HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 November 2006

BARACLUDE 0.5 mg film-coated tablet B / 30
(CIP : 376289-7) 30 aluminium blisters of 1 tablet

BARACLUDE 1 mg film-coated tablet B / 30
(CIP : 376291-1) 30 aluminium blisters of 1 tablet

BARACLUDE 0.05 mg/ml oral solution in a bottle B/1
(CIP : 376292-8) One 210 ml polyethylene bottle with a child-resistant closure and a polypropylene measuring spoon

Applicant : BRISTOL-MYERS SQUIBB

entecavir
List I

Medicinal product available only on an initial six-month medical prescription to be issued by specialists and/or departments specialised in gastroenterology, hepatology, internal medicine or infectious diseases
Unrestricted renewal

Date of Marketing Authorisation: 26 June 2006

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for use by hospitals

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

Entecavir

1.2. Background

This medicinal product is a new nucleoside analogue indicated for the treatment of chronic hepatitis B virus (HBV) in adult patients with compensated liver disease.

1.3 Indication

BARACLUDE is indicated for the treatment of chronic hepatitis B virus (HBV) in adult patients with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine animotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

This indication is based on clinical trial data in HBeAg-positive and HBeAg-negative patients for the HBV virus, in patients who have never been treated with a nucleoside analogue and patients with lamivudine-refractory HBV.

1.4 Dosage

Treatment must be initiated by a doctor specialised in the management of chronic hepatitis B.

BARACLUDE must be taken orally once a day.

Nucleoside naive patients:
the recommended dosage is 0.5 mg once daily, with or without food.

Lamivudine-refractory patients (i.e. with evidence of viraemia during their treatment with lamivudine or lamivudine resistance mutations): the recommended dosage is 1 mg once daily and it must be taken, in this case, on an empty stomach (more than 2 hours before the next meal or more than 2 hours after the last meal).

Treatment duration: the optimum duration for this treatment is not known. The treatment can be discontinued as follows:

- In HBeAg-positive patients treatment must be administered until at least HBe seroconversion (loss of HBeAg and HBV DNA with the detection of anti-HBe antibodies, based on two consecutive serum samples taken at least 3 to 6 months apart) or until HBs seroconversion, or in the case of a loss of efficacy.

- In HBeAg-negative patients treatment must be administered until at least HBs seroconversion or in the case of proven loss of efficacy. If treatment is prolonged for more than two years, a regular reassessment is recommended to confirm that it is still appropriate to continue the treatment for the patient.

Children and adolescents, elderly, renal impairment, hepatic impairment: see Summary of Product Characteristics (SPC).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2006)

J : Anti-infectives for systemic use
05 : Antivirals for systemic use
A : Direct acting antivirals
F : Nucleoside and nucleotide reverse transcriptase inhibitors
10 : Entecavir

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines (Hepatitis B)

Nucleoside and nucleotide analogue
- lamivudine (ZEFFIX)*
- adefovir (HEPSERA)*

These 2 proprietary medicinal products have a complementary indication for the treatment of chronic hepatitis B in patients with decompensated liver disease.

2.1 Medicines with a similar therapeutic aim

Interferon alfa-2a (ROFERON): chronic hepatitis B, chronic hepatitis C and indications in oncology

Interferon alfa-2b (INTRONA): chronic hepatitis B, chronic hepatitis C and indications in oncology

Interferon alfa-2b (VIRAFERON): during radiation

Peginterferon alfa-2a (PEGASYS): chronic hepatitis B, chronic hepatitis C

3 ANALYSIS OF DATA AVAILABLE

The clinical information is made up of 3 comparative clinical studies involving patients affected by chronic hepatitis B virus (HBV) with compensated liver disease.

3.1. Efficacy

Three randomised, double-blind comparative clinical studies were carried out in order to evaluate the efficacy and safety of entecavir (BARACLUDE) compared to lamivudine (ZEFFIX) during a period of 52 weeks:

- 2 studies involving HBeAg-positive nucleoside naive patients with a wild-type hepatitis B virus (Study 022) [1] and HBeAg-negative patients with a mutant hepatitis B virus (Study 027)[2] receiving a dose of entecavir 0.5 mg/ day.
- 1 study involving HBeAg-positive lamivudine-refractory patients (Study 026)[3] receiving a dose of entecavir 1 mg/day.

