Public Assessment Report
HEVAPIR®

PRODUCT INFORMATION

Drug Name	:	HEVAPIR®
Active Substance	:	Entecavir 0.5 mg
Dosage Form	:	Dispersible tablets
Registrant	:	PT. Dipa Pharmalab Intersains
Manufacturer	:	Chia Tai Tianqing Pharmaceutical Group Co., Ltd, Lianyungang, China
Registration Category	:	New dosage form
Proposed indication	:	Hevapir® dispersible tablets is indicated for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.
Proposed Posology	:	**Compensated liver disease** The recommended dose for chronic hepatitis B virus infection in nucleoside-treatment-naive adults and adolescents 16 years of age and older is 0.5 mg once daily, with or without food. The recommended dose in adults and adolescents (≥16 years of age) with a history of hepatitis B viremia while receiving lamivudine resistance mutations is 1 mg once daily, which must be taken on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal). **Decompensated liver disease** The recommended dose for adults 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 2 hours before the next meal). **Renal Impairment** In subjects with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased (see section Pharmacokinetic properties). Dosage adjustment is recommended for patients with creatinine clearance <50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in the table.

Creatinine Clearance (mL/min)	Usual Dose (0.5 mg)	Lamivudine-Refractory or Decompensated Liver Disease (1 mg)
30 - < 50	0.5 mg every 48 hours	1 mg every 48 hours
10 - < 30	0.5 mg every 72 hours	1 mg every 72 hours
< 10	0.5 mg every 7 days	1 mg every 7 days
Hemodialysis* or CAPD	0.5 mg every 7 days	1 mg every 7 days

* If administered on hemodialysis day, administer Hevapir® after the hemodialysis session

Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

Duration of Therapy

The optimal duration of treatment for patients with chronic hepatitis B virus infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

INTRODUCTION

The drug with the active substance Entecavir has been approved in Indonesia in tablet dosage form with strengths of 0.5 mg and 1 mg, namely Baraclude® which is produced by Myers Squibb, Indiana, USA.

QUALITY ASPECTS

Hevapir® is available in dispersible tablets dosage form contains the active ingredient Entecavir 0.5 mg and excipients consisting of betacyclodextrin, microcrystalline cellulose, crospovidone, silicon dioxide, povidone k30, sodium lauryl sulfate and magnesium stearate.

ACTIVE SUBSTANCE

The raw material for the active substance Entecavir has the appearance of a white or pale white crystalline powder, odorless, tasteless.

Entecavir monohydrate possesses three chiral centers, which located at the 1, 3 and 4 position of the five-membered ring, and the configuration is S, R, S respectively.

Characterization has

been carried out for description parameters, solubility, optical rotation, enantiomer and crystal polymorphism.

The chemical structure of Entecavir has been demonstrated based on element analysis, spectroscopy (UV, mass, IR, 1H- and 13C-NMR), calorimetry, thermogravimetric analysis, X-ray powder diffraction and single-crystal X-ray.

The specifications for the active substance have been determined to consist of a description (visual), solubility (visual), optical rotation, identification [high performance liquid chromatography (HPLC)], pH, related substances (HPLC), enantiomer (HPLC), residual solvent [gas chromatography (GC)], toluene (GC), water content, residue on ignition, heavy metals dan assay (HPLC).

The active substance stability test carried out showed that the active substance raw material was stable at a temperature of 25°C for 24 months.

Finished product

The finished drug is produced in dispersible tablets dosage form white, round, with embossed letters RZ on both sides.

The production process is carried out using a wet granulation process, and critical stages are also identified, including *in-process control*. Process validation has been carried out on 3 production scale batches. Process validation results show the ability of the process to produce finished drugs that meet the specified acceptance criteria.

Drug specifications have been determined, namely description (visual), identification (HPLC), related substance (HPLC), enantiomer, dissolution (HPLC), content uniformity, microbial limits, description, dispersion uniformity, friability and assay (HPLC).

The parameters in the specifications are selected by considering, among other things, the results of batch tests used in clinical trials, long-term stability data, production process variability as well as analytical methods and relevant process development data. The analytical method used has been validated. The results of the batch analysis provide results that meet the required specifications.

Stability data from 6 batches of production scale drugs was carried out at a temperature of 40°C/75% RH for 6 months and in zone IVB, namely at a temperature of 30°C/75% RH for 36 months with results that met the required specifications.

The finished product stability test carried out showed that the finished product was stable at a temperature of 30°C for 24 months.

Conclusion

From the quality aspect, Hevapir® medicinal product Dispersible Tablets considered for acceptance.

