HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

5 October 2011

BARACLUDE 0.5 mg film-coated tablet
B/30 (CIP code: 376 289-7)

BARACLUDE 1 mg film-coated tablet
B/30 (CIP code: 376 291-1)

BARACLUDE 0.05 mg/ml oral solution
B/1 bottle (CIP code: 376 292-8)

Applicant: BRISTOL-MYERS SQUIBB

entecavir
ATC Code: J05AF10 (Antivirals for systemic use)

List I

Medicinal product for initial bi-annual prescription for the use of specialists and/or gastroenterology, hepatology, general medicine or infectology departments only
Renewal not restricted.

Date of the Marketing Authorisation (centralised procedure): 26 June 2006

Reason for request: Inclusion on list of products refundable by National health Insurance and for hospital use for the extension in the indication for adult patients with chronic hepatitis B with **decompensated liver disease** (corrigendum to Marketing Authorisation of 28 February 2011).

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Entecavir

1.2. Indication (including the extension of the indication ***in Bold***)

"BARACLUDE is indicated for the treatment of adult patients with chronic hepatitis B (HBV) virus infection (see section 5.1 of SPC) presenting with:

- a compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels, and histological evidence of inflammation and/or fibrosis.
- **decompensated liver disease (see section 4.4 of the SPC).**

For both compensated and decompensated liver disease, this indication is based on clinical study data in nucleoside naïve patients with HBeAg positive and HBeAg negative HBV infection. With respect to patients with lamivudine-refractory hepatitis, see sections 4.4 and 5.1 of the SPC."

1.3. Dosage

"Treatment should be initiated by a doctor specialising in the management of chronic hepatitis B infection.
BARACLUDE should be taken orally, once daily.

Compensated liver disease

Nucleoside naïve patients: the recommended dosage 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 of the SPC): the recommended dose is 1 mg once daily, which must be taken on an empty stomach (more than 2 hours before or more than two hours after a meal) (see section 5.2 of the SPC).

Decompensated liver disease

For patients with decompensated liver disease, the recommended dose is 1 mg once daily, which must be taken on an empty stomach more than two hours before or more than two hours after a meal) (see section 5.2 of the SPC). For patients with lamivudine resistant HBV, see sections 4.4 and 5.1 of the SPC.

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

- In HBeAg positive patients, treatment should be administered at least until HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection on two consecutive serum samples at least 3-6 months apart) or until HBs seroconversion or there is loss of efficacy (see section 4.4 of the SPC).
- In HBeAg negative patients, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment for more than two 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."

For use in paediatric patients and adolescents, the elderly, renal impairments, hepatic impairment: see the Summary of Product Characteristics

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J : Anti-infectives for systemic use
J05 : Antivirals for systemic use
J05A : Direct acting antivirals
J05AF : Non-nucleoside reverse transcriptase inhibitors
J05AF10 : Entecavir

2.2. Medicines in the same therapeutic category

These are nucleoside or nucleotide analogues indicated in the treatment of chronic hepatitis B infection.

Products (DCI)	**Indication**
ZEFFIX (lamivudine)* - 100 mg, film-coated tablet, B/28 - 5 mg/ml, os, 240 ml Commercialisation: 20/08/1999	Treatment of adult patients with chronic hepatitis B presenting with: - **compensated liver disease** and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels, and histological evidence of inflammation and/or fibrosis. **Treatment with lamivudine should occur only if there is no other appropriate or available antiviral with a higher genetic barrier** - **decompensated liver disease in combination with a second antiviral with no cross-over resistance to lamivudine**
HEPSERA (adefovir dipivoxil)* - 10 mg, tablet, B/30 Commercialisation: 08/04/2003	Treatment of adult patients with chronic hepatitis B presenting with: - **compensated liver** disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels, and histological evidence of inflammation and fibrosis; - **decompensated liver** disease.
SEBIVO (telbivudine)** 600 mg film-coated tablet B/28 Commercialisation : 15/04/2008	Treatment of chronic hepatitis B in adults with **compensated liver disease** and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels, and histological evidence of inflammation and/or fibrosis.
VIREAD (tenofovir disoproxil)* 245 mg film-coated tablet B/30 Commercialisation: 14/02/2002 (Marketing Authorisation for HBV since 12/09/2008)	Treatment of adult patients with chronic hepatitis B presenting with: • compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels, and histological evidence of inflammation and/or fibrosis. • **decompensated liver disease** Viread is also indicated, in combination with other antivirals, for the treatment of adult patients, over 18 years old, with HIV-1.