[1] Chang TT, Gish RG et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med. 2006; 354 (10): 1001-10
[2] Lai CL Shouval D et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med. 2006; 354 (10): 1011-20
[3] Sherman M, Yurdaydin C et al. Entecavir for treatment of lamivudine refractory, HBeAg- positive chronic hepatitis B. Gastroenterology. 2006 ; 130:2039-2049

The treatment duration was 52 weeks.

The efficacy of the treatment was evaluated based on a histological endpoint at 48 weeks (study 022 - study 027) and on a composite histological, virological and biochemical endpoint (study 026).

The response to treatment based on virological endpoints at 48 weeks determined whether treatment would be continued beyond 52 weeks:

- complete virological responders* at 48 weeks discontinued their treatment at 52 weeks and had a 24-week follow-up period after the end of treatment
- partial virological responders** at 48 weeks continued their treatment beyond 52 weeks until they achieved a complete response or until the 96th week at the latest.

(*complete virological responders = viral load ≤ 700,000 copies/ml and loss of the HBe antigen in HBeAg-positive patients or ALT normalisation < 1 x ULN in HBeAg-negative patients
** partial virological responders = viral load ≤ 700,000 copies/ml)

Given their concomitant clinical developments, no comparative clinical study was carried out versus adefovir.

3.1.1 **Studies carried out on nucleoside-naive patients** (studies 022 and 027)

Study 022 was carried out in 709 adult patients with a wild-type hepatitis B virus (HBeAg-positive):

- 354 patients were included in the entecavir group receiving a dose of 0.5 mg/day
- 355 patients were included in the lamivudine group receiving a dose of 100 mg/day

Study 027 was carried out in 638 adult patients with a mutant hepatitis B virus (HBeAg-negative):

- 325 patients were included in the entecavir group receiving a dose of 0.5 mg/day
- 313 patients were included in the lamivudine group receiving a dose of 100 mg/day

Both studies included treatment-naive adult patients with compensated liver disease, an active viral replication quantified by measuring the HBV DNA, a chronic hepatitis B infection defined by a seropositive HBsAg with histological evidence and elevated ALT levels. No patient co-infected by HBV and HIV was included in these studies.

Primary endpoint (studies 022 and 027)
The primary endpoint was the percentage of patients who achieved a histological improvement by week 48 in relation to the baseline (a liver biopsy was carried out during the 48th week).

This improvement was defined in terms of improvement in the Knodell necroinflammatory score (a drop of at least 2 points in the Knodell HAI score) with no worsening of fibrosis.

Secondary endpoints (studies 022 and 027)
The main secondary endpoints were the following:

- reduction in viral load (log_{10} copies/ml)
- undetectable HBV DNA (< 300 copies/ml in PCR)
- ALT normalisation (≤ 1 x ULN)
- HBeAg seroconversion (loss of HBeAg and the HBV DNA with detection of anti-HBe antibodies / study 022).

The statistical analysis was initially to be carried out based on the assumption of non-inferiority. In the case of evidence of non-inferiority, a statistical analysis was planned in order to demonstrate entecavir's superiority in relation to lamivudine.

Results of studies 022 and 027 in terms of efficacy based on the primary endpoint and main secondary endpoints during the 48th week of treatment (modified ITT, missing data = failure)

	HBeAg-positive N (%) (Study 022)		P	**HBeAg-negative N (%) (Study 027)**		p
	Entecavir 0.5mg Once daily	Lamivudine 100mg Once daily		Entecavir 0.5mg Once daily	Lamivudine 100mg Once daily	
N	314[a]	314[a]		296[a]	287[a]	
Histological improvement[5]	**226 (72%)**	**195 (62%)**	**<0.05**	**208 (70%)**	**174 (61%)**	**<0.05**
N	354	355		325	313	
Reduction in viral load (log_{10} copies/ml)	-6.86 ± 2.0	-5.39 ± 2.6	<0.05	-5.04 ± 1.7	-4.53 ± 1.9	<0.05
Undetectable HBV DNA (< 300 copies/ ml PCR)[c]	236 (67%)	129 (36%)	<0.05	293 (90)	225 (72)	<0.05
ALT normalisation (≤ 1 x ULN)	242 (68%)	213 (60%)	<0.05	253 (78)	222 (71)	<0.05
HBeAg seroconversion	74 (21%)	64 (18%)	NS	-	-	-
Complete virological responders*	74 (21%)	67(19%)	NS	275 (85%)	245 (78%)	<0.05
Partial virological responders*	247(70%)	165 (46%)		34 (10%)	34 (11%)	

