HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 January 2011

VIREAD 245 mg film-coated tablets
B/30 (CIP code: 358 500-1)

Applicant : GILEAD SCIENCES

tenofovir disoproxil (as fumarate)
ATC code: J05AF07

List I
Medicine for initial hospital prescription annually. Unrestricted renewal

Date of Marketing Authorisation (centralised procedure): 12 September 2008 - revised on 6 September 2010

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use in the extension of indication for adult patients suffering from chronic hepatitis B who have **decompensated liver disease**.

Medical, Economic and Public Health Assessment Division.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tenofovir disoproxil (as fumarate)

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

"HIV-1 infection
VIREAD is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults over 18 years of age.
The demonstration of benefit of VIREAD in HIV-1 infection is based on results of one study in antiretroviral treatment-naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which VIREAD was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml).
The choice of VIREAD to treat antiretroviral experienced patients with HIV-1 should be based on individual viral resistance testing and/or treatment history of patients.

Hepatitis B infection
VIREAD is indicated for the treatment of chronic hepatitis B (see section 5.1) in adults with:

- compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active hepatic inflammation and/or fibrosis
- **decompensated liver disease (see sections 4.4, 4.8 and 5.1 of the SPC)".**

1.3. Dosage

"Therapy should be initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B.
In exceptional circumstances in patients having particular difficulty in swallowing, VIREAD can be administered following disintegration of the tablet in at least 100 ml of water, orange juice or grape juice.

Adults: The recommended dose for the treatment of HIV or for the treatment of chronic hepatitis B is 245 mg (one tablet) to be taken once daily with food.

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

- In HBeAg-positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or there is evidence of loss of efficacy (see section 4.4).
Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.

- In HBeAg-negative patients without cirrhosis, 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.

Paediatric patients: This medicinal product must not be used in children below the age of 18 due to insufficient data on tolerance and efficacy (see section 5.2. of the SPC).

Elderly: No data are available on which to make a dosage recommendation for patients over the age of 65 years (see section 4.4).

Renal impairment*:* Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal impairment.
There are limited data on the tolerance and efficacy of tenofovir disoproxil fumarate in patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).
Long-term tolerance data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min).
Therefore, in patients with renal impairment tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks.
Dose interval adjustments are recommended for patients with creatinine clearance < 50 ml/min.

Mild renal impairment (creatinine clearance 50-80 ml/min): Limited data from clinical studies support once daily dosing of tenofovir disoproxil fumarate in patients with mild renal impairment.

Moderate renal impairment (creatinine clearance 30-49 ml/min): Administration of 245 mg tenofovir disoproxil (as fumarate) every 48 hours is recommended based on modelling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal impairment requiring haemodialysis, but has not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored in these patients (see sections 4.4 and 5.2).

Severe renal impairment (creatinine clearance < 30 ml/min) and haemodialysis patients: Adequate dosage adjustments cannot be applied due to lack of alternative tablet strengths. Therefore, use in this group of patients is not recommended. If no alternative treatment is available, prolonged dose intervals may be used as follows:

Severe renal impairment: 245 mg tenofovir disoproxil (as fumarate) may be administered every 72-96 hours (dosing twice a week).

Haemodialysis patients: 245 mg tenofovir disoproxil (as fumarate) may be administered every 7 days following completion of a haemodialysis session*.

These dosage adjustments have not been confirmed in clinical studies. Simulations suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response to treatment. Therefore, clinical response to treatment and renal function should be closely monitored (see sections 4.4 and 5.2 of the SPC).

* Generally, once weekly dosing assuming three haemodialysis sessions per week, each of approximately 4 hours duration, or after 12 hours cumulative haemodialysis.

No dosage recommendations can be given for non-haemodialysis patients with creatinine clearance < 10 ml/min.

Hepatic impairment: No dosage adjustment is required in patients with hepatic impairment (see sections 4.4 and 5.2 of the SPC).

If VIREAD is discontinued in patients with chronic hepatitis B with or without HIV co-infection, these patients should be closely monitored for any evidence of exacerbation of hepatitis (see section 4.4 of the SPC).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J : General antiinfectives for systemic use
J05 : Antivirals for systemic use
J05A : Direct-acting antivirals
J05AF : Nucleoside and nucleotide reverse transcriptase inhibitors
J05AF07 : tenofovir

2.2. Medicines in the same pharmaco-therapeutic category

Nucleoside or nucleotide analogues indicated in the treatment of chronic hepatitis B.