* Guidelines from the European Association for the Study of the Liver (EASL: expert report, Clinical Practical guidelines, Journal of Hepatology 2009) recommend entecavir (BARACLUDE) and tenofovir (VIREAD) as first-line treatments for patients with decompensated liver disease. ZEFFIX, HEPSERA are no longer recommended as first-line treatments due to their lower antiviral activity and them being weaker genetic barriers.

** Medicinal products that do not have Marketing Authorisation for the treatment of patients with hepatitis B and decompensated liver disease.

2.3. Medicines with a similar therapeutic aim

Not applicable

3 ANALYSIS OF AVAILABLE DATA

3.1. Data in the treatment of HBV in patients with compensated liver disease (conclusion of the opinion of the TC of 29 November 2006)

The clinical file was made up of three comparative clinical studies of adult patients with chronic hepatitis B infection, presenting with compensated liver disease.

Committee conclusions on these studies

- Nucleoside naïve patients:

In HBeAg positive patients carrying the wild-type hepatitis B virus, and HBeAg negative patients carrying a mutant hepatitis B virus, entecavir has been more effective than lamivudine after 48 weeks of treatment, in terms of histological, virological (reduction in the viral load – percentage of patients with undetectable HBV DNA) and biochemical (standardisation of ALT) improvements. The percentage of patients with HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe antibody detection) was not statistically different between the two entecavir and lamivudine groups in HBeAg positive patients.

The tolerance profiles for both entecavir and lamivudine were comparable.

No emergence of resistance was observed at 96 weeks in patients treated with entecavir, who were non carriers of resistance mutations to lamivudine on inclusion.

- Lamivudine-refractory patients

In HBeAg positive patients carrying the wild-type hepatitis B virus, entecavir was more effective than lamivudine after 48 weeks of treatment in terms of histological, virological (reduction in the viral load – undetectable HBV DNA) and biochemical (standardisation of ALT) improvement. The percentage of patients with HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe antibody detection) was not statistically different between the two entecavir and lamivudine groups.

The tolerance profiles for entecavir and lamivudine were comparable.

The total frequency of virologic breakthrough due to entecavir resistance mutations was 9% between the 48th and 96th week in lamivudine resistant patients.

3.2. Extension of the indication to treat HBV in patients with decompensated liver disease

The file is supported by the results at 24 and 48 weeks[1] of a phase III clinical study (Study AI463048), which lasted 96 weeks, that compared the efficacy and tolerance of entecavir (BARACLUDE) versus adefovir (HEPSERA) in patients with decompensated liver disease.

Study data at 96 weeks, included in the file for reference purposes only, was not analysed in this document as it is currently being assessed by the EMA.

[1] Liaw YF, Raptopoulou-Gigi M, Cheinquer H et coll. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: A randomized open-label study. Hepatology. 2011 Apr 18. doi: 10.1002/hep.24361.

- **Study method**

This was a phase III randomised, open-label multicentre study.
Patients included needed to be at least 16 and have decompensated liver disease (CPT score[2] ≥ 7), a viral load (plasma HBV DNA) ≥ 10^5 copies/ml. Transplant patients were eligible provided that liver decompensation was due to HBV infection and not because of rejection. Patients that had been previously treated with lamivudine, famciclovir, interferon alpha or other immunomodulators were also eligible.
The main non-inclusion criteria were:
- ALT > 15 x Upper Limit of Normal (ULN),
- recent history of pancreatitis,
- co-infection with HIV, HCV or HDV,
- another liver disease (alcohol related, auto-immune etc.)
- previous treatment with entecavir, adefovir, tenofovir

Treatments

The patients were randomised (ratio 1:1) to receive, as open-label:
- entecavir, at a dose of 1 mg, to be taken once daily,
- adefovir, at a dose of 10 mg to be taken once daily.