[a] patients with a histology that can be assessed (Knodell necroinflammatory score ≥ 2 at baseline)
[b] primary endpoint
[c] Roche Cobas Amplicor PCR assay (LLOQ = 300 copies/ml)

*complete virological responders = viral load ≤ 700,000 copies/ml and loss of the HBe antigen in HBeAg-positive patients or ALT normalisation < 1.25 x ULN in HBeAg-negative patients
** partial virological responders = viral load ≤ 700,000 copies/ml

At 48 weeks of treatment, the efficacy of entecavir in treatment-naive patients with a wild-type (HBeAg-positive) or mutant (HBeAg-negative) virus was statistically superior in terms of histological improvement to that of lamivudine based on the Knodell necroinflammatory scores: 72% versus 62% in HBeAg-positive patients and 70% versus 61% in HBeAg-negative patients.

Furthermore, a higher percentage of patients were observed in the entecavir group than the lamivudine group with:

- a reduction in the viral load (compared to the baseline)
- an undetectable viral load
- ALT normalisation.

The percentage of patients with HBeAg seroconversion was not statistically different between the two entecavir and lamivudine groups.

Follow-up of complete virological responders for 24 weeks after the end of the 52-week treatment in studies 022 and 027
(viral load ≤ 700,000 copies/ml and loss of HBe antigen or ALT normalisation < 1.25 x ULN):

After 52 weeks of treatment and 24 weeks of follow-up in complete virological responders, the complete virological response was maintained in:

- 42/74 (57%) HBeAg-positive patients in the entecavir group versus 22/67 (33%) patients in the lamivudine group (Study 022)
- 126/275 (46%) HBeAg-negative patients in the entecavir group versus 76/245 (31%) patients in the lamivudine group (Study 027)

Follow-up of partial virological responders (viral load ≤ 700,000 copies/ml) who continued their treatment beyond the 52 weeks of treatment (median of 96 weeks):
After a second year of treatment for the HBeAg-positive partial virological responders, the virological responses among the entecavir group improved.

Thirteen/243 (15%) patients in the entecavir group and 26/164 (16%) patients in the lamivudine group became complete virological responders (viral load ≤ 700,000 copies/ml and loss of the HBe antigen), although the percentages noted for patients with HBeAg seroconversion were low (21% at 48 weeks and 31% at 96 weeks), without any significant difference between the two entecavir and lamivudine treatment groups at 96 weeks.

Total number of complete virological responders and total number of patients with HBsAg seroconversion observed during the 2 years of treatment:
HBeAg-positive patients

- The total number of complete virological responders was: 111/354 (31%) patients in the entecavir group and 93/355 (26%) in the lamivudine group.
- The total number of patients with HBsAg seroconversion was: 6/354 patients in the entecavir group and 8/355 patients in the lamivudine group.

HBeAg-negative patients

- The total number of complete virological responders was: 286/325 (88%) patients in the entecavir group and 253/313 (81%) in the lamivudine group.
- The total number of patients with HBsAg seroconversion was: 0/325 in the entecavir group and 1/313 patients in the lamivudine group.

3.1.2 <u>Studies carried out on lamivudine-refractory patients</u> (study 026)

Study 026 was carried out in 246 adult patients with a lamivudine-refractory, HBeAg-positive wild-type virus:

- 141 patients in the entecavir group received a dose of 1 mg/day
- 145 patients in the lamivudine group received a dose of 100 mg/day.

Patients being treated with lamivudine at the time of inclusion either received entecavir or continued with their lamivudine treatment during the study.

The patients with a wild-type hepatitis B virus (HBeAg-positive) were adult patients with lamivudine-refractory virus (85% presented with lamivudine-resistant mutations at the time of inclusion), with compensated liver disease, an active viral replication quantified by measuring the HBV DNA, a chronic hepatitis B infection defined by a seropositive HBsAg with histological evidence and elevated ALT levels. No patients co-infected by HBV and HIV were included in these studies.

Primary endpoint:
The primary endpoint was defined by 2 sub-endpoints:

- Histological endpoint: histological improvement (a drop of at least 2 points in the Knodell necroinflammatory score) with no worsening of fibrosis.
- Composite endpoint: percentage of patients with a HBV DNA < 700,000 copies/ml and an ALT normalisation (< 1.25 x ULN).

