not serologic or biochemical response criteria continued blinded treatment. Patients who did not have a virologic response were offered alternative treatment.

Nucleoside-naive:
HBeAg positive (study 022): blinded treatment with entecavir for up to 96 weeks continued for 243 (69%) entecavir-treated subjects and 164 (46%) lamivudine-treated subjects. This resulted in 180 (74%) entecavir subjects and 60 (37%) lamivudine subjects achieving HBV DNA < 300 copies/ml by PCR at the end of dosing (up to 96 weeks). 193 (79%) entecavir subjects achieved ALT ≤ 1 X ULN (normalization) compared to 112 (68%) lamivudine subjects. HBeAg seroconversion occurred in 26 (11%) entecavir subjects and 20 (12%) lamivudine subjects.

74 (21%) entecavir subjects and 67 (19%) lamivudine subjects met the definition of response at Week 48, discontinued study drugs, and were followed off treatment for 24 weeks. Among entecavir responders, 26 (35%) subjects had HBV DNA <300 copies/mL, 55 (74%) subjects had ALT normalization, and 56 (76%) subjects sustained HBeAg seroconversion at the end of follow-up. Among lamivudine responders, 20 (30%) subjects had HBV DNA <300 copies/mL, 41 (61%) subjects had ALT normalization, and 47 (70%) subjects sustained HBeAg seroconversion at the end of follow-up.

HBeAg negative (study 027): blinded treatment with entecavir up to 96 weeks (n = 325) continued in 26 (8%) entecavir-treated subjects and 28 (9%) lamivudine-treated subjects. In year 2, 22 entecavir and 16 lamivudine subjects had HBV DNA < 300 copies/ml by PCR. 7 entecavir-treated subjects achieved ALT normalisation versus 6 lamivudine-treated subjects at the end of dosing (up to 96 weeks). At week 48, 275 (85%) entecavir-treated and 245 (78%) lamivudine-treated patients met the definition of response, discontinued study drugs, and were followed off treatment for 24 weeks. Few subjects in each treatment arm had HBV DNA < 300 copies/ml by PCR at end of follow-up. ALT normalisation (≤ 1 times ULN) occurred in 126 (46%) entecavir- treated and 84 (341%) lamivudine-treated patients at end of follow-up.

Liver biopsy results: 57 patients from the pivotal nucleoside-naive studies 022 (HBeAg positive) and 027 (HBeAg negative) who enrolled in a long-term rollover study were evaluated for long-term liver histology outcomes. The entecavir dosage was 0.5 mg daily in the pivotal studies (mean exposure 85 weeks) and 1 mg daily in the rollover study (mean exposure 177 weeks), and 51 patients in the rollover study initially also received lamivudine (median duration 29 weeks). Of these patients, 55/57 (96%) had histological improvement as previously defined (see above), and 50/57 (88%) had a ≥ 1-point decrease in Ishak fibrosis score. For patients with baseline Ishak fibrosis score ≥ 2, 25/43 (58%) had a ≥ 2-point decrease. All (10/10) patients with advanced fibrosis or cirrhosis at baseline (Ishak fibrosis score of 4, 5 or 6) had a ≥ 1 point decrease (median decrease from baseline was 1.5 points). At the time of the long-term biopsy, all patients had HBV DNA < 300 copies/ml and 49/57 (86%) had serum ALT ≤ 1 times ULN. All 57 patients remained positive for HBsAg.

Lamivudine-refractory:
HBeAg positive (study 026): treatment with entecavir for up to 96 weeks (n = 141) resulted in cumulative response rates of 30% for HBV DNA < 300 copies/ml by PCR, 85% for ALT normalisation and 17% for HBeAg seroconversion.
For the 77 patients who continued entecavir treatment beyond 52 weeks (median 96 weeks), 40% of patients had HBV DNA < 300 copies/ml by PCR and 81% had ALT normalisation (≤ 1 times ULN) at end of dosing.

