SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HEPATOVIR-B 0.5 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Entecavir 0.5 mg (as entecavir monohydrate)
Excipient(s) with known effect:
Lactose monohydrate 120 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White colored, biconvex, triangular shaped film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

HEPATOVIR-B is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults (16 years and over) with:

- Compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.
- Decompensated liver disease.

4.2 Posology and method of administration

Unless otherwise recommended by the physician;

Posology

Compensated liver disease

Nucleoside naive patients: the recommended dose in adults is 0.5 mg once daily, with or without food.

Lamivudine-refractory patients (i.e. history of hepatitis B viremia while on lamivudine therapy or known lamivudine resistance [LVD resistant, commonly called YMDD] mutations): the recommended dose is 1 mg once daily, which must be taken on an empty stomach (more than 2 hours before and more than 2 hours after a meal) (see section 4.4).

Decompensated liver disease

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

Frequency and duration of administration

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

- In HBeAg positive patients, treatment should be administered at least until 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 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.

Method of administration
HEPATOVIR-B should be taken orally. In nucleoside-naive patients, the recommended dose is 0.5 mg once daily, with or without food. HEPATOVIR-B in lamivudine-refractory HBV patients or decompensated patients must be taken on an empty stomach (more than 2 hours before and more than 2 hours after a meal).

Additional information on special populations
Renal/Hepatic impairment
Entecavir is primarily eliminated by the kidneys. 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 hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A reduction of the daily dose using HEPATOVIR-B 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. 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.

The recommended dosage for HEPATOVIR-B in patients with renal impairment

Creatinine clearance (mL/min)	**HEPATOVIR-B dosage***	
	Nucleoside naive patients	**Lamivudine-refractory or decompensated liver disease**
≥50	0.5 mg once daily	1 mg once daily
30-49	0.25 mg once daily* OR 0.5 mg every 48 hours	0.5 mg once daily
10-29	0.15 mg once daily* OR 0.5 mg every 72 hours	0.3 mg once daily* OR 0.5 mg every 48 hours
<10 Hemodialysis or CAPD**	0.05 mg once daily* OR 0.5 mg every 5-7 days	0.1 mg once daily* OR 0.5 mg every 72 hours

* For doses <0.5 mg, entecavir oral solution is recommended.
** On hemodialysis days, administer entecavir after hemodialysis.
CAPD=continuous ambulatory peritoneal dialysis

No dose adjustment of HEPATOVIR-B is required in patients with hepatic impairment.

Pediatric population
Safety and efficacy of entecavir in pediatric patients below 16 years of age have not been established. It is not recommended for use in the pediatric population.

Geriatric population
No dosage adjustment of HEPATOVIR-B based on age is required.

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

4.3 Contraindications
It is contraindicated in patients with hypersensitivity to entecavir or to any of the excipients.

4.4 Special warnings and precautions for use
Lactic acidosis/hepatomegaly with steatosis
Occurrences of lactic acidosis (in the absence of hypoxemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues. As entecavir is a nucleoside analogue, this risk cannot be excluded. Treatment with nucleoside analogues should be discontinued when rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown etiology occurs. Benign digestive symptoms, such as nausea, vomiting and abdominal pain, might be indicative of lactic acidosis development. Severe cases, sometimes with fatal outcome, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate. Caution should be exercised when prescribing nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease. These patients should be followed closely.
To differentiate between elevations in 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.

Exacerbations of hepatitis
Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterized by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline (see section 4.8). Among entecavir-treated patients, on-treatment exacerbations had a median time of onset of 4-5 weeks. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with advanced liver disease or cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis therapy (see section 4.2). Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported.

Among entecavir-treated nucleoside naive patients, post-treatment exacerbations had a median time to onset of 23-24 weeks, and most were reported in HBeAg negative patients (see section 4.8). Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted.

Patients with decompensated liver disease
A higher rate of serious hepatic adverse events (regardless of causality) in both treatment groups of a controlled clinical trial (see section 5.1) 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. In addition, patients with decompensated liver disease may be at higher risk for lactic acidosis. Therefore, clinical and laboratory parameters should be closely monitored in this patient population (see sections 4.8 and 5.1).