Proprietary drugs (INN)	**Indications**
ZEFFIX (lamivudine) - 100 mg, film-coated tablets, B/28 - 5 mg/ml, oral solution, 240 ml On the market since 20/08/1999	Treatment of adults with chronic hepatitis B and: - **compensated liver disease** with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active hepatic inflammation and/or fibrosis - **decompensated liver disease in combination with another antiviral where cross-resistance to lamivudine is not present**
HEPSERA (adefovir dipivoxil) - 10 mg, tablets, B/30 On the market since 08/04/2003	Treatment of adults with chronic hepatitis B and: - **compensated liver disease** with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active hepatic inflammation and fibrosis - **decompensated liver disease**.
BARACLUDE (entecavir)* - 0.5 mg, film-coated tablets, B/30 - 1 mg, film-coated tablets, B/30 - 0.05 mg/ml, oral solution, 210 ml On the market since 04/09/2006	Treatment of adults with chronic hepatitis B virus (HBV) and **compensated liver disease** with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active hepatic 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.
SEBIVO (telbivudine)* 600 mg, film-coated tablets, B/28 Official Gazette: 15/04/2008	Treatment of adults with chronic hepatitis B and **compensated liver disease** with evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active hepatic inflammation and/or fibrosis.

* Medicinal products which have not been granted 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. Reminder of data regarding the treatment of HBV in patients suffering from compensated liver disease (Conclusion of the Transparency Committee's opinion dated 8 July 2009)[1]

In a group of patients who had for the most part never undergone treatment before (590 patients who had had no treatment / 51 patients who had undergone treatment) HBeAg-negative patients who were carriers of a mutant hepatitis B virus (study GS-US-174-0102) and HBeAg-positive patients who were carriers of a wild hepatitis B virus (study GS-US-174-0103), tenofovir was found to be more effective than adefovir after 48 weeks of treatment in terms of complete response (defined as an HBV DNA level of < 400 copies/ml and an improvement of at least 2 points in the Knodell necro-inflammatory score without any deterioration in the Knodell fibrosis score: 71% versus 49% in HBeAg-negative patients ($p < 0.001$) and 67% versus 12% in HBeAg-positive patients ($p < 0.001$).
The percentages of patients with an HBV DNA viral load of < 400 copies/ml were higher in the tenofovir groups than in the adefovir groups.
In contrast, no significant difference between the two treatment groups was observed in terms of histological response, defined as an improvement of at least 2 points in the Knodell necro-inflammatory score without any deterioration in the Knodell fibrosis score.
In HBeAg-positive patients (study GS-US-174-0103), the percentage of patients with normalised ALT values and HBsAg loss was higher than in the adefovir group and no difference between the two treatment groups was observed in terms of HBeAg seroconversion.

In patients previously treated with a nucleoside (n = 51), combined a-posteriori analysis carried out after 48 weeks of two sub-groups in studies GS-US-174-0102 and GS-US-174-0103 showed that complete response after 48 weeks was similar to that observed among patients who had not received any prior treatment (n = 375).

After 96 weeks of treatment, the virological response (HBV viral plasma load ≤ 400 copies/ml), the biochemical response (normalisation of ALT values) and the serological response (HBeAg loss, HBe seroconversion in HBeAg-positive patients, HBsAg loss and HBs seroconversion) were maintained in the patients treated with tenofovir in both studies.

No data on the duration of treatment is available.

Genotype resistance tests were carried out on all patients taking part in studies GS-US-174-0102 and GS-US-174-0103 who had HBV DNA levels > 400 copies/ml in week 48 (n = 39) and week 96 (n = 24).
No mutation associated with tenofovir resistance was observed in patients taking part in studies GS-US-174-0102 and GS-US-174-0103 who had HBV DNA levels > 400 copies/ml in week 48 and week 96.