Secondary endpoints:
The main secondary endpoints were the following:

- Reduction in viral load (log_{10} copies/ml)
- Undetectable HBV DNA (< 300 copies/ml in PCR)
- ALT normalisation (≤ 1 x ULN)
- HBeAg seroconversion (loss of HBeAg and the HBV DNA with detection of anti-HBe antibodies).

The statistical analysis was initially to be carried out based on the assumption of non-inferiority. Having demonstrated non-inferiority, a statistical analysis was carried out in order to demonstrate entecavir's superiority in relation to lamivudine.

Results of study 026 in terms of efficacy based on the primary endpoint and main secondary endpoints at the 48th week of treatment (modified ITT, missing data = failure)

	HBeAg-positive N (%) **(Study 026)**		**p**
	Entecavir 1mg Once daily	Lamivudine 100 mg Once daily	
N	124[a]	116[a]	
Histological improvement[5]	**64 (55%)**	**32 (28%)**	**< 0.05**
Undetectable HBV DNA and ALT normalisation (< 1.25 x ULN)	**77 (55%)**	**6(4%)**	**< 0.05**
N	141	145	
Reduction in viral load (log_{10} copies/ml)	-5.11 ± 0.196	-0.48 ± 0.175	< 0.05
Undetectable HBV DNA (< 300 copies/ml in PCR)[c]	27 (19%)	2 (1)	< 0.05
ALT normalisation (≤ 1 x ULN)	86 (61%)	22 (15%)	< 0.05
HBeAg seroconversion	11 (8%)	4 (3%)	NS
Complete virological responders*	13(9%)	1 (1%)	< 0.05
Partial virological responders**	80(57%)	7 (5%)	

[a] Patients with evaluable histology at the time of inclusion (Knodell necroinflammatory score ≥ 2 at baseline)
[b] Primary endpoint
[c] Roche Cobas Amplicor PCR assay (LLOQ = 300 copies/ml)
*Complete virological responders = viral load ≤ 700,000 copies/ml and loss of HBe antigen
** Partial virological responders = viral load ≤ 700,000 copies/ml)

At 48 weeks of treatment, the efficacy of entecavir in patients with a chronic hepatitis B infection, resistant to lamivudine and with a wild-type (HBeAg-positive) virus was statistically superior to that of lamivudine:

- In terms of histological improvement in the Knodell necroinflammatory score (55% versus 28%, p<0.05) and
- in virological and biochemical terms on the 2nd composite virological and biochemical subendpoint (55% versus 4%, p<0.05).

Furthermore, at 48 weeks of treatment, a higher percentage of patients was observed in the entecavir group than the lamivudine group with:

- A reduction in the viral load (compared to the baseline)
- An undetectable viral load and
- ALT normalisation.

The percentage of patients with HBeAg seroconversion was not statistically different in the two groups (entecavir and lamivudine).

Follow-up of partial virological responders (viral load ≤ 700,000 copies/ml) who continued their treatment beyond the 52 weeks of treatment (study 026):
The partial virological responders (HBV DNA < 700,000 copies/ml) at 48 weeks continued their treatment beyond the 52 weeks (77 patients in the entecavir group - 3 patients in the lamivudine group). Nine on 77 patients in the entecavir group and 0/3 patients in the lamivudine group became complete responders (viral load ≤ 700,000 copies/ml and loss of the HBe antigen).

Total number of complete virological responders (viral load ≤ 700,000 copies/ml) and loss of the HBe antigen and the total number of patients with HBsAg seroconversion observed during the 2 years of treatment:
The number of cumulative complete virological responders was 22/141 in the entecavir group versus 1/145 in the lamivudine group.

The number of cumulative patients with HBsAg seroconversion was: 1/141 in the entecavir group and 0/145 patients in the lamivudine group.

3.1.3 Other data

A meta-analysis comparing of the efficacy of entecavir with that of lamivudine and adefovir, for which only an abstract is available (40th Annual Meeting of the European Association for the Study of the Liver / Paris 13-17 April 2005), has neither been evaluated by the registration authorities nor analysed below.

The indirect comparisons enclosed in this file are not sufficiently detailed to assess their level of evidence.

