SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Entecavir 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains entecavir monohydrate corresponding to 1 mg of entecavir.

Excipients with known effect

Each film-coated tablet contains 241.94 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

Pink oval shaped tablet with score line on both sides with a length 12.8 mm and thickness of 4.8 mm.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Entecavir is indicated for the treatment of chronic hepatitis B virus (HBV) infection (see section 5.1) in adults 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 (see section 4.4)

For both compensated and decompensated liver disease, this indication is based on clinical trial data in nucleoside naive patients with HBeAg positive and HBeAg negative HBV infection. With respect to patients with lamivudine-refractory hepatitis B, see sections 4.2, 4.4 and 5.1.

Entecavir is also indicated for the treatment of chronic HBV infection in nucleoside naive paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, and 5.1.

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 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 (more than 2 hours before and more than 2 hours after a meal) (see section 5.2). In the presence of LVDr mutations, 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 (see section 4.4.).

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 (more than 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.

Paediatric population

For appropriate dosing in the paediatric population, Entecavir oral solution or Entecavir 0.5 mg film-coated tablets are available.

The decision to treat paediatric patients should be based on careful consideration of individual patient needs and with reference to current paediatric treatment guidelines including the value of baseline histological information. The benefits of long-term virologic suppression with continued therapy must be weighed against the risk of prolonged treatment, including the emergence of resistant hepatitis B virus.

Serum ALT should be persistently elevated for at least 6 months prior to treatment of paediatric patients with compensated liver disease due to HBeAg positive chronic hepatitis B; and for at least 12 months in patients with HBeAg negative disease.

Paediatric patients with body weight of at least 32.6 kg, should be administered a daily dose of one 0.5 mg tablet, with or without food. An oral solution may be available for patients with body weight less than 32.6 kg.

Duration of therapy for paediatric patients

The optimal duration of treatment is unknown. In accordance with current paediatric practice guidelines, treatment discontinuation may be considered as follows:

- In HBeAg positive paediatric patients, treatment should be administered for at least 12 months after achieving undetectable HBV DNA and HBeAg seroconversion (HBeAg loss and anti-HBe detection on two consecutive serum samples at least 3-6 months apart) or until HBs seroconversion or there is loss of efficacy. Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation (see section 4.4).
- In HBeAg negative paediatric patients, treatment should be administered until HBs seroconversion or there is evidence of loss of efficacy.

Pharmacokinetics in paediatric patients with renal or hepatic impairment have not been studied.

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. 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)	**Entecavir dosage***	
	Nucleoside naïve 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, haemodialysis 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 haemodialysis days, administer entecavir after haemodialysis.

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

Method of administration

Entecavir should be taken orally.

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.

Exacerbations of hepatitis: spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline (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 B 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) 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. 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 aetiology occur. Benign digestive symptoms, such as nausea, vomiting and abdominal pain, might be indicative of lactic acidosis development. Severe cases, sometimes with fatal outcome, were associated with pancreatitis, liver failure/hepatic steatosis, renal failure and higher levels of serum lactate. Caution should be exercised when prescribing nucleoside analogues to any patient (particularly obese women)

with hepatomegaly, hepatitis or other known risk factors for liver disease. These patients should be followed closely.

To differentiate between elevations in 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.

Paediatric population: A lower rate of virologic response (HBV DNA < 50 IU/ml) was observed in paediatric patients with baseline HBV DNA ≥ 8.0 log10 IU/ml (see section 5.1). Entecavir should be used in these patients only if the potential benefit justifies the potential risk to the child (e.g. resistance). Since some paediatric patients may require long-term or even lifetime management of chronic active hepatitis B, consideration should be given to the impact of entecavir on future treatment options.

Liver transplant recipients: renal function should be carefully evaluated before and during entecavir therapy in liver transplant recipients receiving cyclosporine or tacrolimus (see section 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.

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: 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/mm3).

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: patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. A lactose-free entecavir oral solution is available for these individuals.

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. Entecavir 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.

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

Breast-feeding

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. Breast-feeding should be discontinued during treatment with Entecavir.

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

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).

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 (≥ 1/10); common (≥ 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.

System Organ Class	Frequency	Adverse Reaction
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.

Description of selected adverse reactions

Laboratory test abnormalities: In clinical studies with nucleoside-naive patients, 5% had ALT elevations > 3 times baseline, and < 1% had ALT elevations > 2 times baseline together with total bilirubin > 2 times upper limit of normal (ULN) and > 2 times baseline. Albumin levels < 2.5 g/dl occurred in < 1% of patients, amylase levels > 3 times baseline in 2%, lipase levels > 3 times baseline in 11% and platelets < 50,000/mm3 in < 1%.

