WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HP035 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Entecavir (as monohydrate) 0.5 mg

Each tablet contains about 90.5 mg of lactose monohydrate. For the list of excipients, see section 6-1

3. PHARMACEUTICAL FORM

Film-coated tablet

[HP035 trade name] is a white to off-white, round, film-coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'A' debossed (stamped into) one side and '11' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HP035 trade name] is indicated for the treatment of chronic hepatitis B virus (HBV) infection with any of the following features:

- Significant fibrosis or cirrhosis based on clinical criteria;
- Hepatitis B virus DNA exceeding 2000 units/mL and alanine aminotransferase (ALT) level above the upper limit of normal (ULN) *or*, if HBV DNA assay is not available, persistently raised ALT levels over 6 to 12 months;
- Presence of co-infections (such as HIV infection, hepatitis C or D); a family history of liver cancer or cirrhosis; immune suppression; comorbidities (such as diabetes, liver steatosis); or extrahepatic manifestations of HBV infection (such as glomerulonephritis or vasculitis).

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Therapy should be started by a health care provider experienced in the management of chronic hepatitis B infection.

Posology

Adults and adolescents

Compensated liver disease

The recommended dose in adults and adolescents is 0.5 mg once daily, with food or between meals.

Decompensated liver disease

The recommended dose for adults and adolescents with decompensated liver disease is 1 mg once daily, which must be taken on an empty stomach (at least 2 hours after a meal and at least 2 hours before the next meal).

Duration of therapy

Antiviral hepatitis B treatment is lifelong. Discontinuation of treatment may be considered exceptionally for people without clinical evidence of cirrhosis:

- who can be followed carefully after discontinuation and long term for reactivation, and

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

- if there is evidence of loss of HBeAg (a marker of viral replication) and seroconversion to anti-HBe (for people initially HBeAg-positive) and after completing at least 1 additional year of treatment, and
- in association with persistently normal ALT levels and persistently undetectable HBV DNA levels (if HBV DNA testing is available).

If HBV DNA testing is not available: discontinuation of treatment may be considered for people with persistently absent HBsAg (hepatitis B surface antigen) and after completing at least 1 additional year of treatment, regardless of previous HBeAg status.

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

Paediatric population

[HP035 trade name] should only be used for children and adolescents weighing at least 30 kg.

[HP035 trade name] is not suitable for patients weighing less than 30 kg and other products should be checked for availability.

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

The recommended dose in paediatric patients weighing at least 30 kg is 0.5 mg once daily with food or between meals.

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

Special populations

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).

Renal impairment

The clearance of entecavir decreases with decreasing creatinine clearance (see section 5.2). Dose adjustment is recommended for patients with creatinine clearance of less than 50 mL/minute, including those on haemodialysis or continuous ambulatory peritoneal dialysis.

Creatinine clearance	**[HP035 trade name] dose**	
	Patients with compensated liver disease	**Patients with decompensated liver disease**
At least 50 mL/minute	0.5 mg once daily	1 mg once daily
30–49 mL/minute	0.5 mg every 48 hours	0.5 mg once daily or 1 mg every 48 hours
10–29 mL/minute	0.5 mg every 72 hours	1 mg every 72 hours
Less than 10 mL/minute Haemodialysis or continuous ambulatory peritoneal dialysis	0.5 mg every 7 days	1 mg every 7 days

Hepatic impairment

No dose adjustment is required in patients with hepatic impairment.

Missed dose

If a dose is missed, it should be taken as soon as possible. The patients should then take the next regular dose at the usual time.

If it is almost time for the next dose, the missed dose should be skipped, and the next dose should be taken at the usual time. The patient should not take a double dose to make up for a forgotten dose.

Method of administration

[HP035 trade name] should be taken by mouth.

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

Virological response to treatment should be closely monitored in patients with renal impairment.

Exacerbations of hepatitis

Periodic monitoring of hepatic function is recommended during treatment.