The protocol included an adjustment of the dosage based on creatinine clearance: reduce the daily dose for patients treated with entecavir and the dosage interval for patients treated with adefovir.

Patients should be treated for a minimum duration of 24 weeks, which may be extended to 96 weeks from the first dose taken by the last randomised patient. After the first 24 weeks of treatment, therapeutic decisions will be made, depending on the virological response of the patient:
- patients not responding at 24 weeks (reduction in viral load < 1 log10 compared with the initial value of HBV DNA) can continue with treatment or have it stopped, based on the decision made by the clinical investigator,
- patients not responding at 52 weeks (HBV DNA viral load ≥ 10^4 copies/ml and a reduction < 2 log10 in viral load) should cease treatment as part of the study

Endpoints

- Primary efficacy endpoint
  - mean reduction in HBV DNA viral load (log_{10} copies/ml) at the 24th week of treatment, adjusted for the viral load at inclusion and lamivudine resistance.

- Secondary endpoints
  These include:
  - reduction in viral load (HBV DNA) at the 48th week of treatment,
  - viral load < 300 copies/ml, at weeks 24 and 48,
  - standardisation of ALT (≤ 1 x ULN in patients presenting with a level at inclusion > 1 x ULN) at weeks 24 and 48,
  - improvement in Child-Pugh-Turcotte score at 48th week,
  - improvement in MELD (Model for End-Stage Liver Disease[3]) score at the 48th week of treatment.

[2] The **Child-Pugh-Turcotte (CPT) score** is given based on five parameters (blood bilirubin, blood albumin, prothrombin levels, presence or not of ascites or encephalopathy) which highlights the severity of the liver disease. The higher the score, the more severe the liver disease. Classically compensated cirrhoses are Child A (score 5-6 points) and decompensated cirrhoses have Child B (7-9 points) or C (10-15 points) scores. Liver transplantation is discussed from a CPT score ≥ 7.
[3] The **MELD Score** allows the degree of hepatocellular impairment to be assessed, based on blood creatinine levels, total plasma bilirubin levels and the International Normalised Ratio (INR).

➢ Results

- Study population

  A total of 431 patients were selected, and from those 195 were randomised to receive one of the two treatments being studyled (entecavir, n = 101; adefovir, n = 94).
  The medical and demographic characteristics of patients included are shown in Table 1.

Table 1: Characteristics of the patients on inclusion (randomised patients)

	Entecavir 1 mg n =101	**Adefovir 10 mg n = 94**	**Total n = 195**
Mean age (years)	51 ± 1.2	53 ± 1.1	52 ± 0.8
Male: n (%)	78 (78)	64 (70)	142 (74)
Asian	55 (55)	49 (54)	104 (54)
Caucasian	35 (35)	28 (31)	63 (33)
HBeAg positive patients, n (%)	54 (54)	50 (55)	104 (54)
HBV DNA, mean (log_{10} copies/ml)	7.53 ± 0.183	8.16 ± 0.228	7.83 ± 0.146
ALT (UI/l), mean	99.2 ± 11.12	100.0 ± 8.56	99.6 ± 7.09
Presence of lamivudine resistance mutation, n (%)	36 (36)	30 (33)	66 (35)
Child-Pugh-Turcotte score, mean	8.81 ± 0.198	8.35 ± 0.190	8.59 ± 0.139
Child-Pugh-Turcotte class, n (%)			
A (score between 5 and 6 points)	7 (7)	10 (11)	17 (9)
B (score between 7 and 9 points)	63 (63)	61 (67)	124 (65)
C (score between 9 and 15 points)	30 (30)	20 (22)	50 (26)
MELD score, mean	17.07 ± 0.500	15.30 ± 0.484	16.23 ± 0.354

