HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

8 July 2009

VIREAD 245 mg film-coated tablets
Bottle 30 tablets (CIP: 358 500-1)

Applicant: GILEAD SCIENCES

Tenofovir disoproxil (as fumarate)

ATC code: J05AFO7

List I
Medicine requiring initial annual hospital prescription. Unrestricted renewal

Date of Marketing Authorisation: 12 September 2008 – corrected version 22 April 2009
Centralised procedure

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use in the extension of indication to adult patients with chronic hepatitis B.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tenofovir disoproxil (as fumarate)

1.2. Indication

Reminder:

"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 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 infection should be based on individual viral resistance testing and/or treatment history of patients."

Extension of indication:

"*Hepatitis B infection:* VIREAD is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

This indication is based on histological, virological, biochemical and serological responses mainly in adult nucleoside-naïve patients with HBeAg positive and HBeAg negative chronic hepatitis B with compensated liver function."

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) once daily taken orally 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 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: VIREAD is not recommended for use in children below the age of 18 years due to insufficient data on safety and efficacy (see section 5.2).

Renal insufficiency: Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) and long term safety 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 disease 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 dose 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).
These dose 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. Therefore clinical response to treatment and renal function should be closely monitored."
Haemodialysis patients - Elderly patients – Patients with liver failure: cf. SPC

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

J : 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 therapeutic category

2.2.1. Comparator medicines

The medicinal products which are strictly comparable are the nucleoside and nucleotide analogues indicated in the treatment of chronic hepatitis B.

Medicinal products (INN)	**Indications**
ZEFFIX (lamivudine) - 100 mg, film-coated tablets, B/28 - 5 mg/ml, oral solution, 240 ml Market launch: 20/08/1999	Treatment of chronic hepatitis B in adult patients with: - **compensated liver disease** with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and/or fibrosis - **decompensated liver disease**
HEPSERA (adefovir dipivoxil) - 10 mg, tablets, B/30 Market launch: 08/04/2003	Treatment of chronic hepatitis B in adult patients with: - **compensated liver disease** with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver 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 Market launch: 04/09/2006	Treatment of chronic hepatitis B virus (HBV) infection in adult patients with **compensated liver disease** and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and/or fibrosis. This indication is based on data from clinical studies in patients with HBeAg-positive and HBeAg-negative HBV infection, nucleoside analogue-naive patients and patients with lamivudine-refractory hepatitis B.
SEBIVO (telbivudine) 600 mg film-coated tablets B/28 Official Journal: 15/04/2008	SEBIVO is indicated in the treatment of chronic hepatitis B in adult patients with **compensated** liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and/or fibrosis.

2.2.2. Medicines with a similar therapeutic aim

The medicines with a similar therapeutic aim are the interferon alfa products (whether or not pegylated) indicated in the treatment of chronic hepatitis B:

Medicinal products (INN)	Indications in hepatitis B
INTRONA (interferon alfa-2b) Solution for injection (i.v. route) Market launch: 03/2001	Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B who have markers for hepatitis B viral replication (presence of HBV DNA and HBeAg), elevated alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and/or fibrosis.
PEGASYS (peginterferon alfa-2b) Solution for injection (i.v. route) Market launch: 04/2003	Chronic hepatitis B: PEGASYS is indicated for the treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and viral replication, elevated ALT levels and histological evidence of liver inflammation and/or fibrosis.
ROFERON-A (interferon alfa-2a) Solution for injection (i.v. route) Market launch: 10/2000	Adult patients with histological evidence of chronic hepatitis B who have markers for viral replication, i.e. HBV DNA or HBeAg.

3 ANALYSIS OF AVAILABLE DATA

The clinical dossier is made up of 4 clinical studies in adult patients chronically infected with the hepatitis B virus and with compensated liver disease.

3.1. Efficacy

- Two comparative, randomised, double-blind Phase III clinical studies compared the efficacy of tenofovir (VIREAD) with that of adefovir (HEPSERA) over a period of 48 weeks. This first phase of treatment was followed by open-label treatment with tenofovir (VIREAD) for up to 240 weeks (in progress).
These 2 studies were conducted in (treatment-naive and pretreated) HBeAg-negative patients who were carriers of a mutant hepatitis B virus (Study GS-US-174-0102) and in HBeAg-positive patients (treatment-naive with the exception of 8 pretreated patients) who were carriers of a wild-type hepatitis B virus (Study GS-US-174-0103).