<u>*Special populations*</u>
Patients with decompensated liver disease: in study 048, 191 patients with HBeAg positive or negative chronic HBV infection and evidence of hepatic decompensation, defined as a CTP score of 7 or higher, received entecavir 1 mg once daily or adefovir dipivoxil 10 mg once daily. Patients were either HBV-treatment-naïve or pretreated (excluding pretreatment with entecavir, adefovir dipivoxil or tenofovir disoproxil fumarate). At baseline, patients had a mean CTP score of 8.59 and 26% of patients were CTP class C. The mean baseline Model for End Stage Liver Disease (MELD) score was 16.23. Mean serum HBV DNA by PCR was 7.83 $\log_{10}$ copies/ml and mean serum ALT was 100 U/l; 54% of patients were HBeAg positive, and 35% of patients had LVDr substitutions at baseline.
Entecavir was superior to adefovir dipivoxil on the primary efficacy endpoint of mean change from baseline in serum HBV DNA by PCR at week 24. Results for selected study endpoints at weeks 24 and 48 are shown in the table.

Selected Endpoints at Week 48, Subjects with Decompensated Liver Disease:

	Week 24		Week 48	
	ETV 1 mg once daily	Adefovir Dipivoxil 10 mg once daily	ETV 1 mg once daily	Adefovir Dipivoxil 10 mg once daily
n	100	91	100	91
HBV DNA[a]				
Proportion undetectable (<300 copies/ml)[b]	49%*	16%	57%*	20%
Mean change from baseline ($\log_{10}$ copies/ml)[c]	-4.48*	-3.40	-4.66	-3.90
Stable or improved CTP score [b,d]	66%	71%	61%	67%
MELD score Mean change from baseline [c,e]	-2.0	-0.9	-2.6	-1.7
HBsAg loss [b]	1%	0	5%	0
Normalization of:[f]				
ALT (≤1 X ULN)[b]	46/78 (59%)*	28/71 (39%)	49/78 (63%)*	33/71 (46%)
Albumin (≥1 X LLN)[b]	20/82 (24%)	14/69 (20%)	32/82 (39%)	20/69 (29%)
Bilirubin (≤1 X ULN)[b]	12/75 (16%)	10/65 (15%)	15/75 (20%)	18/65 (28%)
Prothrombin time (≤1 X ULN)[b]	9/95 (9%)	6/82 (7%)	8/95 (8%)	7/82 (9%)

[a] Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/ml).
[b] NC=F (noncompleter=failure), meaning treatment discontinuations before the analysis week, including reasons such as death, lack of efficacy, adverse event, noncompliance/loss-to-follow-up, are counted as failures (e.g., HBV DNA ≥ 300 copies/ml)
[c] NC=M (noncompleters=missing)
[d] Defined as decrease or no change from baseline in CTP score.
[e] Baseline mean MELD score was 17.1 for ETV and 15.3 for adefovir dipivoxil.
[f] Denominator is patients with abnormal values at baseline.
*p<0.05
ULN=upper limit of normal, LLN=lower limit of normal.

The time to onset of HCC or death (whichever occurred first) was comparable in the two treatment groups; on-study cumulative death rates were 23% (23/102) and 33% (29/89) for patients treated with entecavir and adefovir dipivoxil, respectively, and on-study cumulative rates of HCC were 12% (12/102) and 20% (18/89) for entecavir and adefovir dipivoxil, respectively.
For patients with LVDr substitutions at baseline, the percentage of patients with HBV DNA <300 copies/ml was 44% for entecavir and 20% for adefovir at week 24 and 50% for entecavir and 17% for adefovir at week 48.

HIV/HBV co-infected patients receiving concomitant HAART: study 038 included 67 HBeAg positive and 1 HBeAg negative patients co-infected with HIV. Patients had stable controlled HIV (HIV RNA < 400 copies/ml) with recurrence of HBV viraemia on a lamivudine-containing HAART regimen.
HAART regimens did not include emtricitabine or tenofovir disoproxil fumarate. At baseline entecavir-treated patients had a median duration of prior lamivudine therapy of 4.8 years and median CD4 count of 494 cells/mm^3 (with only 5 subjects having CD4 count < 200 cells/mm^3). Patients continued their lamivudine-regimen and were assigned to add either entecavir 1 mg once daily (n = 51) or placebo (n = 17) for 24 weeks followed by an additional 24 weeks where all received entecavir. At 24 weeks the reduction in HBV viral load was significantly greater with entecavir (-3.65 vs an increase of 0.11 log_{10} copies/ml). For patients originally assigned to entecavir treatment, the reduction in HBV DNA at 48 weeks was -4.20 log_{10} copies/ml, ALT normalisation had occurred in 37% of patients with abnormal baseline ALT and none achieved HBeAg seroconversion.