Mean ± standard error

Thirty-nine (38%) patients from the entecavir group and 35 (39%) patients from the adefovir group had already been treated with at least one hepatitis B specific medicinal product, primarily lamivudine (39 patients from the entecavir group and 34 patients from the adefovir group). Previous treatment with interferon was reported in three patients from the entecavir group and four from the adefovir group. Patients had a mean creatinine clearance of 84.5 ± 2.31 ml/min.
One hundred and thirty three (68%) patients completed the first 48 weeks of the study and 58 (30 %) patients stopped before week 48. The main reason for ceasing treatment was death (16% in the entecavir group versus 18% in the adefovir group).

- Efficacy

  Entecavir was superior to adefovir for the primary efficacy endpoint: mean reduction of serum HBV DNA at week 24 compared with the start of the study, adjusted for viral load at inclusion and lamivudine resistance (difference -1.74, IC 95% = [-2.30, -1.18], p < 0.0001).
  Results for the endpoints at week 24 and at week 48 are shown in Table 2.

Table 2: Efficacy endpoints at week 24 and at week 48 (ITTm analysis: patients having received at least one dose of treatment)

Parameter	Week 24		Week 48	
	Entecavir 1 mg n = 100	Adefovir 10 mg n = 91	Entecavir 1 mg n = 100	Adefovir 10 mg n = 91
Mean reduction in viral load (HBV DNA log10 copies/ml)	-4,48*	-3,40	-4,66	-3,90
HBV DNA< 300 copies/ml, (%)	49*	16	57*	20
HBeAg negative reaction, n/N (%)	0/54 (0)	7/51 (14)	6/54 (11)	9/51 (18)
HBe seroconversion, n/N (%)	0/54 (0)	6/51 (12)	3/54 (6)	5/51 (10)
AgHBs disappearance, n/N (%)	1/100 (1)	0/91 (0)	5/100 (5)	0/91 (0)
ALT standardised (≤ 1 X ULN)[a], n/N (%)	46/78 (59)*	28/71 (39)	49/78 (63)*	33/71 (46)
CPT score stable or improved, n/N (%)	66/100 (66)	65/91 (71)	61/100 (61)	61/91 (67)
CPT score improved, n/N (%)	25/93 (27)	22/81 (27)	35/93 (38)	29/81 (36)
MELD score: mean development	-2.0	-0.9	-2.6	-1.7

[a] Denominator: patients presenting with abnormal levels at the start of the study.
* p<0.05

In patients with lamivudine-resistance mutations at the start of the study, the viral response (HBV DNA < 300 copies/ml) was 44% in the entecavir group versus 20% in the adefovir group at week 24 and 50% versus 17% at week 48.

- Adverse effects

  The incidence of adverse events was 89% (91/102) in the entecavir group versus 97% (86/89) in the adefovir group. The main adverse events observed during the study are summarised in Table 3 (exposure for approximately two years, study on going).

Table 3: The most commonly occurring adverse events (≥ 15% in one of the two groups)

Event	**Entecavir 1 mg n = 102, (%)**	**Adefovir 10 mg n = 89, (%)**
Fever	21 (21)	19 (21)
Upper respiratory tract infection	19 (19)	14 (16)
Peripheral oedema	18 (18)	21 (24)
Ascites	17 (17)	18 (20)
Cough	17 (17)	15 (17)
Abdominal pain	16 (16)	13 (15)
Diarrhoea	15 (15)	18 (20)
Lengthening of prothrombin time	14 (14)	14 (16)
Fatigue	13 (13)	13 (15)
Malignant liver tumour	12 (12)	15 (17)
Headaches	7 (7)	18 (20)

The incidence of serious adverse events (69% versus 66%)[4] and grade 3 or 4 events (54% versus 47%)[5] and treatment cessation as the result of the occurrence of adverse events (7% versus 6%) was comparable in the two treatment groups. The most frequent serious adverse or grade 3 or 4

[4] Death, life-threatening prognosis, significant or definitive invalidity/incapacity, hospitalisation or prolonged hospitalisation, congenital abnormality, overdose, abuse and dependence, medically significant event.
[5] Grade 3: Incapacity to perform normal daily activities; Grade 4: Invalid, significant disability to subject/patient despite symptomatic treatment.

events were hepatic impairment, a specific case of hepatic impairment (increase in bilirubin, lengthening of prothrombin time, hepatic encephalopathy) and complications associated with a case of decompensated cirrhosis, for example ascites (bacterial peritonitis, sepsis/septic shock).