- One randomised, double-blind Phase II clinical study compared the efficacy of tenofovir (VIREAD) alone versus bitherapy with a combination of tenofovir (VIREAD) and emtricitabine (EMTRIVA) in HBeAg-positive and HBeAg-negative patients who had had an incomplete response to treatment with adefovir (HEPSERA) over a period of more than 24 weeks (Study GS-US-174-0106). EMTRIVA is not indicated in Hepatitis B.

- One randomised, double-blind clinical study compared tenofovir (VIREAD) 245 mg with adefovir (HEPSERA) 10 mg in patients co-infected with HIV/HBV and pretreated with lamivudine (study ACTG 5127) for 48 weeks.

In view of their concomitant clinical development, no comparative clinical studies have been conducted in relation to entecavir (BARACLUDE) and telbivudine (SEBIVO).

3.1.1 Two Phase III studies conducted in treatment-naive and pretreated HBeAg-negative patients (Study GS-US-174-0102) and in HBeAg-positive patients (Study GS-US-174-0103)

Method: The two studies[1] were conducted using a similar methodology.
They compared, after randomisation, the efficacy of tenofovir (VIREAD) and adefovir (HEPSERA) in HBeAg-negative patients (presumed pre-core mutation) and HBeAg-positive patients after 48 weeks of double-blind treatment. This first phase of treatment was followed by open-label treatment with tenofovir (VIREAD) for up to 240 weeks:

- 375 HBeAg-negative patients in study GS-US-174-0102 (tenofovir group, N=250; adefovir group, N = 125)
- 266 HBeAg-positive patients in study GS-US-174-0103 (tenofovir group, N = 176; adefovir group, N =90)

A liver biopsy was performed in the 6 months preceding treatment and at 48 weeks.

Inclusion criteria common to the 2 studies:

- Men or women aged between 18 and 69
- Compensated liver disease
- Knodell necroinflammatory score ≥ 3
- Negative HIV, HCV, HDV serologies

[1] Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Eng J Med 2008d; 359:2442-55

Specific inclusion criteria:

Study GS-US-174-0102:

- HBeAg-negative patients (carriers of a mutant virus)
- Whether or not treated with lamivudine (n=41) or emtricitabine (n=2)
- Serum HBV DNA>10^5 copies/ml
- ALT ≥ ULN and < 10 x ULN

Study GS-US-174-0103:

- HBeAg-positive patients (carriers of a wild-type virus)
- Treatment-native patients (with the exception of 8 patients pretreated with lamivudine/deviation from the protocol)
- Serum HBV DNA>10^6 copies/ml
- ALT ≥2 and <10 x ULN

Treatments:

- Tenofovir group: 300 mg once daily
- Adefovir group: 10 mg once daily

Primary efficacy endpoint:

The primary efficacy endpoint was the percentage of patients with a complete response at 48 weeks (intention-to-treat population).

Complete response was a composite virological and histological criterion defined by:

- serum HBV DNA levels < 400 copies/ml

and

- a reduction in the Knodell necroinflammatory score of at least 2 points (without worsening of the fibrosis)

This composite criterion did not include a biochemical criterion (reduction in transaminase levels in the liver), which was assessed as a secondary endpoint.

Secondary endpoints, notably:

- Percentage of patients with a histological response (reduction in the Knodell necroinflammatory score of at least 2 points (without worsening of the fibrosis)
- Median reduction in the viral load (HBV DNA) compared with baseline
- Percentage of patients with a plasma HBV load ≤ 400 copies/ml
- Percentage of patients with normalised ALT levels
- Percentage of patients with HBeAg loss and HBe seroconversion (detection of anti-HBe antibodies)
- Percentage of patients with HBsAg loss and HBs seroconversion (detection of anti-HBs antibodies)

Characteristics of patients on inclusion, notably:

	Study GS-US-174-0102 (HBeAg-negative patients)		**Study GS-US-174- 0103** (HBeAg-positive patients)	
Characteristics	**Tenofovir (N=250)**	**Adefovir (N=125)**	**Tenofovir (N=176)**	**Adefovir (N=90)**
Age, average (years)	44	43	34	34
Male, %	77	78	68	71
Geographical origin, %				
Caucasian patients	64	65	52	51
Asian patients	25	24	36	36
HBV DNA, average (log_{10} copies/ml)	6.86	6.98	8.64	8.88
ALT (IU/mol), average	128	164	142	155
Previous treatment with lamivudine, %	17	18	4*	0
Knodell necroinflammatory score, average	7.8	7.8	8.3	8.5
Knodell fibrosis score, average	2.3	2.4	2.3	2.5
Knodell fibrosis score = 4 (cirrhosis), %	19	20	20	21
HBV genotype				
A, %	12	11	24	21
B, %	9	14	15	11
C, %	12	10	25	30
D, %	64	63	32	35

*8 patients (4%) previously treated with lamivudine were included despite the eligibility criteria

Results at 48 weeks

Results of study GS 174-0102 and study GS 174-0103 in terms of the efficacy of tenofovir (VIREAD) and adefovir (HEPSERA) in respect of the primary efficacy endpoint and the secondary endpoints after 48 weeks of treatment (ITT)

	Study GS 174-0102 (AgHBe-negative patients)			Study GS 174-0103 (AgHBe-positive patients)		
Endpoints	Tenofovir 245 mg n = 250	Adefovir 10 mg n = 125	p	Tenofovir 245 mg n = 176	Adefovir 10 mg n = 90	p
Primary endpoint: **Complete response** (n/N)[a] (virological and histological)	**71%** (177/250)	**49%** (61/125)	**p < 0.001**	**67%** (117/176)	**12%** (11/90)	**p < 0.001**
Histological response (n/N)[b]	72% (181/250)	69% (86/125)	NS	74% (131/176)	68% (61/90)	NS
Median reduction in HBV DNA levels (log_{10} copies/ml)	**-4.7**	**-4.0**	**p <0.05**	**-6.4**	**-3.7**	**p <0.05**
HBV DNA (%) **< 400 copies/ml** (< 69 IU/ml)	**93%** (233/250)	**63%** (79/125)	**p < 0.001**	**76%** (134/176)	**13 %** (12/90)	**p < 0.001**
ALT (%) Normalised ALT[d]	76% 180/250	77% 91/125	NS	**68%** 115/169	**54%** 49/90	**p = 0.032**
HBe serology HBeAg loss/	N/A	N/A	N/A	22% (34/153)	18% (14/80)	NS
HBe seroconversion	N/A	N/A	N/A	21% (32/153)	18% (14/80)	NS
HBs serology HBsAg loss/	0/250	0/125	-	**3% (5/158)**	**0% (0/82)**	**p = 0.018**
HBs seroconversion	0/250	0/125	-	1% (2/158)	0% (0/82)	NS

[a] complete response defined as an HBV DNA level of < 400 copies/ml and an improvement in the Knodell necroinflammatory activity score of at least 2 points without any worsening of the Knodell fibrosis score
[b] improvement in the Knodell necroinflammatory activity score of at least 2 points without any worsening of the Knodell fibrosis score
[c] the median reduction in the HBV DNA level compared with baseline is only a reflection of the difference between the baseline HBV DNA level and the detection limit (DL) of the test
[d] the population taken into account for the analysis of ALT normalisation was made up solely of those patients whose ALT levels were higher than the ULN at the start of the study. N/A= Not applicable

After 48 weeks of treatment, in patients who were mainly treatment-naive (590 / 51 pretreated patients) and carriers of a mutant (HBeAg-negative) or wild-type (HBeAg-positive) virus, the efficacy of tenofovir was superior to that of adefovir, with a complete response rate of 71% compared with 49% (HBV DNA levels < 400 copies/ml and improvement in the Knodell necroinflammatory activity score of at least 2 points without any worsening of the Knodell fibrosis score) in the HBeAg-negative patients and 67% compared with 12% in the HBeAg-positive patients.