3.2 Clinical resistance

In the case of nucleoside naive patients (n = 549) and had received entecavir for up to 48 weeks, the genotypic analyses of the serum HBV DNA did not highlight any mutations in the gene of the HBV DNA polymerase associated with phenotypic susceptibility to entecavir. No emergence of resistance was observed at 96 weeks in patients without lamivudine resistance mutations at the time of inclusion.

In the case of lamivudine-refractory patients treated for 48 weeks using entecavir, the genotypic and phenotypic analyses of the isolates identified in 6% of patients (12/189), the emergence of entecavir resistance mutations when lamivudine resistance mutations (rtM204V/I and/or rtL180M) were present.

The total frequency of virological rebound due to entecavir resistance mutations was 9% (14/154) between weeks 48 and 96.

Entecavir resistance mutations were observed at the time of inclusion in 23/272 (6.2%) of lamivudine-refractory patients, indicating that treatment using lamivudine can select these resistance mutations and that they can exist at a low frequency before initiating treatment with entecavir.

Entecavir presents a more favourable resistance profile than that of lamivudine, which generates a higher resistance frequency (15-20% per year).

3.3 Adverse effects

The evaluation of the adverse effects is based on four clinical studies (3 phase III studies and 1 phase II study) during which 1720 patients with chronic hepatitis B were treated with entecavir 0.5 mg/day (n = 679), entecavir 1 mg/day (n = 183) or lamivudine (n = 858) for 107 weeks.

The most common adverse effects of any severity were:

- headaches (9%)
- fatigue (6%)
- dizziness (4%)
- nausea (3%).

Data for nucleoside naive patients who had never been treated with a nucleoside analogue (HBeAg-positive and HBeAg-negative):
Common undesirable effects (≥1/100, < 1/10) *:*

- insomnia
- headaches, dizziness, drowsiness
- vomiting, diarrhoea, nausea, dyspepsia
- fatigue.

Treatment which extended beyond 48 weeks for a mean period of 96 weeks did not highlight any modifications in entecavir's safety profile.

During treatment an ALT elevation[4] was observed in 2% of patients treated with entecavir as opposed to 4% treated with lamivudine.

After the end of treatment, an ALT elevation[5] was observed in 6% of patients treated with entecavir as opposed to 10% of patients treated with lamivudine. The ALT elevation occurred on average 23-24 weeks after the end of treatment and 86% (24/28) of these ALT elevations occurred in HBeAg-negative patients.

Data for lamivudine-refractory patients
Very common undesirable effects (≥1/10)*:*

- headaches

Common undesirable effects (≥1/100, < 1/10)*:*

- insomnia
- dizziness, drowsiness
- vomiting, diarrhoea, nausea, dyspepsia
- fatigue

[4] > 10 x ULN and > 2 x baseline

[5] (> 10 x ULN and > 2 x reference level [minimum value between the baseline value and the value from the last laboratory analyses])

Treatment which extended beyond 48 weeks for a mean duration of 96 weeks did not highlight any modifications in entecavir's safety profile observed during the first year of treatment described above.

During treatment an ALT elevation[4] was observed in 2% of patients treated with entecavir as opposed to 11% treated with lamivudine.

After the discontinuation of treatment none of the patients treated with lamivudine developed an ALT elevation as opposed to 11% of patients treated with entecavir.

Periodic monitoring of hepatic function is recommended during treatment.
Acute exacerbations of hepatitis have been reported in patients who have discontinued their treatment.

The evaluation of the carcinogenicity studies from preclinical information highlighted the occurrence of lung tumours in mice and brain gliomas in rats.

The evaluation of the clinical information did not highlight any increased risk of malignant tumours occurring in patients treated with entecavir compared to those treated with lamivudine, or compared with the incidence normally observed in patients with chronic hepatitis B virus.

However, it appeared necessary to set up as part of the risk management plan a long-term follow-up study (study AI463-080) aimed at evaluating the progression of the disease, the potential risk of cancers being induced and the mortality rate.

3.4 Conclusion

Nucleoside naive patients who have never been treated with a nucleoside analogue

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

The safety profiles for entecavir and lamivudine were comparable.

No emergence of resistance was observed at 96 weeks in patients treated with entecavir, who had no lamivudine resistance mutations at the time of inclusion.

Lamivudine-refractory patients

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

The safety profiles for entecavir and lamivudine were comparable.

The total frequency of virological rebound due to entecavir resistance mutations was 9% between weeks 48 and 96 in lamivudine-refractory patients.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Hepatitis B is a common viral illness which is potentially life-threatening.