The cumulative levels of increase in serum creatinine greater than or equal to 0.5 mg/dl were comparable in the two treatment groups (17% versus 24%).

The occurrence of hepatocellular carcinoma (HCC) or death was comparable in the two treatment groups: the cumulative level of HCC during the study was 12% versus 20% and the cumulative mortality rate was 23% versus 33%; the causes of death were generally linked to hepatic function, as expected with this type of patient.

The incidence of grades 2 to 4 adverse events considered as being associated with the treatment was 12% in the two treatment groups. These events were, on the whole, comparable in the two treatment groups and of the same nature as those already known and included in the SPC. New grade 2 to 4 adverse events judged as being linked to the treatment observed during the study included: reduction in blood bicarbonates (entecavir 2%, adefovir 0%) and renal impairment (entecavir < 1%, adefovir 2%).

Biological analysis abnormalities: at 48 weeks, only 1% of patients treated with entecavir presented with ALT elevations > two times the initial level with total bilirubin > two times the ULN and > 2 times the initial level. No patient presented with ALT elevations > 10 times the ULN. Albumin levels < 2.5 g/dl were observed in 30% of patients, lipase levels > three times the initial level in 10% and platelets < 50,000/mm^3 in 20% of patients.

A warning was included in the SPC (section 4.4 of SPC) indicating that: in patients with decompensated liver disease, in particular those with Child-Pugh-Turcotte (CPT) class C disease, a higher rate of serious hepatic adverse events was observed compared with patients with compensated liver function. In addition, patients with decompensated liver disease may also run a higher risk of lactic acidosis and adverse renal events such as hepatorenal syndrome. Consequently, clinical and biological parameters must be closely monitored for this population.

3.3. Updating of resistance and tolerance information

Since the last assessment by the Committee, resistance data at three years then at five years were analysed by EMA based on genotype and phenotype data for patients treated for up to five years. This new information forms the basis of the SPC updates.

Analysis of successive periodic safety update reports (PSUR) has led to updates to sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SPC.

3.3.1. Updating of resistance information observed for adults treated with entecavir (See SPC)

- in naïve patients, the emergence of genotypic entecavir resistance mutations is estimated to be 0.2% at one year of treatment, 0.5% at two years, and 1.2% at three, four and five years. Emerging genotypic entecavir resistance with virologic breakthrough is estimated to be 0.2% at one and two years, and 0.8% at three, four and five years of treatment.
- for lamivudine-resistant HBV patients, the risk of developing a resistance to entecavir is greater than for those patients not resistant to lamivudine, and this increases with time. In studies carried out on lamivudine-resistant patients, the cumulative probability of the emergence of genotypic entecavir resistance was 6% after one year of treatment, 15% at two years, 36% at three years, 47% at four years and 51% at five years. Genotypic entecavir resistance with virologic breakthrough was 1% at one year, 11% at two years, 27% at three years, 41% at four years and 44% at five years.

This data has led to stating the position entecavir has for lamivudine-resistant patients (see paragraph 4.4 of SPC: Special warnings and precautions for use):
"Pre-existing lamivudine-resistant HBV is associated with an increased risk of 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-over resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy ".

3.3.2. Updating of tolerance information

Since the initial Marketing Authorisation for BARACLUDE, 11 PSURs have been completed and submitted to the authorities.
Analysis of the successive PSUR has led to an update to section 4.8 (undesirable effects) mentioning the following adverse effects considered as resulting from treatment with entecavir:

- Rash,
- Alopecia,
- Anaphylactoid reaction,

and in addition cases of lactic acidosis have been reported, often in association with hepatic decompensation, other serious medical conditions or drug exposures.

