1-8 Summary of product Characteristics

1-8-1 Name of the proprietary

TUTICAVIR 0.5

1-8-2 Name of the Non proprietary

Entecavir Tablets USP 0.5 mg

1-8-3 International Non-proprietary Name (INN) of the Active Ingredients

Entecavir Monohydrate USP

1-8-4 Pharmaceutical form:

Film-Coated Tablet.

1-8-5 Presentation:

10 tablets packed in Blister pack of 211 mm Printed Aluminium foil with 215 mm Silver Base foil, 3 such Blister is packed in an individual pre-printed carton with Package insert.

1-8-6 Route of administration:

Oral

1-8-7 Qualitative and Quantitative composition in active substances and excipients

S. No.	Materials Name	Specification	Qty/ Tablet (mg)	Functional category
1.	**Entecavir monohydrate**	**USP**	**0.50#**	**Active**
2.	Microcrystalline Cellulose 101	BP	69.50	Diluent
3.	Lactose Monohydrate	BP	61.50	
4.	Povidone (K-30)	BP	2.50	Binder
5.	Purified Water*	BP	0.070 mL	Solvent
6.	Crospovidone (Type A)	USP	15.00	Disintegrant
7.	Magnesium Stearate	BP	1.00	Lubricant
	Core Tablet Weight		**150.00**	
8.	Tabcoat TC Yellow TC - 520002	IH	2.500	Coating Material
9.	Spraycel White (SCMB 3181)	IH	2.500	
10.	Isopropyl Alcohol*	BP	0.028 mL	Solvent
11.	Methylene Chloride*	USP	0.065 mL	
	Coated Tablet Weight		**155.00**	

As Entecavir anhydrous

*Do not contribute to the average weight of the tablet.

1-8-8 Pharmacological Class:

Nucleoside analogue (HBV polymerase inhibitor)

1-8-9 Therapeutic Class:

Antiviral

1-8-10 Therapeutic Indication :

Entecavir Tablets USP 0.5 mg is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults and for decompensated liver disease.

1-8-11 Contra- Indications:

Hypersensitivity to the active substance or to any of the excipients present in this formulation

1-8-12 Adverse effects:

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.

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.

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

1-8-13 Precaution and Warning

Renal Impairment: Dosage adjustment is recommended for patients with renal impairment. 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. 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.

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. 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.

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. 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

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). 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. 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).

1-8-13-1 Precautions for use during Pregnancy and lactation

Pregnancy

Pregnancy: The potential risk for humans is unknown. Entecavir should not be used during pregnancy unless clearly necessary.

Breast-feeding:

It is unknown whether entecavir is excreted in human milk. Breast-feeding should be discontinued during treatment with Entecavir.

1-8-13-2 Precautions when driving

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.

1-8-14 Interactions with other Drugs:

Since entecavir is predominantly eliminated by the kidney, 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 tenovfovir were observed.

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

1-8-15 Dosage and method of Administration:

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): 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). 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.

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).

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.

- 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 0.5 mg film-coated tablets are available and for dosages below 0.5 mg an oral solution may be 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.

- 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.

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

Renal impairment: the clearance of entecavir decreases with decreasing creatinine clearance. 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

Oral use.

1-8-16 Over dosage:

In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

1-8-17 Incompatibilities

None stated

1-8-18 Shelf life

24 months

1-8-18-1 Shelf life for the reconstituted forms, if applicable before and after reconstitution:

Not applicable

1-8-19 Storage condition:

Store below 30°C. Protect from light and moisture.

1-8-20 Nature of packaging:

10 tablets packed in Blister pack of 211 mm Printed Aluminium foil with 215 mm Silver base foil, 3 such Blister is packed in an individual pre-printed carton with Package insert.

Primary Packaging	211 mm Printed Aluminium foil 215 mm Silver Base Foil
Secondary Packaging	Printed Carton & Package insert.

1-8-21 Registering for a Poisons List: Not applicable