HIV/HBV co-infected patients not receiving concomitant HAART: entecavir has not been evaluated in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment. Reductions in HIV RNA have been reported in HIV/HBV co-infected patients receiving entecavir monotherapy without HAART. In some cases, selection of HIV variant M184V has been observed, which has implications for the selection of HAART regimens that the patient may take in the future. Therefore, entecavir should not be used in this setting due to the potential for development of HIV resistance (see section 4.4).

Liver transplant recipients: the safety and efficacy of entecavir 1 mg once daily were assessed in a single-arm study in 65 patients who received a liver transplant for complications of chronic HBV infection and had HBV DNA <172 IU/ml (approximately 1000 copies/ml) at the time of transplant.
The study population was 82% male, 39% Caucasian, and 37% Asian, with a mean age of 49 years; 89% of patients had HBeAg-negative disease at the time of transplant. Of the 61 patients who were evaluable for efficacy (received entecavir for at least 1 month), 60 also received hepatitis B immune globulin (HBIg) as part of the post-transplant prophylaxis regimen. Of these 60 patients, 49 received more than 6 months of HBIg therapy. At Week 72 post-transplant, none of 55 observed cases had virologic recurrence of HBV [defined as HBV DNA ≥50 IU/ml (approximately 300 copies/ml)], and there was no reported virologic recurrence at time of censoring for the remaining 6 patients. All 61 patients had HBsAg loss post-transplantation, and 2 of these later became HBsAg positive despite maintaining undetectable HBV DNA (<6 IU/ml). The frequency and nature of adverse events in this study were consistent with those expected in patients who have received a liver transplant and the known safety profile of entecavir.

Clinical resistance in adults: patients in clinical trials initially treated with entecavir 0.5 mg (nucleoside-naive) or 1.0 mg (lamivudine-refractory) and with an on-therapy PCR HBV DNA measurement at or after Week 24 were monitored for resistance.

Through Week 240 in nucleoside-naive studies, genotypic evidence of ETVr substitutions at rtT184, rtS202, or rtM250 was identified in 3 patients treated with entecavir, 2 of whom experienced virologic breakthrough (see table). These substitutions were observed only in the presence of LVDr substitutions (rtM204V and rtL180M).

Emerging Genotypic Entecavir Resistance Through Year 5, Nucleoside-Naive Studies					
	Year 1	Year 2	Year 3[a]	Year 4[a]	Year 5[a]
Patients treated and monitored for resistance[b]	663	278	149	121	108
Patients in specific year with:					
- emerging genotypic ETVr[c]	1	1	1	0	0
- genotypic ETVr[c] with virologic breakthrough[d]	1	0	1	0	0
Cumulative probability of:					
- emerging genotypic ETVr[c]	0.2%	0.5%	1.2%	1.2%	1.2%
- genotypic ETVr[c] with virologic breakthrough[d]	0.2%	0.2%	0.8%	0.8%	0.8%

[a] Results reflect use of a 1-mg dose of entecavir for 147 of 149 patients in Year 3 and all patients in Years 4 and 5 and of combination entecavir-lamivudine therapy (followed by long-term entecavir therapy) for a median of 20 weeks for 130 of 149 patients in Year 3 and for 1 week for 1 of 121 patients in Year 4 in a rollover study.

[b] Includes patients with at least one on-therapy HBV DNA measurement by PCR at or after week 24 through week 58 (Year 1), after week 58 through week 102 (Year 2), after week 102 through week 156 (Year 3), after week 156 through week 204 (Year 4), or after week 204 through week 252 (Year 5).

[c] Patients also have LVDr substitutions.

[d] ≥ 1 $\log_{10}$ increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.