Spontaneous exacerbations can occur in chronic hepatitis B. They are characterised by transient increases in serum ALT. After starting antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline (see section 5.1). Among entecavir-treated patients on-treatment exacerbations had a median time of onset of 4–5 weeks.

In patients with compensated liver disease, 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 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. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limiting. However, severe exacerbations, including fatalities, have been reported.

Among entecavir-treated patients who had not previously been treated with a nucleoside analogue, post-treatment exacerbations had a median time to onset of 23–24 weeks, and most were reported in HBeAg-negative patients (see section 5.1). Hepatic function should be monitored with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, hepatitis B treatment may be resumed.

Decompensated liver disease

Serious hepatic adverse events (regardless of causality) were more frequent in patients, in particular those with Child-Turcotte-Pugh (CTP) class C disease, compared to patients with compensated liver function. Also, patients with decompensated liver disease may be at higher risk for lactic acidosis and for renal adverse events such as hepatorenal syndrome. Therefore, clinical and laboratory parameters should be closely monitored in patients with decompensated liver disease.

Lactic acidosis and severe hepatomegaly with steatosis

Lactic acidosis (without hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. It may also occur with entecavir since it is a nucleoside analogue. Treatment with nucleoside analogues should be discontinued if aminotransferase levels rise rapidly, hepatomegaly worsens, or metabolic or lactic acidosis of unknown aetiology occur.

Benign digestive symptoms, such as nausea, vomiting and abdominal pain, might be indicative of lactic acidosis. Severe cases, sometimes with fatal outcome, were associated with pancreatitis, liver failure or

hepatic steatosis, renal failure, and higher levels of serum lactate. The risk of lactic acidosis and liver damage should be considered when prescribing nucleoside analogues to patients (particularly obese women) with hepatomegaly, hepatitis or other risk factors for liver disease. These patients should be followed closely.

To differentiate between rises in aminotransferases due to response to treatment and increases potentially related to lactic acidosis, the health care provider should check that changes in ALT are associated with improvements in other laboratory markers of chronic hepatitis B.

Paediatric population

Virological response (HBV DNA less than 50 units/mL) was lower in paediatric patients with baseline HBV DNA of at least 8.0 $\log_{10}$ units/mL. Entecavir should be used in these patients only if the potential benefit justifies the risk (e.g. of developing resistance). Since some paediatric patients may require long-term or even lifelong management of chronic active hepatitis B, the impact of entecavir on future treatment options should be considered.

Liver transplant recipients

Renal function should be carefully evaluated before and during entecavir therapy in liver transplant recipients receiving ciclosporin or tacrolimus (see section 5.2).

General

Patients should be advised that entecavir therapy may not eliminate the risk of hepatitis B virus transmission and they should therefore still take appropriate precautions.

Excipients

Contains lactose

Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary.

The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients

Patients who are allergic to cow's milk proteins must not be given this medicine unless strictly necessary.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Since entecavir is predominantly eliminated by the kidney, co-administration with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of either medicine. Apart from lamivudine, adefovir dipivoxil and tenofovir disoproxil, the effects of entecavir co-administration with medicines that are excreted renally or affect renal function have not been evaluated. Patients should be monitored closely for adverse reactions when entecavir is co-administered with such medicines.

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. Therefore, CYP450-mediated drug interactions are unlikely with entecavir.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with [HP035 trade name] because the potential risks to the developing foetus are unknown.

Pregnancy

Studies in animals show reproductive toxicity at high doses (see section 5.3). The risk for humans is unknown. [HP035 trade name] should not be used during pregnancy unless clearly necessary. There are no

data on the effect of entecavir on hepatitis B virus transmission from mother to infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of hepatitis B virus.

Breast-feeding

It is unknown whether entecavir is present in breast milk. Toxicological data from animals show presence of entecavir in milk (see section 5.3). As a precaution, breast-feeding should be discontinued during treatment with [HP035 trade name].