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).

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 second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy.

Co-Infection with HIV
HEPATOVIR-B has not been evaluated in patients who are co-infected with human immunodeficiency virus (HIV) and hepatitis B virus and who are not concurrently receiving effective HIV therapy. Limited clinical experience suggests there is a potential for the development of HIV resistance if HEPATOVIR-B is used to treat chronic hepatitis B infection in patients with untreated HIV infection (see section 5.1). Therefore, therapy with HEPATOVIR-B is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) (see sections 4.8 and 5.1). HEPATOVIR-B has not been studied as a treatment for HIV infection and is not recommended for this use.

Renal impairment
Dosage adjustment is recommended for patients with renal impairment (see section 4.2).

Liver transplant recipients
The safety and efficacy of HEPATOVIR-B in liver transplant recipients are unknown. Renal function should be carefully evaluated before and during HEPATOVIR-B therapy in liver transplant recipients receiving an immunosuppressant that may affect renal function, such as cyclosporine or tacrolimus (see sections 4.2 and 5.2).

Co-infection with hepatitis C or D
There are no data on the efficacy of entecavir in patients co-infected with hepatitis C or D virus.

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 120 mg lactose per 0.5 mg daily dose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine as it contains lactose monohydrate.

4.5 Interactions with other medicinal products and other forms of interaction
Since entecavir is predominantly eliminated by the kidneys (see section 5.2), co-administration of HEPATOVIR-B 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 HEPATOVIR-B is co-administered 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 CYP450 enzyme system. Therefore, CYP450 mediated drug interactions are unlikely to occur with entecavir.
Administration of entecavir with food decreased absorption by 18-20% (see section 4.2).

Additional information on special populations
Pediatric population
There is no specific interaction study conducted on this patient group.

4.6 Fertility, pregnancy and lactation
General recommendation
Pregnancy category is C.

Women with childbearing potential/Contraception
Women of childbearing potential should use effective contraception. There are no adequate studies from the use of entecavir in pregnant women.

Pregnancy
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. Animal studies are insufficient with respect to effects on pregnancy, embryonal and fetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown.

HEPATOVIR-B should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether entecavir is excreted in human milk. Available toxicological data in animals have shown excretion of entecavir in milk. A risk to the infants cannot be excluded. HEPATOVIR-B should not be used during breast-feeding.

Fertility
No effects were observed on fertility in male rats at exposures >160 times human exposure at 0.5 mg/day (>90 times at 1 mg/day). In female rats, no effects on fertility or early embryonic development were observed at exposures >165 times human exposure at 0.5 mg/day (>94 times at 1 mg/day) (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. No effect on such activities is expected based on the pharmacokinetic profile of entecavir. However, 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 post-marketing 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 in order of frequency as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Immune system disorders
Rare: anaphylactoid reaction

Psychiatric disorders
Common: insomnia

Nervous system disorders
Common: headache, dizziness, somnolence

Gastrointestinal disorders
Common: vomiting, diarrhea, nausea, dyspepsia

Hepatobiliary disorders
Common: increased transaminases

Skin and subcutaneous tissue disorders
Uncommon: alopecia, rash

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
In clinical studies with nucleoside-naive patients, 5% had ALT elevations >3×baseline, and <1% had ALT elevations >2×baseline together with total bilirubin >2×upper limit of normal (ULN) and >2×baseline. Albumin levels <2.5 g/dl occurred in <1% of patients, amylase levels >3×baseline in 2%, lipase levels >3×baseline in 11% and platelets <50,000/mm^3 in <1%.

In clinical studies with lamivudine-refractory patients, 4% had ALT elevations >3×baseline, and <1% had ALT elevations >2×baseline together with total bilirubin >2×ULN and >2×baseline. Amylase levels >3×baseline occurred in 2% of patients, lipase levels >3×baseline in 18% and platelets <50,000/mm^3 in <1%.