ASPECTS OF SAFETY EFFECTIVENESS

Non-Clinical Studies

No non-clinical studies were submitted.

Clinical Studies

The evaluation was carried out in one bioequivalence study: Study No. ZDTQ 2016-004.

A bioequivalence study was conducted on Entecavir Dispersible Tablets (Hevapir®) compared with the originator product Entecavir Tablets (Baraclude®) with study design a

single-center, randomized, open, single- dose, two-cycle, two-cross bioequivalence study in 26 healthy adult subjects under fasting condition. The study results showed bioavailability equivalent to Entecavir Tablets (Baraclude®) based on:

- The AUC_{0-t} value test product are 13.65 ± 2.62 h.ng/mL and AUC_{0-t} reference product are 13.17 ± 2.47 h.ng/mL. Geometric mean ratio AUC_{0-t} test product compare with reference are 103.66% with 90% CI are 100.30 – 107.13%.
- The $AUC_{0-\infty}$ value test product are 17.17 ± 3.57 h.ng/mL and $AUC_{0-\infty}$ reference product are 15.34 ± 2.95 h.ng/mL. Geometric mean ratio $AUC_{0-\infty}$ test product compare with reference are 103.90 % with 90% CI are 97.42 % – 110.81%.
- The C_{max} value test product with reference product has a value comparable that is 4.74 ± 1.33 ng/mL and 4.74 ± 0.98 ng/mL. Geometric mean ratio C_{max} test product compare with reference are 97.71% with 90% CI are 89.22 % – 107.01%.

Table 13

Pharmacokinetic Parameters Descriptive Statistics of Test Product (T) and Reference Product (R)

Parameter (unit)	Arithmetic mean ± SD (% CV) (N=26)	
	Test product	Reference product
C_{max} (ng/mL)	4.74 ± 1.33 (28.07%)	4.74 ± 0.98 (20.71%)
*T_{max} (hr)	0.5 [0.33, 2.0]	0.75 [0.33, 1.0]
AUC_{0-t} (hr*ng/mL)	13.65 ± 2.62 (19.20%)	13.17 ± 2.47 (18.77%)
$AUC_{0-\infty}$ (hr*ng/mL)	17.17 ± 3.57 (20.83%)	15.34 ± 2.95 (19.25%)
λ_z (1/hr)	0.0128 ± 0.0034 (26.26%)	0.0145 ± 0.0052 (35.86%)
$t_{1/2}$ (hr)	57.46 ± 14.24 (24.79%)	52.83 ± 15.41 (29.16%)
* T_{max} is expressed as Median [Minimum, Maximum]		

Pharmacokinetic parameters (unit)	Geometric mean and ratio (N=26)			Intra-individual variation of subjects % CV	90% CI	Power %
	Test product (T)	Reference product (R)	(T/R)%			
C_{max} (ng/mL)	4.53	4.64	97.71%	19.34%	89.22% - 107.01%	97.6%
AUC_{0-t} (h·ng/mL)	13.40	12.93	103.66%	6.95%	100.30% - 107.13%	≥ 99.9%
$AUC_{0-\infty}$ (h·ng/mL)	16.59	15.97	103.90%	5.89%	97.42% - 110.81%	≥ 99.9%

Safety data showed no serious side effects or deaths. There were no clinically significant abnormalities in vital signs before and after drug administration during the study.

DECISION

Registration Hevapir ® 0.5 mg Dispersible Tablets agreed to be accepted with the following considerations:

- Hevapir® 0.5 mg Dispersible Tablets accepted with indications adapted to Baraclude® Tablets, namely with additional information on things to consider before using Entecavir.
- The results of the equivalence study demonstrated the efficacy and safety of Hevapir® comparable to innovator product Baraclude®, Entecavir 0.5 mg tablets.

Approved indications are:

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

The following points should be considered when initiating therapy with Hevapir®:

- This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside treatment-naive and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative chronic HBV infection and compensated liver disease.
- Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease.
- Virologic, biochemical, serologic, and safety data are available for a limited number of adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy.

Public Assessment Report
HEVAPIR®

INFORMASI PRODUK

Nama Obat	:	HEVAPIR®
Zat Aktif	:	Entecavir 0,5 mg
Bentuk Sediaan	:	Tablet *dispersible*
Pendaftar	:	PT. Dipa Pharmalab Intersains
Produsen	:	Chia Tai Tianqing Pharmaceutical Group Co., Ltd, Lianyungang, China
Kategori Registrasi	:	Bentuk sediaan baru
Indikasi yang diajukan	:	*Hevapir® dispersible tablets is indicated for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.*
Posologi yang diajukan	:	***Compensated liver disease***

The recommended dose for chronic hepatitis B virus infection in nucleoside-treatment-naive adults and adolescents 16 years of age and older is 0.5 mg once daily, with or without food.