The last PSUR available covers the period from 29 March 2010 to 28 September 2010 and was submitted to the CHMP in November 2010.
Given the sales figures, it is estimated that approximately 225,000 patients have been treated with entecavir during the first quarter of 2010, 4,683 of which were in France.

During the period covered by the last PSUR, no new tolerance signals were observed, except for one isolated incident of thrombotic thrombocytopenic purpura.

3.4. Conclusion

The tolerance profile and efficacy for entecavir in adult patients (> 16 years) with chronic hepatitis B with **decompensated liver disease** has been assessed in a controlled, open-label phase III clinical study (AI463048), lasting 96 weeks (study on going), comparing the efficacy and the tolerance of entecavir (BARACLUDE, 1 mg taken once daily) versus adefovir (HEPSERA, 10 mg taken once, daily).

Patients included (n =195: entecavir, n = 101; adefovir, n = 94) had a mean age of 52 years, decompensated liver disease with a CPT score ≥ 7 (mean score 8.6), 54% were HBeAg positive and the mean viral load (HBV plasma DNA) was 7.8 $\log_{10}$ copies/ml. Approximately 38% of patients were previously treated with lamivudine and the presence of lamivudine-resistance mutations was 35%.

Data at week 24 and 48 of the study showed superiority for entecavir compared with adefovir in terms of virologic efficacy:

mean reduction of serum HBV DNA levels at week 24 compared with the start of the study, adjusted for viral load at inclusion and lamivudine resistance[6]: difference: -1.74 [-2.30, -1.18], p < 0.0001. This difference has been maintained up to 48 weeks.

proportion of patients with an undetectable viral load (HBV DNA < 300 copies/ml): 49% versus 16% [difference 33%] at 24 weeks and 57% versus 20% [difference 38%] at week 48. In patients with lamivudine-resistance at the start of the study, this virologic response was 44% in the entecavir group versus 20% in the adefovir group at week 24 and 50% versus 17% at week 48.

Furthermore, entecavir was more effective than adefovir after 24 and 48 weeks of treatment in terms of biochemical improvement (standardisation of ALT at 48 weeks: 63% versus 46%).
However, the percentage of patients with HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe antibody detection at 48 weeks: 6% versus 10%) and improvement in liver impairment (CPT score stable or improved at 48 weeks: 61% versus 67%; and progress of the MELD score: - 2.6 versus -1.7) were not different for either entecavir or adefovir.

6 Primary efficacy endpoint

Concerning tolerance, the incidence of grade 2 to 4 adverse events considered as being linked to treatment was comparable between entecavir and adefovir (12%) and these were, on the whole, of the same nature as those already known and included on the SPC. New grade 2 to 4 adverse events judged as being linked to the treatment observed during the study included: reduction in blood bicarbonates (entecavir 2%, adefovir 0%) and renal impairment (entecavir < 1%, adefovir 2%).
A warning was included in the SPC (section 4.4 of the SPC) indicating that for patients with decompensated liver disease, in particular those with Child-Pugh-Turcotte (CPT) class C disease, a higher rate of serious hepatic adverse events was observed (regardless of causality) compared with patients with compensated liver function. In addition, patients with decompensated liver disease may also run a higher risk of lactic acidosis and adverse renal events such as hepatorenal syndrome. Consequently, clinical and biological parameters must be closely monitored for this population.

The updating of resistance data, going up to five years, confirms that entecavir has a higher genetic resistance barrier in nucleoside naïve patients. However, lamivudine-resistant patients have a higher risk of developing subsequent resistance, regardless of the liver disease type.
Consequently, entecavir monotherapy is not an ideal option in cases of lamivudine resistance, in particular for patients with decompensated liver disease who are more vulnerable in cases of virologic breakthrough.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Chronic Hepatitis B is a disease that can lead to cirrhosis and its complications, which are hepatocellular carcinoma and cirrhosis decompensation. Cirrhosis decompensation, which is associated with hepatocellular insufficiency and portal hypertension, may lead to complications such as jaundice, hepatic encephalopathy, ascites and spontaneous infection or haemorrhaging via rupture of the oesophageal varix or gastric cardias. Cirrhosis decompensation is a very unfavourable prognostic element.