Exacerbations during treatment: in studies with nucleoside naive patients, on treatment ALT elevations >10×ULN and >2×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×ULN and >2×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 of hepatitis have been reported in patients who have discontinued anti-hepatitis B virus therapy, including therapy with entecavir (see section 4.4). In studies in nucleoside-naive patients, 6% of entecavir-treated patients and 10% of lamivudine-treated patients experienced ALT elevations (>10×ULN and >2×reference [minimum of baseline or last end-of-dosing measurement]) during post-treatment follow-up. Among entecavir-treated nucleoside-naive patients, ALT elevations had a median time to onset of 23-24 weeks, and 86% (24/28) of ALT elevations occurred in HBeAg negative patients. In studies in lamivudine refractory patients, with only limited numbers of patients being followed up, 11% of entecavir-treated patients and no lamivudine-treated patients developed ALT elevations during post-treatment follow-up.

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.

d. Other special populations
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). Relative to the adverse reactions

noted in section *b. Tabulated list of adverse reactions*, one additional adverse reaction [decrease in blood bicarbonate (2%)] was observed in entecavir-treated patients through week 48. The on-study cumulative death rate was 23% (23/102), and causes of death were generally liver-related, as expected in this population. The on-study cumulative rate of hepatocellular carcinoma (HCC) was 12% (12/102). Serious adverse events were generally liver-related, with an on-study cumulative frequency of 69%. Patients with high baseline CTP score were at higher risk of developing serious adverse events (see section 4.4).

Laboratory test abnormalities: through week 48 among entecavir-treated patients with decompensated liver disease, none had ALT elevations both >10×ULN and >2×baseline, and 1% of patients had ALT elevations >2×baseline together with total bilirubin >2×ULN and >2×baseline. Albumin levels <2.5 g/dL occurred in 30% of patients, lipase levels >3×baseline in 10% and platelets <50,000/mm^3 in 20%.

Experience in patients co-infected with HIV
The safety profile of entecavir in a limited number of HIV/HBV co-infected patients on lamivudine-containing HAART regimens was similar to the safety profile in monoinfected HBV patients (see section 4.4).

Gender/age: there was no apparent difference in the safety profile of entecavir with respect to gender (≈ 25% women in the clinical trials) or age (≈ 5% of patients >65 years of age).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Direct-effective antivirals
ATC code: J05AF10

Mechanism of action
Entecavir is a guanosine nucleoside analogue with potent and selective activity against HBV polymerase. It is phosphorylated to the active triphosphate (TP) form, which has an intracellular half-life of 15 hours. Intracellular TP levels are directly related to extracellular entecavir concentrations, with no significant accumulation beyond initial plateau levels. By competing with the natural substrate deoxyguanosine TP, entecavir-TP functionally inhibits all 3 activities of the viral polymerase: (1) priming of the HBV polymerase, (2) reverse transcription of the negative strand 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 lamivudine-resistant HBV (rtL180M, rtM204V) was 0.026 μM (range 0.010–0.059 μM). In contrast, no clinically relevant activity was noted against HIV type 1 (EC_{50} value >10 μM) grown in cell culture. 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 greater than 4 times the C_{max} was not antagonistic to the anti-HIV activity in cell culture of these six NRTIs or emtricitabine.

Resistance in cell culture
Relative to wild-type HBV, LVD-resistant viruses containing rtM204V and rtL180M substitutions within the reverse transcriptase exhibit 8-fold decreased susceptibility to entecavir. Incorporation of additional entecavir-resistant amino acid changes rtT184, rtS202 and/or rtM250 decreases entecavir susceptibility in cell culture. Substitutions observed in clinical isolates (rtT184A, C, F, G, I, L, M or S; rtS202 C, G or I; and/or rtM250I, L or V) further decreased entecavir susceptibility 16- to 741-fold relative to wild-type virus. The entecavir-resistant substitutions at residues rtT184, rtS202 and rtM250 alone have only a modest effect on entecavir susceptibility and have not been observed in the absence of lamivudine resistance substitutions in more than 1000 patient samples sequenced. Resistance is mediated by reduced inhibitor binding to the altered HBV reverse transcriptase, and resistant HBV exhibits reduced replication capacity in cell culture.