The tolerance profile at 48 weeks in studies GS-US-174-0102 and GS-US-174-0103 for patients in the tenofovir groups was similar to that for patients in the adefovir groups, with the exception of nausea (5.4% versus 0.9%), diarrhoea (1.4% versus 0.5%) and abdominal pain (1.6% versus 0.9 %).
No new adverse effects or any change in the tolerance profile (nature or severity of adverse effects) was observed when treatment with tenofovir was continued until it had been administered for 96 weeks.
Cases of renal damage, renal impairment, elevated creatinine levels, hypophosphataemia and proximal tubulopathy (including Fanconi's syndromes) have been reported for patients being treated with tenofovir in a clinical setting.

[1] See Transparency Committee's opinion dated 8 July 2009: review of the proprietary drug VIREAD in the extension of indication for the treatment of adults with chronic hepatitis B (VIREAD 245 mg tablet. EI Opinion 2-CT 6313)

Very little investigation has been carried out into the renal tolerance of tenofovir for patients with renal impairment (creatinine clearance < 80 ml/min). Therefore, in patients with renal insufficiency, tenofovir should only be used if the potential benefits of treatment are considered to outweigh the potential risks.

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

The dossier is based on a phase II study (GS-US-174-0108) lasting 168 weeks (study not yet completed), the principal aim of which was to assess the tolerance of tenofovir disoproxil fumarate (VIREAD), emtricitabine plus tenofovir disoproxil fumarate (TRUVADA) and entecavir (BARACLUDE) in patients with decompensated liver disease. The secondary objectives included assessment of efficacy and of the resistance profile.

- Methodology

This is a phase II, double-blind, multi-centre, randomised study.
Patients had to be aged between 18 and 69, have decompensated liver disease (CPT score[2] of 7 to 12, or have previously had a CPT score ≥ 7 and ≤ 12 on inclusion), plasma HBV DNA ≥ 10^3 copies/ml, ALT level < 10 x the upper end of the normal range and creatinine clearance ≥ 50 ml/min.
Patients with HIV, HCV or HVD, hepatocellular cancer and who had previously been treated with tenofovir, entecavir or adefovir dipivoxil for at least 24 months were not eligible for the study.

Eligible patients were randomised (N=112) on a 2:2:1 ratio to one of the following treatment groups:

- 45 subjects were treated with tenofovir disoproxil as fumarate (VIREAD 245 mg, one tablet daily).
- 45 subjects were treated with a fixed combination of 200 mg emtricitabine and 245 mg tenofovir disoproxil as fumarate (TRUVADA, one tablet daily).
- 22 subjects were treated with entecavir 0.5 mg or 1 mg (BARACLUDE, one tablet daily). The dose of entecavir was 1 mg daily in the case of patients who had been exposed to lamivudine for more than six months and/or who had a history of lamivudine resistance mutations.

In the case of patients with a poor virological response to treatment (fall in HBV plasma DNA ≥ 2 log10 copies / ml compared to the level on inclusion and HBV plasma DNA > 10,000 copies / ml [or HBV plasma DNA > 1,000 copies / ml in the case of subjects with a baseline viral load of < 10,000 copies / ml] in week 8), the investigator had the option to transfer the patients to TRUVADA on an open-label basis from week 8.

Study treatments were evaluated over a period of 48 weeks.

The two primary efficacy endpoints were tolerance criteria:

- discontinuation of treatment because of an adverse event
- confirmed rise in serum creatinine ≥ 0.5 mg/dl or a confirmed serum phosphates level < 2 mg/dl.

The secondary criteria included assessment of clinical efficacy in terms of:

- virological response (HBV plasma viral load ≤ 400 copies/ml)
- biochemical response (normalisation of ALT levels)
- fall of ≥ 2 points in the CPT score compared to the early stage of the study
- serological response (HBeAg loss and seroconversion)

[2] The **Child-Pugh Turcotte (CPT) score** is calculated on the basis of five parameters (bilirubinaemia, albuminaemia, prothrombin rate, whether or not the patient has ascites or encephalopathy) which indicate the severity of the liver condition. The higher the score, the more severe the liver condition. The conventional classification is that compensated cirrhosis is regarded as Child A (score 5-6 points) and decompensated cirrhosis as Child B (7-9 points) or C (10-15 points). Liver transplant is considered for patients with a CPT score of ≥ 7.