The recommended dose in adults and adolescents (≥16 years of age) with a history of hepatitis B viremia while receiving lamivudine resistance mutations is 1 mg once daily, which must be taken on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).

Decompensated liver disease

The recommended dose for adults 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 2 hours before the next meal).

Renal lmpairment

ln subjects with renal impairment, the apparent oral clearance of entecavir decreased as creatinine clearance decreased (see section Pharmacokinetic properties). Dosage adjustment is recommended for patients with creatinine clearance <50 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as shown in the table.

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< 10	*0.5 mg every 7 days*	*1 mg every 7 days*
Hemodialysis or CAPD*	*0.5 mg every 7 days*	*1 mg every 7 days*

** If administered on hemodialysis day, administer Hevapir® after the hemodialysis session.*

Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment.

Duration of Therapy

The optimal duration of treatment for patients with chronic hepatitis B virus infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown.

PENGANTAR

Obat dengan zat aktif Entecavir telah disetujui di Indonesia dalam bentuk sediaan tablet dengan kekuatan 0.5 mg dan 1 mg yaitu Baraclude® yang diproduksi oleh Myers Squibb, Indiana, USA.

ASPEK MUTU

Hevapir® tersedia dalam bentuk sediaan tablet *dispersible* mengandung zat aktif Entecavir 0,5 mg dan eksipien terdiri atas *betacyclodextrin, microcrystalline cellulose, crospovidone, silicon dioxide, povidone k30, sodium lauryl sulfate* dan *magnesium stearate*.

ZAT AKTIF

Bahan baku zat aktif Entecavir memiliki pemerian serbuk kristal putih atau putih pucat, tidak berbau, tidak berasa.

Entecavir monohidrat memiliki tiga pusat kiral, yang terletak di posisi 1, 3 dan 4 dari cincin beranggota lima, dan konfigurasinya masing-masing adalah S, R, S.
Telah dilakukan karakterisasi untuk parameter pemerian, kelarutan, rotasi optik, *enantiomer* dan polimorfisme kristal.

Struktur kimia Entecavir telah ditunjukkan berdasarkan uji element analysis, spektroskopi (UV, massa, IR, 1H- dan 13C-NMR), kalorimetri, *thermogravimetric analysis, X-ray powder diffraction* dan *single-crystal X-ray*.

Spesifikasi zat aktif telah ditetapkan terdiri dari pemerian (*visual*), kelarutan (*visual*), rotasi optik, identifikasi [*high performance liquid chromatography* (HPLC)], pH, *related*

substances (HPLC), *enantiomer* (HPLC), *residual solvent* [*gas chromatography* (GC)], toluene (GC), *water content, residue on ignition*, *heavy metals* dan assay (HPLC).

Uji stabilitas zat aktif yang dilakukan menunjukkan bahan baku zat aktif stabil pada suhu 25°C selama 24 bulan.

Produk Jadi

Obat jadi diproduksi dalam bentuk sediaan tablet *dispersible* berwarna putih, bulat, dengan huruf timbul RZ pada kedua sisinya.

Proses produksi dilakukan dengan menggunakan proses granulasi basah, dan juga dilakukan identifikasi terhadap tahapan kritikal, termasuk *in-process control*. Validasi proses telah dilakukan terhadap 3 bets skala produksi. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

Spesifikasi obat telah ditetapkan yaitu deskripsi (visual), identifikasi (HPLC), *related substance* (HPLC), *enantiomer*, disolusi (HPLC), keseragaman kandungan, batas mikroba, pemerian, *dispersion uniformity*, friabilitas dan *assay* (HPLC).

Parameter dalam spesifikasi dipilih dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang, variabilitas proses produksi maupun metode analisis dan data pengembangan proses yang relevant. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Data stabilitas dari 6 bets obat skala produksi telah dilakukan pada suhu 40°C/75% RH selama 6 bulan dan pada zona IVB yaitu pada suhu 30°C/75% RH selama 36 bulan dengan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Uji stabilitas produk jadi yang dilakukan menunjukkan produk jadi stabil pada suhu 30°C selama 24 bulan.

Kesimpulan

Dari aspek mutu, produk obat Hevapir® tablet *dispersible* dipertimbangkan untuk diterima.

ASPEK KHASIAT KEAMANAN

Studi Nonklinik

Tidak ada studi non klinik yang diserahkan.