In clinical studies with lamivudine-refractory patients, 4% had ALT elevations > 3 times baseline, and < 1% had ALT elevations > 2 times baseline together with total bilirubin > 2 times ULN and > 2 times baseline. Amylase levels > 3 times baseline occurred in 2% of patients, lipase levels > 3 times baseline in 18% and platelets < 50,000/mm3 in < 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 log10/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 times ULN and > 2 times 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.

Paediatric Population

The safety of entecavir in paediatric patients from 2 to < 18 years of age is based on two ongoing clinical trials in subjects with chronic HBV infection; one Phase 2 pharmacokinetic trial (study 028) and one Phase 3 trial (study 189). These trials provide experience in 195 HBeAg-positive nucleoside-treatment-naïve subjects treated with entecavir for a median duration of 99 weeks. The adverse reactions observed in paediatric subjects who received treatment with entecavir were consistent with those observed in clinical trials of entecavir in adults (see a. Summary of the safety profile and section 5.1) with the following exception in the paediatric patients:

- Very common adverse reactions: neutropenia.

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 times ULN and > 2 times baseline, and 1% of patients had ALT elevations > 2 times baseline together with total bilirubin > 2 times ULN and > 2 times baseline. Albumin levels < 2.5 g/dl occurred in 30% of patients, lipase levels > 3 times baseline in 10% and platelets < 50,000/mm3 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 (highly active antiretroviral therapy) 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 authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: 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 Ki for HBV DNA polymerase is 0.0012 μM. Entecavir-TP is a weak inhibitor of cellular DNA polymerases α, β, and δ with Ki 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 (Ki > 160 μM).

Pharmacodynamic Effects

Antiviral activity: entecavir inhibited HBV DNA synthesis (50% reduction, EC50) at a concentration of 0.004 μM in human HepG2 cells transfected with wild-type HBV. The median EC50 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 EC50 values ranging from 0.026 to > 10 μM; the lower EC50 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: relative to wild-type HBV, LVDr viruses containing rtM204V and rtL180M substitutions within the reverse transcriptase exhibit 8-fold decreased susceptibility to entecavir. Incorporation of additional ETVr amino acid changes rtT184, rtS202 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. Lamivudine-resistant strains harboring rtL180M plus rtM204V in combination with amino acid substitution rtA181C conferred 16- to 122-fold reductions in entecavir phenotypic susceptibility. The ETVr 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 LVDr 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 times ULN and baseline HBV DNA ≤ 9.0 log10 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.

	Nucleoside Naive			
	HBeAg Positive (study022)		**HBeAg Negative (study027)**	
	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 (log10 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 normalisation (≤ 1 times ULN)	68%*	60%	78%*	71%
HBeAg Seroconversion	21%	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 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.

	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%
n	141	145
Viral load reduction (log10 copies/ml)[c]	-5.11*	-0.48
HBV DNA undetectable (< 300 copies/ml by PCR)[c]	19%*	1%
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): 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 normalisation, 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 normalisation, 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 normalisation (≤ 1 times 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 normalisation versus 77% for HBV DNA < 300 copies/ml by PCR and 84% for ALT normalisation 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 normalisation (≤ 1 times 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 (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.
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).

Long-Term Follow-Up Study

Study 080 was a randomized, observational open label Phase 4 study to assess long-term risks of entecavir treatment (ETV, n-6,216) or other standard of care HBV nucleoside (acid) treatment (non-ETV) (n-6,162) for up to 10 years in the subjects with chronic HBV (CHB) infection. The principal clinical outcome events assessed in the study were overall malignant neoplasms (composite event of HCC and non-HCC malignant neoplasms), liver related HBV disease progression, non-HCC malignant neoplasms, HCC, and deaths, including liver related deaths. In this study, ETV was not associated with an increased risk of malignant neoplasms compared to use of non-ETV, as assessed by either the composite endpoint of overall malignant neoplasms (ETV n=331, non-ETV n=337; HR=0.93 [0.8-1.1]), or the individual endpoint of non-HCC malignant neoplasm (ETV n=95, non-ETV n=81; HR=1.1 [0.82-1.5]). The reported events for liver-related HBV disease progression and HCC were comparable in both ETV and non-ETV groups. The most commonly reported malignancy in both ETV and non-ETV groups was HCC followed by gastrointestinal malignancies.

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-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 log10 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.

	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	-2.0	-0.9	-2.6	-1.7

baseline[c,e]				
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/mm3 (with only 5 subjects having CD4 count < 200 cells/mm3). 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 log10 copies/ml). For patients originally assigned to entecavir treatment, the reduction in HBV DNA at 48 weeks was -4.20 log10 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.