➢ Results

Most of the subjects (N=112) were male (83.9%), Asian (53.6%) or Caucasian (42%), aged between 18 and 69 (average age 51). They had been suffering from chronic hepatitis B, defined by HBsAg-positivity for at least six months, and most of them (65.2%) were HBeAg-negative. The average HBV DNA on inclusion was 5.9 log10 copies/ml and 63.4% had serum ALT levels above the upper limit of normal (ULN). Median serum creatinine clearance was 86 ml/min (min-max: 45 - 139) in the tenofovir group, 96 ml/min (49 – 137) in the emtricitabine/tenofovir group and 93.5 ml/min (52 – 137) in the entecavir group. The median Child-Pugh-Turcotte (CPT) score was 7 (5 –12) in the various treatment groups. Very few patients had a CPT score of > 9 (16 patients in total, of whom seven were in the tenofovir group). Approximately half of the patients (52%) had previously been treated with lamivudine (40% of them for at least six months). 21% had previously been treated with adefovir dipivoxil and 19% had mutations associated with resistance to adefovir dipivoxil and/or lamivudine.

The analyses were based on the population of patients who had been randomised and treated (at least one dose of a study drug), with the exception of the analyses relating to:

- ALT normalisation: patients with ALT levels > ULN (upper limit of normal) on entry to the study were taken into consideration;
- fall of > 2 points in the CPT score: patients with a CPT score of ≥ 7 on entry into the study were taken into consideration;
- HBeAg loss and HBe seroconversion: patients with an HBeAg level of > 0 on entry into the study were taken into consideration.

The results are described without a statistical test hypothesis because of the small size of the cohort (table 1).

Table 1: tolerance of use and efficacy parameters for patients who were decompensated in week 48

Parameter	**Study 174-0108**		
	Tenofovir disoproxil 245 mg (N = 45)	Emtricitabine 200 mg/ tenofovir disoproxil 245 mg (N = 45)	Entecavir (0.5 or 1 mg) (N = 22)
Primary efficacy endpoints (tolerance)			
Discontinuation of treatment because of adverse effects, n/N (%)	3/45 (7%)	2/45 (4%)	2/22
Confirmed increase of serum creatinine to ≥ 0.5 mg/dl or confirmed serum phosphate level < 2 mg/dl, n/N (%)	4/45 (9%)	3/45 (7%)	1/22
Secondary endpoints (efficacy)			
HBV DNA < 400 copies/ml, n/N (%)	31/44 (70%)	36/41 (88%)	16/22
Normal ALT, n/N (%)	25/44 (57%)	31/41 (76%)	12/22
Normalised ALT, n/N	12/26	16/25	7/17
Fall of ≥ 2 points in the CPT score compared to the start of the study, n/N	7/27	12/25	5/12
HBeAg loss	3/14	4/15	0/7
HBe seroconversion	3/14	2/15	0/7

In the group being treated with tenofovir, 3 (7%) patients discontinued treatment because of an adverse effect; in 4 (9%) patients, a confirmed increase in serum creatinine to ≥ 0.5 mg/dl or a confirmed serum phosphate level < 2 mg/dl was observed in the first 48 weeks of treatment.

In terms of efficacy, the virological response (HBV plasma viral load ≤ 400 copies/ml) was approximately 70% in the tenofovir group.

Resistance: resistance was analysed after one year on a sample of 13 viraemic patients (with HBV DNA > 400 copies/ml), eight of whom were in the tenofovir group. No tenofovir resistance mutation was identified.

3.3. Conclusion

The tolerance of use and efficacy profile of tenofovir disoproxil fumarate in adults suffering from chronic hepatitis B with **decompensated liver disease** was assessed in a double-blind phase II controlled clinical study (GS-US-174-0108) in which patients were treated with tenofovir disoproxil fumarate (n = 45), emtricitabine plus tenofovir disoproxil fumarate (n = 45) or entecavir (n = 22) for 48 weeks.

The patients taking part in this study had been suffering from decompensated chronic hepatitis B for at least six months, and most of them (65.2%) were HBeAg-negative, with a median CPT score of 7 (5-12). Median serum creatinine clearance was 86 ml/min (min-max: 45-139) in the tenofovir group.