Studi Klinik

Evaluasi dilakukan pada satu studi bioekivalensi: Study No. ZDTQ 2016-004.

Studi bioekivalensi dilakukan pada Hevapir® tablet *dispersible* dibandingkan dengan obat komparator Baraclude® tablet (produksi Bristol-Myers Squibb Company) dengan desain *single center, randomized, open, single dose, two cycle, two cross bioequivalence study* pada 26 subjek dewasa sehat dalam kondisi puasa. Hasil studi menunjukkan bioavailabilitas ekivalen dengan Baraclude® tablet berdasarkan:

- Nilai AUC_{0-t} obat uji 13,65 ± 2,62 h.ng/mL dan AUC_{0-t} obat komparator 13,17 ± 2,47 h.ng/mL. Rasio rata-rata geometrik AUC_{0-t} obat uji dibandingkan komparator adalah 103,66% dengan CI 90% adalah 100,30 % – 107,13%.
- Nilai $AUC_{0-\infty}$ obat uji 17,17 ± 3,57 h.ng/mL dan $AUC_{0-\infty}$ obat komparator 15,34 ± 2,95 h.ng/mL. Rasio rata-rata geometri $AUC_{0-\infty}$ obat uji dibandingkan komparator adalah 103,90 % dengan CI 90% adalah 97,42 % – 110,81%.
- Nilai C_{max} obat uji dibandingkan obat komparator mempunyai nilai sebanding yaitu 4,74 ± 1,33 ng/mL dan 4,74 ± 0,98 ng/mL. Rasio rata-rata geometrik obat uji C_{max} dibandingkan komparator adalah 97,71% dengan CI 90% adalah 89,22 % – 107,01%.

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**T_{max} (hr)*	*0.5 [0.33, 2.0]*	*0.75 [0.33, 1.0]*
*AUC_{0-t} (hr*ng/mL)*	*13.65 ± 2.62 (19.20%)*	*13.17 ± 2.47 (18.77%)*
*$AUC_{0-\infty}$ (hr*ng/mL)*	*17.17 ± 3.57 (20.83%)*	*15.34 ± 2.95 (19.25%)*
λ_z (1/hr)	*0.0128 ± 0.0034 (26.26%)*	*0.0145 ± 0.0052 (35.86%)*
$t_{1/2}$ (hr)	*57.46 ± 14.24 (24.79%)*	*52.83 ± 15.41 (29.16%)*
** T_{max} is expressed as Median [Minimum, Maximum]*		

Pharmacokinetic parameters (unit)	***Geometric mean and ratio (N=26)***			***Intra-individual variation of subjects % CV***	***90% CI***	***Power %***
	Test product (T)	***Reference product (R)***	***(T/R)%***			
C_{max} (ng/mL)	*4.53*	*4.64*	*97.71%*	*19.34%*	*89.22% - 107.01%*	*97.6%*
AUC_{0-t} (h·ng/mL)	*13.40*	*12.93*	*103.66%*	*6.95%*	*100.30% - 107.13%*	*≥ 99.9%*
$AUC_{0-\infty}$ (h·ng/mL)	*16.59*	*15.97*	*103.90%*	*5.89%*	*97.42% - 110.81%*	*≥ 99.9%*

Data keamanan menunjukkan tidak ada efek samping yang serius dan kematian. Tidak ada kelainan tanda-tanda vital yang signifikan secara klinik sebelum dan setelah pemberian obat selama studi.

KEPUTUSAN

Registrasi Hevapir® 0,5 mg Tablet *Dispersible* disepakati untuk diterima dengan pertimbangan sebagai berikut:

- Hevapir® 0,5 mg tablet *dispersible* diterima dengan indikasi yang disesuaikan dengan Baraclude® Tablet, yaitu dengan penambahan informasi hal-hal yang menjadi pertimbangan sebelum menggunakan Entecavir.
- Hasil studi ekivalensi menunjukkan bahwa khasiat dan keamanan Hevapir® sebanding dengan innovator Baraclude®, Entecavir tablet 0,5 mg.

Indikasi yang disetujui yaitu:

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

The following points should be considered when initiating therapy with Hevapir®:

- *This indication is based on histologic, virologic, biochemical, and serologic responses in nucleoside treatment-naive and lamivudine-resistant adult subjects with HBeAg-positive or HBeAg-negative chronic HBV infection and compensated liver disease.*
- *Virologic, biochemical, serologic, and safety data are available from a controlled study in adult subjects with chronic HBV infection and decompensated liver disease.*
- *Virologic, biochemical, serologic, and safety data are available for a limited number of adult subjects with HIV/HBV co-infection who have received prior lamivudine therapy.*