Fertility

Toxicology studies have not shown impaired fertility in animals given entecavir (see section 5.3).

4.7 Effects on ability to drive and use machines

Dizziness, fatigue and somnolence are common side effects of [HP035 trade name], 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 with a possible relation to entecavir were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%). Exacerbations of hepatitis have also been reported during entecavir therapy and after discontinuing it (see section 5.1).

Tabulated list of adverse reactions

Assessment of adverse reactions is based on post-marketing surveillance and four clinical studies in which 1720 patients with chronic hepatitis B infection and compensated liver disease received double-blind treatment with entecavir or lamivudine for up to 107 weeks. In these studies, adverse effects, including laboratory abnormalities, were comparable for entecavir 0.5 mg daily, entecavir 1 mg daily, and lamivudine.

Continued entecavir treatment for a median duration of 96 weeks did not reveal any new adverse effects.

The undesirable effects of entecavir are listed below by body system or organ. Frequencies are defined as follows: very common (at least 1 in 10), common (1 in 100 to 1 in 10) uncommon (1 in 1000 to 1 in 100), or rare (1 in 10 000 to 1 in 1000).

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	raised transaminases, exacerbation of hepatitis during treatment (generally resolving with continued treatment), exacerbation of hepatitis after treatment

Skin and subcutaneous tissue disorders

Uncommon	rash, alopecia
Frequency	side effects

General disorders and administration site conditions

Common	fatigue

Investigations

Common	raised bilirubin, raised lipase, raised amylase, raised creatinine, hyperglycaemia, haematuria
Uncommon	decreased albumin levels, thrombocytopenia (platelets count less than 50 000/µL)

Description of selected adverse reactions

Abnormal liver function tests include raised transaminases (including alanine transaminase, ALT), raised bilirubin, and decreased albumin levels (see also section 5.1).

Hepatitis may be exacerbated during treatment, typically 4 to 5 weeks after starting [HP035 trade name] (see section 5.1). Acute exacerbation may also occur on stopping treatment (see section 5.1).

Lactic acidosis has been reported, often in association with hepatic decompensation, other serious medical conditions or drug exposures (see section 4.4).

Paediatric population

In studies among patients aged from 2 to under 18 years, the pattern of adverse reactions was similar to that in adults, except that neutropenia was a very common adverse effect in paediatric patients (see section 5.1).

Other special populations

The pattern of adverse effects in patients with decompensated liver disease was similar to other patients but an additional side effect was decreased blood carbonate (2%) after around 48 weeks (see section 5.1). Patients with high Child-Turcotte-Pugh score were at higher risk of serious events including hepatocellular carcinoma and death from liver-related cause.

The safety profile of entecavir in a limited number of patients co-infected with HIV and hepatitis B virus, receiving lamivudine-containing highly active antiretroviral therapy regimens, was similar to the safety profile of patients with just hepatitis B.

There was no apparent difference in the safety profile of entecavir with respect to gender (about 25% women in the clinical trials) or age (about 5% of patients aged over 65 years).

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

There is limited experience of entecavir overdose. Healthy individuals who received up to 20 mg daily 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 toxicity and given 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 active against HBV polymerase, is efficiently phosphorylated to the active triphosphate form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine triphosphate, entecavir-triphosphate 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-triphosphate K_i for HBV DNA polymerase is 0.0012 μM. Entecavir-triphosphate 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 (Ki > 160 μM).

Antiviral activity

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

An analysis of the inhibitory activity of entecavir against laboratory and clinical HIV-isolates using a variety of cells and assay conditions yielded EC_{50} values ranging from 0.026 μM to > 10 μM; the EC_{50} values were lower 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 lost susceptibility to entecavir.

In HBV combination assays in cell culture, the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, lamivudine, stavudine, tenofovir or zidovudine did not antagonise 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.