The results observed after 48 weeks treatment are reassuring from the point of view of clinical data previously observed in patients with compensated liver disease: the virological response (HBV DNA < 400 copies/ml) was around 70% and no unexpected adverse effect was found. Three patients (7%) discontinued treatment because of an adverse effect; in 4 (9%) patients, a confirmed increase in serum creatinine ≥ 0.5 mg/dl or a confirmed serum phosphate level < 2 mg/dl was observed in the first 48 weeks of treatment. It should be noted that this study included very few patients with a CPT score > 9 (16 patients in total, seven of whom were in the tenofovir group); as these patients are exposed to a greater risk of renal or hepatic adverse effects, it is recommended that renal and hepatobiliary parameters be monitored closely in this patient population (see section 4.4 of the SPC, Special warnings and precautions for use).
No tenofovir resistance mutation was identified in the 48 weeks of treatment.

This data is limited given the small size of the cohort, and no conclusions can be drawn in respect of a comparison between tenofovir fumarate and entecavir. Additional data from this study (which is continuing and in which patients will be monitored for 168 weeks) is expected and will enable long-term tolerance of use and efficacy to be assessed.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Chronic hepatitis B is a disease that can lead to cirrhosis and its complications (hepatocellular carcinoma and decompensated cirrhosis). Decompensated cirrhosis, a condition which involves hepatocellular insufficiency and portal hypertension, can lead to complications such as jaundice, hepatic encephalopathy, ascites and its spontaneous infection or haemorrhage as a result of the rupture of oesophageal or cardio-tuberous varices. Patients with decompensated cirrhosis have a very poor prognosis.

VIREAD is intended as curative therapy.

The efficacy/adverse effects ratio of this proprietary drug is high because of its antiviral activity and satisfactory resistance profile, provided that the contraindications, special warnings and precautions for use set out in the SPC are respected. The main risk associated with the use of tenofovir is its renal toxicity, especially in this population of cirrhotic patients who are at greater risk of developing renal insufficiency.

This is a first-line therapy.

Few alternative treatments are available for patients with decompensated liver disease.

Public health benefit

Hepatitis B is a minor public health burden in France (< 3,000 DALYs per year lost, according to WHO estimates). The burden represented by patients suffering from decompensated chronic hepatitis B is small at best.

Combating hepatitis B and hepatitis C is a public health priority, and improving the quality of care and quality of life of individuals suffering from chronic hepatitis B (or C) is one of the key strategies of the National Plan to combat Hepatitis B and Hepatitis C for 2009 to 2012.

In the light of its place in therapeutic strategy, VIREAD can be expected to have a minor impact on morbidity and mortality, despite the small amount of clinical data available. The results presented do not a priori raise any problem of transposability into current practice.

Consequently, VIREAD is expected to have a public health benefit in the treatment of decompensated chronic hepatitis B. This benefit is slight.

In view of:
- its efficacy level,
- its resistance profile,
- its place in therapeutic strategy,
- and despite the serious but rare risk of nephrotoxicity,

the actual benefit of this proprietary drug is substantial.

4.2. Improvement in actual benefit (IAB)

In the light of the data available and clinical experience with the use of this proprietary drug in the treatment of chronic hepatitis B, the Committee is of the opinion that VIREAD offers a minor improvement in actual benefit (IAB IV) in the management of adults with chronic hepatitis B and decompensated liver disease, as a result of its antiviral activity and its satisfactory resistance profile.

4.3. Therapeutic use

Recommendations were issued in 2009 by the European Association for the Study of the Liver (EASL)[3].

The aim of antiviral treatment in chronic hepatitis B is to obtain a rapid and significant reduction in the viral load and to stop viral multiplication, and thereafter to maintain this virological control over time. Virological control allows hepatic necro-inflammatory activity to be reduced.

- **In patients with moderate to severe hepatitis without cirrhosis, and patients with cirrhosis but no signs of decompensation,**

Where antiviral treatment appears to be indicated, two first-line strategies can be discussed. The first is based on the use of pegylated or non-pegylated interferon alpha for one year at the most, and the second is based on prescription of a nucleoside or nucleotide analogue for an extended period (certainly for life) for most patients.

Interferon treatment is indicated primarily for patients with compensated liver disease[4], with virological response prediction factors, i.e. a high ALT level (three times the upper limit of normal) and low or moderate viral replication (HBV DNA < 7 log10 UI/mL) before treatment.
The efficacy of treatment is judged in week 12 on the basis of a fall of at least log10 in HBV DNA and an HBV DNA level of less than 2,000 IU/ml in week 24. Treatment is only continued if these criteria are met.
Interferon alpha increases the risk of sepsis and decompensation in patients with advanced cirrhosis.