Paediatric population: Study 189 is an ongoing study of the efficacy and safety of entecavir among 180 nucleoside-treatment-naïve children and adolescents from 2 to < 18 years of age with HBeAg-positive chronic hepatitis B infection, compensated liver disease, and elevated ALT. Patients were randomized (2:1) to receive blinded treatment with entecavir 0.015 mg/kg up to 0.5 mg/day (N = 120) or placebo (N = 60). The randomization was stratified by age group (2 to 6 years; > 6 to 12 years; and > 12 to < 18 years). Baseline demographics and HBV disease characteristics were comparable between the 2 treatment arms and across age cohorts. At study entry, the mean HBV DNA was 8.1 log10 IU/ml and mean ALT was 103 U/l across the study population. Results for the main efficacy endpoints at Week 48 and Week 96 are presented in the table below.

	Entecavir		**Placebo***
	Week 48	**Week 96**	**Week 48**
n	120	120	60
HBV DNA < 50 IU/mL and HBeAg seroconversion[a]	24.2%	35.8%	3.3%
HBV DNA < 50 IU/mL[a]	49.2%	64.2%	3.3.%
HBeAg seroconversion[a]	24.2%	36.7%	10.0%
ALT normalization[a]	67.5%	81.7%	23.3%
HBV DNA < 50 IU/mL[a]			
Baseline HBV DNA < 8 log10 IU/ml	82.6% (38/46)	82.6% (38/46)	6.5% (2/31)
Baseline HBV DNA	28.4%	52.7%	0% (0/29)

≥ 8 log10 IU/ml	(21/74)	(39/74)	

[a] NC=F (noncompleter=failure)

* Patients randomized to placebo who did not have HBe- seroconversion by Week 48 rolled over to open-label entecavir for the second year of the study; therefore randomized comparison data are available only through Week 48.

The paediatric resistance assessment is based on data from nucleoside-treatment-naive paediatric patients with HBeAg-positive chronic HBV infection in two ongoing clinical trials (028 and 189). The two trials provide resistance data in 183 patients treated and monitored in Year 1 and 180 patients treated and monitored in Year 2. Genotypic evaluations were performed for all patients with available samples who had virologic breakthrough through Week 96 or HBV DNA ≥ 50 IU/ml at Week 48 or Week 96 . During Year 2, genotypic resistance to ETV was detected in 2 patients (1.1% cumulative probability of resistance through Year 2).

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 ETVrc 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 log10 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 log10 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]	2e	14e	13e	9e	1e
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 log10 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 log10 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 < 10^4 log10 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).
Integrated Analysis of Phase 2 and 3 Clinical Studies: In a post-approval integrated analysis of entecavir resistance data from 17 Phase 2 and 3 clinical studies, an emergent entecavir resistance-associated substitution rtA181C was detected in 5 out of 1461 subjects during treatment with entecavir. This substitution was detected only in the presence of lamivudine resistance-associated substitutions rtL180M plus rtM204V.

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 Cmax 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. Cmax and Cmin 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 Cmax of 44-46%, and a decrease in AUC of 18-20%. The lower Cmax 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).

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.

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%.

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 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.

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)
Cmax (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

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.

Paediatric population

The steady-state pharmacokinetics of entecavir were evaluated (study 028) in 24 nucleoside naïve and 19 lamivudine-experienced HBeAg-positive paediatric subjects from 2 to < 18 years of age with compensated liver disease.

Entecavir exposure among nucleoside naïve subjects receiving once daily doses of entecavir 0.015 mg/kg up to a maximum dose of 0.5 mg was similar to the exposure achieved in adults receiving once daily doses of 0.5 mg. The Cmax, AUC(0-24), and Cmin for these subjects was 6.31 ng/ml, 18.33 ng h/ml, and 0.28 ng/ml, respectively.
Entecavir exposure among lamivudine-experienced subjects receiving once daily doses of entecavir 0.030 mg/kg up to a maximum dose of 1.0 mg was similar to the exposure achieved in adults receiving once daily doses of 1.0 mg. The Cmax, AUC(0-24), and Cmin for these subjects was 14.48 ng/ml, 38.58 ng·h/ml, and 0.47 ng/ml, respectively.

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 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 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

6.1 List of excipients

Tablet core
Microcrystalline cellulose

Lactose monohydrate

Maize starch pregelatinised

Crospovidone

Magnesium stearate

Film-coating
Titanium dioxide (E 171)

Hypromellose

Macrogol 400

Polysorbate 80
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

Aluminium-Aluminium (OPA/Alu/PVC – Alu) blisters.

30, 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Genus Pharmaceuticals Ltd. (trading as 'STADA'),
Linthwaite,
Huddersfield,
HD7 5QH,
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 06831/0365

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

27/10/2021