Clinical efficacy

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 necro-inflammatory scores (> 10) were associated with greater histological improvement in patients who had not received a nucleoside analogue. Baseline ALT levels ≥ 2 times upper limit of normal 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, most patients had histological and virological responses to treatment.

Safety

Liver function test abnormalities

In studies among patients who had not been treated with a nucleoside analogue, 5% had ALT raised more than 3 times the baseline level, and under 1% had ALT raised more than twice the baseline level together with total bilirubin exceeding twice the upper limit of normal and more than twice the baseline level. Albumin levels were less than 25 g/litre in fewer than 1% of patients, amylase levels were more than 3 times the baseline level in 2%, lipase levels more than 3 times baseline level in 11% and platelets less than 50 000/μL in fewer than 1%.

In studies with lamivudine-refractory patients, 4% had ALT raised more than 3 times baseline level, and under 1% had ALT rises exceeding twice the baseline level together with total bilirubin exceeding twice both

the upper limit of normal and the baseline level. Amylase levels exceeded 3 times the baseline level in 2% of patients, lipase levels exceeded 3 times the baseline level in 18% and platelets to less than 50 000/µL in fewer than 1%.

Exacerbations during treatment

In studies among patients who had not been treated with a nucleoside analogue, on treatment ALT rise exceeded 10 times upper limit of normal and twice the baseline level in 2% of entecavir-treated patients vs 4% of lamivudine-treated patients. In lamivudine-refractory patients, on-treatment ALT rise exceeded 10 times upper limit of normal and twice the baseline level in 2% of entecavir-treated patients vs 11% of lamivudine-treated patients. Among entecavir-treated patients, on-treatment ALT rose after 4–5 weeks on average, generally resolving with continued treatment, and, in most cases, were associated with at least 100-fold reduction in viral load that preceded or coincided with the ALT elevation.

Exacerbations after discontinuation of treatment

Acute exacerbations of hepatitis have been reported in patients who discontinued hepatitis B treatment, including therapy with entecavir. Among patients, ALT rose during post-treatment follow-up in 6% of entecavir-treated patients and 10% of lamivudine-treated patients (ALT exceeded 10 times upper limit of normal and twice the reference [minimum of baseline or last end-of-dosing measurement]). Among entecavir-treated patients who had not received a nucleoside analogue, ALT rose after 23–24 weeks on average, and 86% (24/28) of ALT rises occurred in HBeAg-negative patients. In lamivudine-refractory patients, with only limited numbers of patients being followed up ALT rose in 11% of entecavir-treated patients and no lamivudine-treated patients during post-treatment follow-up.

In the studies entecavir was discontinued if a prespecified response was achieved. If treatment is discontinued without regard to treatment response, the rate of post-treatment ALT flares could be higher.

Adverse events in patients with decompensated liver disease

The safety profile of entecavir in patients with decompensated liver disease was assessed in a randomised open-label comparative study in which patients received treatment with entecavir 1 mg daily (n = 102) or adefovir dipivoxil 10 mg daily (n = 89). Relative to the adverse reactions tabulated in section 4.8, one additional adverse reaction [decrease in blood bicarbonate (2%)] occurred 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 was 12% (12/102). Serious adverse events were generally liver-related, with an on-study cumulative frequency of 69%. Patients with high baseline Child-Turcotte-Pugh score were at higher risk of developing serious adverse events.

Among entecavir-treated patients with decompensated liver disease, none had ALT elevations both above 10 times upper limit of normal and more than twice the baseline levels, and ALT elevations in 1% of patients exceeded twice the baseline together with total bilirubin levels more than 2 times upper limit of normal and more than twice the baseline levels. Albumin levels were less than 25 g/litre in 30% of patients, lipase levels more than 3 times baseline level in 10% and platelet count less than 50,000/µL in 20%.