ETVr substitutions (in addition to LVDr substitutions rtM204V/I ± rtL180M) were observed at baseline in isolates from 10/187 (5%) lamivudine-refractory patients treated with entecavir and monitored for resistance, indicating that prior lamivudine treatment can select these resistance substitutions and that they can exist at a low frequency before entecavir treatment. Through Week 240, 3 of the 10 patients experienced virologic breakthrough (≥ 1 $\log_{10}$ increase above nadir). Emerging entecavir resistance in lamivudine-refractory studies through Week 240 is summarized in the table.

Genotypic Entecavir Resistance Through Year 5, Lamivudine-Refractory Studies					
	Year 1	Year 2	Year 3[a]	Year 4[a]	Year 5[a]
Patients treated and monitored for resistance[b]	187	146	80	52	33
Patients in specific year with:					
- emerging genotypic ETVr[c]	11	12	15	6	2
- genotypic ETVr[c] with virologic breakthrough[d]	2[e]	14[e]	13[e]	9[e]	1[e]
Cumulative probability of:					
- emerging genotypic ETVr[c]	6.2%	15%	36.3%	46.6%	54.45%
- genotypic ETVr[c] with virologic breakthrough[d]	1.1%[e]	10.7%[e]	27%e	41.3% [e]	43.6% [e]

[a] Results reflect use of combination entecavir-lamivudine therapy (followed by long-term entecavir therapy) for a median of 13 weeks for 48 of 80 patients in Year 3, a median of 38 weeks for 10 of 52 patients in Year 4, and for 16 weeks for 1 of 33 patients in Year 5 in a rollover study.

[b] Includes patients with at least one on-therapy HBV DNA measurement by PCR at or after week 24 through week 58 (Year 1), after week 58 through week 102 (Year 2), after week 102 through week 156 (Year 3), after week 156 through week 204 (Year 4), or after week 204 through week 252 (Year 5).
[c] Patients also have LVDr substitutions.
[d] ≥ 1 log_{10} increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.
[e] ETVr occurring in any year; virologic breakthrough in specified year.

Among lamivudine-refractory patients with baseline HBV DNA < 10^7 log_{10} copies/ml, 64% (9/14) achieved HBV DNA < 300 copies/ml at Week 48. These 14 patients had a lower rate of genotypic entecavir resistance (cumulative probability 18.8% through 5 years of follow-up) than the overall study population (see table). Also, lamivudine-refractory patients who achieved HBV DNA < 104 log_{10} copies/ml by PCR at Week 24 had a lower rate of resistance than those who did not (5-year cumulative probability 17.6% [n= 50] versus 60.5% [n= 135], respectively).

In a post-approval integrated analysis of entecavir resistance data from 17 Phase 2 and 3 clinical trials, an emergent entecavir resistance-associated substitution rtA181C was detected in 5 out of 1461 (0.3%) subjects during treatment with entecavir. This substitution was detected only in the presence of lamivudine resistance-associated substitutions rtL180M plus rtM204V.

Cross-resistance: Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, entecavir had 8- to 30-fold less inhibition of HBV DNA synthesis for HBV containing lamivudine and telbivudine resistance substitutions rtM204I/V with or without rtL180M than for wild-type HBV. Decreased phenotypic susceptibility to entecavir is also accorded by substitutions rtM204I/V with or without rtL180M, rtL80I/V, or rtV173L (which are associated with lamivudine and telbivudine resistance). The efficacy of entecavir against HBV harboring adefovir resistance-associated substitutions has not been ascertained in clinical trials. In cell culture, HBV isolates from lamivudine-refractory subjects failing entecavir therapy were susceptible to adefovir but remained resistant to lamivudine. Recombinant HBV genomes encoding adefovir resistance-associated substitutions at either rtN236T or rtA181V had 0.3- and 1.1-fold shifts in susceptibility to entecavir in cell culture, correspondingly.