Clinical experience
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×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 randomized, double blind studies comparing entecavir (ETV) to lamivudine (LVD) in HBeAg positive (022) and HBeAg negative (027) patients are presented in the table.

	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%
n	354	355	325	313
Viral load reduction ($\log_{10}$ copies/mL)[c]	-6.86*	-5.39	-5.04	-4.53
HBV DNA undetectable (<300 copies/mL by PCR)[c]	67%*	36%	90%	72%
ALT normalization (≤1×ULN)	68%*	60%	78%*	71%
HBeAg Seroconversion	2l%	18%		

*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 randomized, double-blind study in HBeAg positive lamivudine-refractory patients, with 85% of patients presenting LVD-resistant 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 given in the table.

	Lamivudine-refractory patients	
	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%
n	141	145
Viral load reduction ($\log_{10}$ copies/mL)[c]	-5.11*	-0.48
HBV DNA undetectable (<300 copies/mL by PCR)[c]	19%*	1%
ALT normalization (≤1×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×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-naïve trials
HBeAg positive (study 022): treatment with entecavir for up to 96 weeks (n=354) resulted in cumulative response rates of 80% for HBV DNA <300 copies/mL by PCR, 87% for ALT normalization, 31% for HBeAg seroconversion and 2% for HBsAg seroconversion (5% for HBsAg loss). For lamivudine (n=355), cumulative response rates were 39% for HBV DNA <300 copies/mL by PCR, 79% for ALT normalization, 26% for HBeAg seroconversion, and 2% for HBsAg seroconversion (3% for HBsAg loss).

At end of dosing, among patients who continued treatment beyond 52 weeks (median of 96 weeks), 81% of 243 entecavir-treated and 39% of 164 lamivudine-treated patients had HBV DNA <300 copies/mL by PCR while ALT normalization (≤1×ULN) occurred in 79% of entecavir-treated and 68% of lamivudine-treated patients.

HBeAg negative (study 027): treatment with entecavir up to 96 weeks (n=325) resulted in cumulative response rates of 94% for HBV DNA <300 copies/mL by PCR and 89% for ALT normalization versus 77% for HBV DNA <300 copies/mL by PCR and 84% for ALT normalization for lamivudine-treated patients (n=313). For 26 entecavir-treated and 28 lamivudine-treated patients who continued treatment beyond 52 weeks (median 96 weeks), 96% of entecavir-treated and 64% of lamivudine-treated patients had HBV DNA <300 copies/mL by PCR at end of dosing. ALT normalization (≤1×ULN) occurred in 27% of entecavir-treated and 21% of lamivudine-treated patients at end of dosing.

For patients who met protocol-defined response criteria, response was sustained throughout the 24-week post-treatment follow-up in 75% (83/111) of entecavir responders vs. 73% (68/93) for lamivudine responders in study 022 and 46% (131/286) of entecavir responders vs. 31% (79/253) for lamivudine responders in study 027. By 48 weeks of post-treatment follow-up, a substantial number of HBeAg negative patients lost response.

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, 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×ULN. All 57 patients remained positive for HBsAg.

Lamivudine-refractory trials

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 normalization 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 normalization (≤1×ULN) at end of dosing.

Age/gender
There was no apparent difference in efficacy for entecavir based on gender (≈ 25% women in the clinical trials) or age (≈ 5% of patients >65 years of age).

Special populations
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-naive 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 LVD-resistant 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.