Paediatric patients

The safety of entecavir in paediatric patients aged from 2 to under 18 years is based on 2 clinical trials in patients with chronic HBV infection; one Phase 2 pharmacokinetic trial and one Phase 3 trial. These trials involved 195 HBeAg-positive nucleoside-treatment-naïve patients treated with entecavir for a median duration of 99 weeks.

Resistance

Adult patients in clinical trials initially treated with entecavir 0.5 mg (not previously treated with a nucleoside analogue) or 1 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 patients not previously treated with a nucleoside, 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 (rtM204Vand rtL180M).

Emerging genotypic entecavir resistance to year 5, in patients not previously treated with a nucleoside analogue					
	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 ETVrc	1	1	1	0	0
– genotypic ETVr[c] with virological 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 virological breakthrough[d]	0.2%	0.2%	0.8%	0.8%	0.8%

[a] Results reflect use of 1 mg 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 to week 58 (Year 1), after week 58 to week 102 (Year 2), after week 102 to week 156 (Year 3), after week 156 to week 204 (Year 4), or after week 204 through week 252 (Year 5).
[c] Patients also have LVDr substitutions.
[d] more than 10-fold increase above nadir in HBV DNA by PCR, confirmed with successive measurements or at the end of the windowed time point.

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 patients during treatment with entecavir. This substitution was detected only in the presence of lamivudine resistance-associated substitutions rtL180M plus rtM204V.

5.2 Pharmacokinetic properties

Pharmacokinetics of Entecavir

Absorption	
Absolute bioavailability	NA*
Oral bioavailability	At least 70%
Food effect	<table><tr><td></td><td>$AUC_{(0-\infty)}$</td><td>C_{max}</td><td>T_{max}</td></tr><tr><td>Low fat or high fat:</td><td>18-20%↓</td><td>44-46%↓</td><td>1-1.5 hrs</td></tr></table>
Distribution	
Volume of distribution (mean)	In excess of total body water (Vz/F 2550 to 7708 L).
Plasma protein binding*in vitro*	≈13%
Tissue distribution	Extensively distributed into tissue
Metabolism	
	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.
Active metabolite(s)	None
Elimination	
Elimination half life	≈ 128-149 h (at steady state)
Mean systemic clearance (Cl/F)	588 ± 154 ml/min
% of dose excreted in urine	About 75%, of which 70% unchanged
% of dose excreted in faeces	6.3%
Pharmacokinetic linearity	More than proportional increase in exposure after single dose administration. Linear pharmacokinetic following multiple doses over the range of 0.1-1 mg
Drug interactions *(in vitro*)	
Transporters	NA
Metabolizing enzymes	NA

*Information not available

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 haemodialysis removed about 13% of the dose, and 0.3% was removed by continuous ambulatory peritoneal dialysis (CAPD). The pharmacokinetics of entecavir following a single 1 mg dose in individuals (without chronic hepatitis B infection) are shown in the table below.

Baseline creatinine clearance (mL/minute)						
	Unimpaired > 80 (n = 6)	Mild >50– ≤80 (n = 6)	Moderate 30–50 (n = 6)	Severe 20–<30 (n = 6)	Severe: managed with haemodialysis (n = 6)	Severe: managed with CAPD (n = 4)
C_{max} (ng/mL) (CV%)	8.1 (30.7)	10.4 (37.2)	10.5 (22.7)	15.3 (33.8)	15.4 (56.4)	16.6 (29.7)
$AUC_{(0\text{-}T)}$ (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/minute) (SD)	383.2 (101.8)	197.9 (78.1)	135.6 (31.6)	40.3 (10.1)	NA	NA
CLT/F (mL/minute) (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 ciclosporin or tacrolimus (n = 9) was about twice the exposure in healthy individuals with normal renal function. Altered renal function contributed to the increase in entecavir exposure in these patients.

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 weight there was no difference in exposure between men and women.