5.2 Pharmacokinetic properties

Absorption: entecavir is rapidly absorbed with peak plasma concentrations occurring between 0.5-1.5 hours. The absolute bioavailability has not been determined. Based on urinary excretion of unchanged drug, the bioavailability has been estimated to be at least 70%. There is a dose-proportionate increase in C_{max} and AUC values following multiple doses ranging from 0.1-1 mg. Steady-state is achieved between 6-10 days after once daily dosing with ≈2 times accumulation. C_{max} and C_{min} at steady-state are 4.2 and 0.3 ng/ml, respectively, for a dose of 0.5 mg, and 8.2 and 0.5 ng/ml, respectively, for 1 mg. The tablet and oral solution were bioequivalent in healthy subjects; therefore, both forms may be used interchangeably.

Administration of 0.5 mg entecavir with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) resulted in a minimal delay in absorption (1-1.5 hour fed vs. 0.75 hour fasted), a decrease in C_{max} of 44-46%, and a decrease in AUC of 18-20%. The lower C_{max} and AUC when taken with food is not considered to be of clinical relevance in nucleoside-naive patients but could affect efficacy in lamivudine-refractory patients (see section 4.2).

Distribution: the estimated volume of distribution for entecavir is in excess of total body water. Protein binding to human serum protein *in vitro* is ≈13%.

Biotransformation: entecavir is not a substrate, inhibitor or inducer of the CYP450 enzyme system. Following administration of 14C-entecavir, no oxidative or acetylated metabolites and minor amounts of the phase II metabolites, glucuronide and sulfate conjugates, were observed.

Elimination: entecavir is predominantly eliminated by the kidney with urinary recovery of unchanged drug at steady-state of about 75% of the dose. Renal clearance is independent of dose and ranges between 360-471 ml/min suggesting that entecavir undergoes both glomerular filtration and net tubular secretion. After reaching peak levels, entecavir plasma concentrations decreased in a biexponential manner with a terminal elimination half-life of ≈128-149 hours. The observed drug accumulation index is ≈2 times with once daily dosing, suggesting an effective accumulation half-life of about 24 hours.

Hepatic impairment: pharmacokinetic parameters in patients with moderate or severe hepatic impairment were similar to those in patients with normal hepatic function.

Renal impairment: entecavir clearance decreases with decreasing creatinine clearance. A 4 hour period of haemodialysis removed ≈13% of the dose, and 0.3% was removed by CAPD. The pharmacokinetics of entecavir following a single 1 mg dose in patients (without chronic hepatitis B infection) are shown in the table below:

	Baseline Creatinine Clearance (ml/min)					
	Unimpaired > 80 (n = 6)	**Mild** > 50; ≤ 80 (n = 6)	**Moderate** 30-50 (n = 6)	**Severe** 20- < 30 (n = 6)	**Severe Managed with Haemodialysis** (n = 6)	**Severe Managed with CAPD** (n = 4)
C_{max} (ng/ml) (CV%)	8.1 (30.7)	10.4 (37.2)	10.5 (22.7)	15.3 (33.8)	15.4 (56.4)	16.6 (29.7)
AUC(0-T) (ng·h /ml) (CV)	27.9 (25.6)	51.5 (22.8)	69.5 (22.7)	145.7 (31.5)	233.9 (28.4)	221.8 (11.6)
CLR (ml/min) (SD)	383.2 (101.8)	197.9 (78.1)	135.6 (31.6)	40.3 (10.1)	NA	NA
CLT/F (ml/min) (SD)	588.1 (153.7)	309.2 (62.6)	226.3 (60.1)	100.6 (29.1)	50.6 (16.5)	35.7 (19.6)

Post-Liver transplant: entecavir exposure in HBV-infected liver transplant recipients on a stable dose of cyclosporine A or tacrolimus (n = 9) was ≈ 2 times the exposure in healthy subjects with normal renal function. Altered renal function contributed to the increase in entecavir exposure in these patients (see section 4.4).

Gender: AUC was 14% higher in women than in men, due to differences in renal function and weight. After adjusting for differences in creatinine clearance and body weight there was no difference in exposure between male and female subjects.

Elderly: the effect of age on the pharmacokinetics of entecavir was evaluated comparing elderly subjects in the age range 65-83 years (mean age females 69 years, males 74 years) with young subjects in the age range 20-40 years (mean age females 29 years, males 25 years). AUC was 29% higher in elderly than in young subjects, mainly due to differences in renal function and weight. After adjusting for differences in creatinine clearance and body weight, elderly subjects had a 12.5% higher AUC than young subjects.The population pharmacokinetic analysis covering patients in the age range 16-75 years did not identify age as significantly influencing entecavir pharmacokinetics.