BARACLUDE falls under the category of curative treatment.

The efficacy/adverse effects ratio of this product is high due to its antiviral activity and its satisfactory resistance profile, as long as the contraindications and the special warnings and precautions for use are followed (see SPC).

This medicinal product is a first-line treatment.

There are very few therapeutic alternatives for patients with decompensated liver disease.

Public health benefit

In France, hepatitis B is a small burden on public health (< 3,000 DALYs lost per year according to WHO estimations). The burden represented by chronic decompensated hepatitis B patients is, at best, small.

The fight against hepatitis B and C is a public health priority and improving the quality of care and quality of life for patients with chronic hepatitis B (or C) is part of the French national strategic plan for the fight against Hepatitis B and C, 2009-2012.

Based on the results versus adefovir, and given the therapeutic use, a small impact in terms of morbidity and mortality can be expected for BARACLUDE. The results presented do not, initially, pose a transposability issue for current practice.

BARACLUDE could contribute in meeting an identified public health need.

Consequently, BARACLUDE is expected to have a public health benefit for decompensated liver disease. As with tenofovir, this benefit may be quantified as being small.

The actual benefit of this medicinal product is substantial.

4.2 Improvement in actual benefit

Based on available data, and due to its antiviral activity and its satisfactory resistance profile, the Committee estimates that BARACLUDE provides, as does VIREAD (tenofovir), a minor improvement in actual benefit (ASMR IV) in the treatment of patients with chronic hepatitis B and decompensated liver disease.

4.3 Therapeutic use

Guidelines were circulated in 2009 by the European Association for the Study of the Liver (EASL)[7].

The aim of antiviral treatment for chronic hepatitis B is to quickly obtain a substantial decrease in viral load and stop the virus multiplying, then sustain this viral control over time. Viral control allows a reduction in necrotic and inflammatory liver activity.

[7] EASL Jury. EASL Clinical practice Guidelines: Management chronic hepatitis B. J Hepatol. 2009; 50:227-42.

- **<u>In patients with moderate to severe hepatitis without cirrhosis and in patients with cirrhosis but no signs of decompensation</u>,**

When the indication of antiviral treatment is offered, two first-line treatment strategies may be discussed. The first is based on the use of interferon alpha (pegylated or non-pegylated) limited to one year; the second is based on the prescription of a nucleoside or nucleotide analogue for a prolonged period, likely to be the rest of their life, for the majority of patients.

- Treatment with interferon is mainly indicated for patients with compensated liver disease[8], with indicative virologic response factors, i.e. elevated ALT levels (three times the Upper Limit of Normality) and low to moderate viral replication (HBV DNA< 7 log10 IU/ml) before treatment.
The efficacy of treatment is judged at the 12th week, based on the reduction of HBV DNA of at least log10, and a HBV DNA level below 2000 IU per ml at week 24, endpoints which are conditions for the continuation of treatment.
Interferon alpha increases the risk of sepsis and decompensation in patients with advanced cirrhosis.

- Treatment with a nucleoside or nucleotide analogue is mainly indicated in HBeAg positive patients with no indicative interferon response, and in the majority of HBeAg negative patients. It is also recommended in all cirrhosis patients, regardless of their HBe status. HBV DNA must be monitored at regular intervals. The aim is for HBV DNA to be undetectable by PCR.
When treatment with a nucleoside or nucleotide analogue is selected, entecavir (BARACLUDE) and tenofovir (VIREAD) are recommended as first-line treatments due to their antiviral activity and their superior resistance profile to other analogues (adefovir, lamivudine and telbuvidine) and as they are relatively safe.