Elderly

The effect of age on the pharmacokinetics of entecavir was evaluated comparing elderly people in the age range 65–83 years (mean age females 69 years, males 74 years) with young adults in the age range 20–40 years (mean age females 29 years, males 25 years). AUC was 29% higher in elderly than in young adults, mainly due to differences in renal function and weight. After adjusting for differences in creatinine clearance and weight, elderly people had a 12.5% higher AUC than young adults. 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 Caucasian and Asian groups as there were too few individuals in the other categories.

Paediatric population

The steady-state pharmacokinetics of entecavir were evaluated in 24 HBeAg-positive paediatric patients who had not previously received a nucleoside analogue. The patients were aged from 2 to under 18 years and had compensated liver disease. Entecavir exposure among these patients receiving once-daily doses of entecavir 0.015 mg/kg up to a maximum dose of 0.5 mg was similar to that in adults receiving once-daily doses of 0.5 mg. The C_{max}, $AUC_{0–24}$, and C_{min} for these patients were 6.31 ng/mL, 18.33 ng·h/mL, and 0.28 ng/mL, respectively.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for entecavir as well as statistical results are summarised in the following table:

Entecavir

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)
t_{max} (h)[#]	0.67 (0.34 – 2.34)	0.84 (0.34 – 2.01)
C_{max} (ng/ml)	10.6 ± 2.7 (10.2)	11.1 ± 2.4 10.9)
AUC_{0-t} (ng.h/ml)	29.0 ± 6.4 (28.3)	29.4 ± 6.1 (28.7)
AUC_{0-inf} (ng.h/ml)	35.3 ± 8.6	36.1 ± 7.9

*geometric mean; #median (range)

5.3 Preclinical safety data

In repeat-dose toxicology studies in dogs, reversible perivascular inflammation occurred 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 adverse effect did not occur in repeat-dose studies in other species, including monkeys given entecavir daily for 1 year at exposures of at least 100 times those in humans.

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

In pregnant rats and rabbits given entecavir, no-effect levels for embryotoxicity and maternal toxicity corresponded to exposures at least 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 occurred at high exposures. In rabbits, embryo-foetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were seen at high exposures. In a peri-postnatal study in rats, no adverse effects on offspring were seen. In a separate study in which entecavir was given to pregnant lactating rats at 10 mg/kg, both foetal exposure to entecavir and secretion of entecavir into milk occurred. In juvenile rats given 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 at least 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.

There was no evidence of genotoxicity 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 occurred at exposures at least 4 and at least twice that in humans at 0.5 mg and 1 mg respectively. Tumour development was preceded by pneumocyte proliferation in the lung in mice but not in rats, dogs, or monkeys, indicating that a key event in lung tumour development in mice was likely to be 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

Core tablet:

Microcrystalline cellulose
Copovidone
Crospovidone
Lactose monohydrate
Magnesium stearate

Film coat:

Hypromellose
Titanium dioxide
Macrogol/PEG
Polysorbate

6.2 Incompatibilities

None

6.3 Shelf life

24 months

In-use period: (for 30 tablet HDPE bottle packs)

Discard the product 30 days after initial opening.

In-use period: (for 100 tablet HDPE bottle packs)

Discard the product 90 days after initial opening.

6.4 Special precautions for storage

Do not store above 30ºC. Avoid excursions above 30ºC.

6.5 Nature and contents of container

Blister pack

Aluminium foil on aluminium foil blister cards, containing 10 tablets. Available in packs of:

1x 10

3 x10.

HDPE bottle:

Round, opaque white plastic (HDPE) bottle containing 30 or 100 tablets. It also contains a sachet of desiccant (drying material). The bottle has an aluminium/plastic foil seal and a white, childproof plastic (polypropylene) screw cap.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. SUPPLIER

RV Lifesciences Limited
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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HP035

9. DATE OF PREQUALIFICATION

19 February 2025

10. DATE OF REVISION OF THE TEXT

March 2025

References

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products