Race: There are no significant racial differences in entecavir pharmacokinetics

Paediatric population: Pharmacokinetic studies have not been conducted in children.

5.3 Preclinical safety data

In repeat-dose toxicology studies in dogs, reversible perivascular inflammation was observed in the central nervous system, for which no-effect doses corresponded to exposures 19 and 10 times those in humans (at 0.5 and 1 mg respectively). This finding was not observed in repeat-dose studies in other species, including monkeys administered entecavir daily for 1 year at exposures ≥ 100 times those in humans.

In reproductive toxicology studies in which animals were administered entecavir for up to 4 weeks, no evidence of impaired fertility was seen in male or female rats at high exposures. Testicular changes (seminiferous tubular degeneration) were evident in repeat-dose toxicology studies in rodents and dogs at exposures ≥ 26 times those in humans. No testicular changes were evident in a 1-year study in monkeys.

In pregnant rats and rabbits administered entecavir, no effect levels for embryotoxicity and maternal toxicity corresponded to exposures ≥ 21 times those in humans. In rats, maternal toxicity, embryo-foetal toxicity (resorptions), lower foetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternebrae, and phalanges), and extra lumbar vertebrae and ribs were observed at high exposures. In rabbits, embryo-foetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed at high exposures. In a peri-postnatal study in rats, no adverse effects on offspring were observed. In a separate study wherein entecavir was administered to pregnant lactating rats at 10 mg/kg, both foetal exposure to entecavir and secretion of entecavir into milk were demonstrated. In juvenile rats administered entecavir from postnatal days 4 to 80, a moderately reduced acoustic startle response was noted during the recovery period (postnatal days 110 to 114) but not during the dosing period at AUC values ≥ 92 times those in humans at the 0.5 mg dose or paediatric equivalent dose. Given the exposure margin, this finding is considered of unlikely clinical significance.

No evidence of genotoxicity was observed in an Ames microbial mutagenicity assay, a mammaliancell gene mutation assay, and a transformation assay with Syrian hamster embryo cells. A micronucleus study and a DNA repair study in rats were also negative. Entecavir was clastogenic to human lymphocyte cultures at concentrations substantially higher than those achieved clinically.

Two-year carcinogenicity studies: in male mice, increases in the incidences of lung tumours were observed at exposures ≥ 4 and ≥ 2 times that in humans at 0.5 mg and 1 mg respectively. Tumour development was preceded by pneumocyte proliferation in the lung which was not observed in rats, dogs, or monkeys, indicating that a key event in lung tumour development observed in mice likely was species-specific. Increased incidences of other tumours including brain gliomas in male and female rats, liver carcinomas in male mice, benign vascular tumours in female mice, and liver adenomas and carcinomas in female rats were seen only at high lifetime exposures. However, the no effect levels could not be precisely established. The predictivity of the findings for humans is not known.

6. PHARMACEUTICAL PARTICULARS

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Cellulose Microcrystalline
Crospovidone (type A)
Hydroxypropyl cellulose (type L)
Magnesium stearate

Tablet coat

Entevir 0.5 mg film-coated tablets
Coating medium (white)
Titanium dioxide (E171)
Lactose monohydrate

Hypromellose
Macrogol 4000

Entevir 1.0 mg film-coated tablets
Coating medium (pink)
Hypromellose
Titanium dioxide (E171)
Polydextrose
Talc
Maltodextrin
Triglycerides, medium chain
Iron oxide red (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Refer to expiry date stated on blister strip.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Entevir is supplied in a cardboard box containing OPA/ALU/PVC - Aluminium foil blisters.

Pack sizes
30 tablets (blister)

7. Manufacturer

Pharmathen International S.A.
Industrial Park Sapes,
Rodopi Prefecture,
Block No 5, Rodopi 69300
Greece

8. Product Registrant

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103 Kallang Avenue #06-02
Singapore 339504