These proprietary medicinal products come within the scope of curative treatment.

The efficacy/adverse effects ratio for these proprietary medicinal products is high.

They are used as a second-line treatment (compensated liver disease).

There are alternative medicinal products available.

Public health benefit:

Hepatitis B represents a moderate public health burden. In the population of the MA indication, the burden is low due to the limited number of people affected in relation to the total number of patients with hepatitis B.

Reducing the morbidity and mortality rate attributable to chronic hepatitis conditions meets a public health need.

Considering the results demonstrating the efficacy of BARACLUDE versus to lamivudine, especially with regard to the prolonged monitoring of viral replication and in spite of no direct demonstration, a potential favourable impact on the population of patients treated may be expected (particularly in terms of preventing hepatocellular carcinoma). Given alternatives available, the size of BARACLUDE's impact on reduction of the morbidity and mortality rate linked to hepatitis B may only be small at the populational level. This impact needs to be confirmed by data on:

- Long-term clinical criteria (cirrhosis, hepatocarcinoma, hepatic impairment and death linked to a hepatic pathology);
- Cancer risk (observed on preclinical data);
- Emergence of long-term resistance;
- Treatment strategies applied in practice;
- Optimum duration of treatment.

BARACLUDE could contribute to meeting an identified public health need.

Consequently, a public health benefit is expected for BARACLUDE.

This benefit may be quantified as weak.

The actual benefit of entecavir in this indication is substantial.

4.2 Improvement in actual benefit

For adult patients affected by chronic hepatitis B virus with a compensated liver disease, entecavir (BARACLUDE) provides a significant improvement in actual benefit (level II) compared to lamivudine (ZEFFIX) in terms of efficacy and less frequent emergence of virological resistance.

4.3 Therapeutic use

In the case of patients with a moderate to severe wild-type (HBeAg-positive) or mutant (HBeAg-negative) hepatitis virus without cirrhosis and of patients with cirrhosis but without any sign of decompensation, the current recommendations[6] are to prescribe:

- First-line: interferon alfa;
- In the case of contraindication, lack of efficacy or poor tolerance of interferon alfa: nucleoside (lamivudine - ZEFFIX) and nucleotide (adefovir - HEPSERA) analogues.

Entecavir (BARACLUDE) can be used in adult patients affected by chronic hepatitis B virus with a compensated liver disease, in the case of contraindication, lack of efficacy or poor tolerance of interferon alfa.

4.4 Target population

According to an InVS (National Health Monitoring Institute) study and CNAMTS[77] among members of the general National Health insurance scheme in 2003-2004, the prevalence of chronic hepatitis B in France was apparently 0.68% among subjects aged 18 to 80 years, i.e. 300,000 people.

Treatment of chronic hepatitis B only involves patients in the active phase of the disease (30% of patients according to the experts), i.e. 90,000 patients.

According to the experts, 5% of patients allegedly have a contraindication to interferon alfa, while the treatment will fail for 70-80% of patients treated with interferon alfa due to lack of efficacy and tolerance.

Based on these figures, among the 90,000 patients with active chronic hepatitis, 64,000 to 73,000 patients will allegedly have a contraindication to, intolerance of or be unsuccessfully treated with interferon alfa.

The target population for BARACLUDE can be estimated then between 64,000 and 73,000 patients.

4.5 Recommendations of the Transparency Committee

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the Marketing Authorisation.

The Committee wishes to be sent, as soon as they are available, the results of the clinical studies currently in progress, in order to clarify better:

- The optimum duration of treatment and the criteria for discontinuing treatment
- The maintenance of virological suppression 24 weeks after discontinuing treatment
- Long-term durability of HBeAg seroconversion
- Frequency of HBsAg seroconversion
- Information on the clinical follow-up of patients (hepatocarcinoma, cirrhosis, hepatic impairment and death linked to a hepatic pathology)
- The emergence of long-term resistance.

[6] EASL Jury. EASL international consensus conference on hepatitis B, *Journal of Hepatology* 2003; 38: 533-540

[7] Estimate of the rates of prevalence of anti-HCV antibodies and hepatitis B virus markers in members of the general National Health insurance scheme in metropolitan France, 2003-2004.

Furthermore, the Committee wishes to be sent within a period of 2 years intermediate findings regarding carcinogenicity from the long-term study included as part of the risk management plan (study AI6430-080).

4.5.1 Packaging: Appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 65%