- Nucleoside or nucleotide analogue treatment is indicated primarily for HBeAg-positive patients with no interferon response prediction factor and for most HBeAg-negative patients. It is also recommended for all patients with cirrhosis irrespective of their HBe status. HBV DNA must also be monitored regularly. The aim is to achieve an HBV DNA level which is undetectable by PCR testing.
Where it is decided to treat a patient with a nucleoside or nucleotide analogue, entecavir (BARACLUDE) and tenofovir (VIREAD) are the recommended first-line treatments because of their antiviral activity and their resistance profile, which is better than those of other analogues (adefovir, lamivudine, telbuvidine). These two substances are also relatively well tolerated.

- **In patients with decompensated liver disease:**

Patients with decompensated cirrhosis should be treated in specialist units in view of the complexity of the antiviral treatment. They may also be suitable for liver transplant.
Terminal liver disease is an urgent medical condition. Treatment is indicated even if the viral load is low, in order to prevent the risk of recurrent viral reactivation. Powerful analogues with a good resistance profile (tenofovir, entecavir) must also be used. However, little data is available regarding the tolerance of these substances in cases of decompensated cirrhosis. Slow clinical improvement is observed over the course of three to six months. However, some patients with very advanced liver disease may not benefit and must be presented for liver transplant. In this case, the benefit of nucleoside analogue treatment will be to reduce the risk of viral relapse on the transplanted organ.

[3] EASL Clinical practice Guidelines: Management chronic hepatitis B: *Journal of Hepatology* 50 (2009) 227-242-540.
[4] Interferon is **contraindicated in patients with decompensated cirrhosis**

Place of VIREAD in therapeutic strategy

VIREAD (tenofovir) is recommended as first-line treatment for patients with hepatitis B and decompensated liver disease because of its virological efficacy and its tolerance and resistance profile.

As tenofovir can cause renal toxicity[5], practitioners are advised to monitor renal function closely, especially in this population of patients with cirrhosis who are at greater risk of developing renal insufficiency. Very little investigation has been carried out into the renal tolerance of tenofovir for patients with renal insufficiency (creatinine clearance < 80 ml/min). **Therefore, in patients with renal insufficiency tenofovir should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Tenofovir is not recommended for patients with severe renal insufficiency (see SPC: contraindications, special warnings and precautions for use).**

4.4. Target population

The target population of patients who might benefit from treatment with tenofovir in the extension of indication is made up of patients with hepatitis B infection and decompensated cirrhosis.

The prevalence of HBs antigen carrier status in mainland France is estimated[6] at 0.65%, (95 % CI: 0.45-0.93), which is equivalent to 280,821 individuals (95% CI: 179,730 - 381,913) chronic HBsAg carriers. A distinction is drawn between asymptomatic chronic carrier status (30% of cases) and chronic hepatic patients (70% of cases)[7]. On the basis of this data, the number of patients with chronic hepatitis B could be estimated at around 196,500 patients.

The incidence of cirrhosis among patients with chronic hepatitis B[8] is 2 to 10%, or 3,930 to 19,600 patients with cirrhosis. The incidence of hepatic decompensation among these patients is estimated at around 4%.

Consequently, the target population for VIREAD in the indication of patients with hepatitis B and decompensated cirrhosis could be estimated at 200 to 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 in the Marketing Authorisation.

4.5.1. Packaging: suitable for the conditions of prescription.

4.5.2. Reimbursement rate: 65% *(for hepatitis B)*

[5] Cases of renal damage, renal insufficiency, elevated creatinine levels, hypophosphataemia and proximal tubulopathy (including Fanconi's syndrome) have been reported for patients being treated with tenofovir disoproxil fumarate in a clinical setting (see SPC).

[6] Meffre C. Prévalence des hépatites B et C en France en 2004 [Prevalence of hepatitis B and C in France in 2004]. Saint-Maurice: Institut de Veille Sanitaire 2007. Available for download at: http://www.invs.sante.fr/publications/2006/prevalence_b_c/vhb_france_2004.pdf .

[7] CMIT. Hépatite virale B [Hepatitis B virus]. In E. PILLY: Vivactis Plus Ed; 2010: pp 355 – 359.

[8] 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