- **<u>In patients with decompensated liver disease:</u>**

Patients with decompensated cirrhosis should be treated in specialist units, given the complexity of the antiviral treatment; these patients could be candidates for a liver transplant.
Terminal stage liver disease is a priority. Treatment is indicated even if the viral load is low, with the aim of preventing the risk of recurrent viral reactivation. In addition, strong analogues with a good resistance profile (tenofovir and entecavir) should be used. Often there is little data on the precautions for use for these molecules for cases of decompensated cirrhosis. Slow clinical improvement is observed over a three to six month period. However, certain patients with extremely advanced liver disease may not be able to see the benefits and should be offered a liver transplant. In these situations, the treatment benefit with a nucleoside analogue will reduce the risk of the virus reoccurring in the transplanted organ.

<u>Therapeutic use of VIREAD (TC opinion of 19 January 2011)</u>

For hepatitis B, in patients with decompensated liver disease, VIREAD (tenofovir) is recommended as a first-line treatment given its virologic efficacy and its tolerance and resistance profile.
As tenofovir may also result in renal poisoning[9], strict monitoring of renal function, in particular in this cirrhotic population at a higher risk of developing renal impairment, is recommended. The renal tolerance of tenofovir has had very little investigation in patients presenting with renal impairment (CrCl < 80 ml/min). Consequently, in patients with renal impairment, tenofovir should only be used if the potential benefits of treatment outweigh the potential risks. In patients with severe renal impairment, the use of tenofovir is not recommended (see SPC: contraindications, special warnings and precautions for use).

<u>The therapeutic use of BARACLUDE</u>

For hepatitis B, in patients with decompensated liver disease, BARACLUDE (entecavir) is recommended as a first-line treatment given its virologic efficacy and its tolerance and resistance profile.

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[8] Interferon is **contraindicated for decompensated cirrhosis**

[9] Cases of renal disorders, renal insufficiency, elevation in creatinine levels, hypophosphataemia and proximal renal tubulopathy (including Fanconi syndrome) were reported in the scope of the use of tenofovir disoproxil fumarate in clinical practice (see SPC).

However, for patients with pre-existing lamivudine resistant HBV, BARACLUDE is not recommended as monotherapy, in particular in those with decompensated liver disease. The SPC states that: "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". Due to its favourable resistance profile and the absence of cross-resistance, treatment with, or in combination with tenofovir monotherapy, is favoured as a first-line treatment in cases of lamivudine resistance.

4.4 Target population

The target population that may benefit from treatment with entecavir with extension of the indication is represented by patients infected with the hepatitis B virus and with decompensated cirrhosis.

The prevalence of carrying the HBs antigen in metropolitan France is estimated[10] as being 0.65%, (IC 95%: 0.45-0.93), which corresponds to 280,821 chronic (IC 95%: 179,730 – 381,913) AgHBs carriers. A distinction is made between asymptomatic chronic carriers (30% of cases) and chronic hepatitis (70% of cases)[11]. Based on this data, the number of patients with chronic hepatitis B could be estimated as approximately 196,500 patients.
Among these patients with chronic hepatitis B[12], the incidence of cirrhosis is from 2 to 10%, or 3930 à 19,600 cirrhosis patients. Among these patients, the incidence of liver decompensation is estimated at approximately 4%.

Therefore, the target population for BARACLUDE in the indication of patients with hepatitis B with decompensated cirrhosis can be estimated as being between 200 and 800 patients.

4.5 Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosages indicated in the Marketing Authorisation.

4.5.1 Packaging: appropriate for the prescription conditions

4.5.2 Reimbursement rate: 65%

[10] Meffre C. Prévalence des hépatites B et C en France en 2004. Saint-Maurice: French Institute for Public Health Surveillance 2007. Available at: http://www.invs.sante.fr/publications/2006/prevalence_b_c/vhb_france_2004.pdf .
[11] CMIT. Hépatite virale B. In E. PILLY : Vivactis Plus Ed; 2010: pp 355 – 359.
[12] EASL International consensus conference on hepatitis B. 13-14 September 2002, Geneva, Switzerland. J Hepatol 2003; 39: S3-S25. http://www.hepfi.org/nnac/pdf/easl_hbv.pdf