	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)	-4.48*	-3.40	-4.66	-3.90
Stable or improved CTP score[b,c]	66%	71%	61%	67%
MELD score Mean change from baseline[d]	-2.0	-0.9	-2.6	-1.7
HBsAg loss[b]	1%	0	5%	0
Normalization of:[e]				
ALT (≤1×ULN)[b]	46/78 (59%)*	28/71 (39%)	49/78 (63%)*	33/71 (46%)
Albumin (≥1×LLN)[b]	20/82 (24%)	14/69 (20%)	32/82 (39%)	20/69 (29%)
Bilirubin (≤1×ULN)[b]	12/75(16%)	10/65(15%)	15/75 (20%)	18/65 (28%)
Prothrombin time (≤1×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] Defined as decrease or no change from baseline in CTP score.
[d] Baseline mean MELD score was 17.1 for ETV and 15.3 for adefovir dipivoxil.
[e] 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 LVD-resistant 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 viremia 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 log10 copies/mL, ALT normalization 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 coinfected 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).

Clinical resistance
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 LVD-resistant 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	16	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%	51.45%
- 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).

5.2 Pharmacokinetic properties

General 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×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% (see section 4.2).

Distribution
The estimated volume of distribution for entecavir is in excess of total body water, suggesting good tissue penetration of the drug. 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 ^{14}C-entecavir, no oxidative or acetylated metabolites and minor amounts of the phase II metabolites, glucuronide and sulfate conjugates, were observed.

Elimination
After reaching peak levels, entecavir plasma concentrations decreased in a bi-exponential 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.

Entecavir is predominantly eliminated by the kidneys 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.

Linearity/non-linearity
There is a dose-proportionate increase in C_{max} and AUC values following multiple doses ranging from 0.1-1 mg.

Characteristics in patients
Renal impairment
Entecavir clearance decreases with decreasing creatinine clearance. According to the pharmacokinetics studies of entecavir following a single 1-mg dose in patients with renal impairment, dosage adjustment is recommended for patients with a creatinine clearance <50 mL/min.

Pharmacokinetic Parameters in Subjects with Selected Degrees of Renal Function

	Baseline Creatinine Clearance (mL/min)				Severe Managed with Hemodialysis (n=6)	Severe Managed with CAPD (n=4)
	Unimpaired	Mild	Moderate	Severe		
	>80	>50≤80	30-50	<30		
	(n=6)	(n=6)	(n=6)	(n=6)		
C_{max} (ng/mL)	8.1 (30.7)	10.4 (37.2)	10.5 (22.7)	15.3 (33.8)	15.4 (56.4)	16.6 (29.7)

(CV%)						
$AUC_{(0-T)}$ (ng•hr/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)
CLR=renal clearance; CLT/F=apparent oral clearance. CAPD=continuous ambulatory peritoneal dialysis						

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

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.

Post-liver transplant
Entecavir exposure in HBV-infected liver transplant recipients on a stable dose of cyclosporine A (n=5) or tacrolimus (n=4) was approximately 2-fold 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.

Race
The population pharmacokinetic analysis did not identify race as significantly influencing entecavir pharmacokinetics. However, conclusions can only be drawn for the Caucasian and Asian groups as there were too few subjects in the other categories.

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-fetal toxicity (resorptions), lower fetal 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-fetal 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 fetal exposure to entecavir and secretion of entecavir into milk were demonstrated.

No evidence of genotoxicity was observed in an Ames microbial mutagenicity assay, a mammalian-cell 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 tumors were observed at exposures ≥4 and ≥2 times that in humans at 0.5 mg and 1 mg respectively. Tumor 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 tumor development observed in mice likely was species-specific. Increased incidences of other tumors including brain gliomas in male and female rats, liver carcinomas in male mice, benign vascular tumors 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

6.1 List of excipients
Lactose monohydrate
Microcrystalline Cellulose Type 102
Povidone K30
Kollidon CL
Magnesium stearate
Polyvinyl alcohol
Talc
Polyethylene glycol
Titanium dioxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at room temperature below 30ºC and in its original package.

6.5 Nature and contents of container
Blister packing material consisting of Aluminum-Opa-PVC on one side and Aluminum-foil on the other side is used as primary packing material. Blisters are placed into a cardboard box. Each cardboard contains 30 tablets and one package leaflet.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.:1
34303 Küçükçekmece /İSTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

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