The following were observed (secondary endpoints):

- a higher percentage of patients with an undetectable viral HBV DNA load of < 400 copies/ml in the tenofovir groups than in the adefovir groups
- a greater average reduction in the viral load in the tenofovir groups than in the adefovir groups
- no significant difference between the treatments in terms of the histological response defined as an improvement in the Knodell necroinflammatory activity score of at least 2 points without any worsening of the Knodell fibrosis score
- a higher percentage of patients who had normalised ALT levels and who achieved HBsAg loss in the tenofovir group than in the adefovir group among the HBeAg-positive patients (study GS-US-174-0103)

No difference was observed between the treatments in terms of HBeAg seroconversion, however.

Retrospective analysis of 2 subgroups at 48 weeks

A pooled analysis of the 2 studies (GS-US-174-0102 and GS-US-174-0103) at 48 weeks was carried out retrospectively in 2 subgroups for:

- the patients pretreated with a nucleoside (n = 51) compared with the treatment-naive patients (n = 375): of the 51 patients pretreated with a nucleoside, 49 had been treated previously with lamivudine and 2 patients with emtricitabine, and they had an average HBV DNA load of 7.2 $\log_{10}$ copies/ml
- the patients with normal ALT levels at baseline (n = 21) compared with the patients with abnormal ALT levels at baseline (n = 405)

In the patients pretreated with a nucleoside compared with nucleoside-naive patients:

- 73% (37/51) compared with 69% (258/375) achieved a complete response to treatment
- 90% (46/51) compared with 88% (330/375) achieved a reduction in HBV DNA levels < 400 copies/ml
- the response to tenofovir was comparable at 48 weeks

In the patients with normal ALT levels at baseline compared with those with abnormal ALT levels at baseline:

- 21/21 compared with 88% (356/405) achieved a reduction in HBV DNA levels < 400 copies/ml
- the response to tenofovir was comparable at 48 weeks

Results at 96 weeks: Follow-up of patients who continued treatment up to 96 weeks

In studies GS-US-174-0102 and GS-US-174-0103, the patients who had been treated under double-blind conditions for 48 weeks (either with tenofovir 245 mg or with adefovir 10 mg) were given the option of continuing the study without any break from treatment, receiving tenofovir under open-label conditions up to week 96.

The percentages of randomised patients in the tenofovir or adefovir groups who continued treatment up to week 96 were:

- 90% (tenofovir) and 88% (adefovir) in study GS-US-174-0102
- 82% (tenofovir) and 92% (adefovir) in study GS-US-174-0103

Results of study GS 174-0102 and study GS 174-0103 in terms of efficacy in respect of the secondary endpoints after 96 weeks of treatment (ITT)

	Study GS 174-0102 (HBeAg-negative patients)			**Study GS 174-0103 (HBeAg-positive patients)**		
Endpoints[a]	Tenofovir 245 mg (96 weeks[b]) N= 250	Adefovir 10 mg followed by tenofovir 245 mg[c] N= 125	p	Tenofovir 245 mg (96 weeks[b]) N= 176	Adefovir 10 mg followed by tenofovir 245 mg[c] N = 90	p
HBV DNA (%) < 400 copies/ml (< 69 IU/ml)	90% 221/234	89% 109/122	NS	76% 126/166	74% 64/86	NS
ALT (%) Normalised ALT[d]	72% 159/221	68% 76/111	NS	60% 96/159	65% 56/86	NS
HBe serology HBeAg loss	N/A	N/A	N/A	26% 41/159	24% 20/83	NS
HBe seroconversion	N/A	N/A	N/A	23% 36/159	20% 17/83	NS
HBs serology HBsAg loss	0% 0/242	0% 0/121	-	5% 9/172	6% 5/86	NS
HBs seroconversion	0% 0/242	0% 0/121	-	4% 7/172	5% 4/86	NS

[a] calculated using a long-term evaluation algorithm (LTE Analysis) – The patients who had to withdraw from the study before week 96 because of an assessment criterion defined in the protocol and those who continued the treatment for the entire 96 weeks were included in the denominator

[b] 48 weeks of double-blind treatment with tenofovir fumarate followed by 48 weeks of open-label treatment with the same medicinal product

[c] 48 weeks of double-blind treatment with adefovir followed by 48 weeks of open-label treatment with tenofovir fumarate

[d] the population taken into account for the analysis of ALT normalisation consisted solely of those patients whose ALT levels were higher than the ULN at the start of the study. N/A: Not applicable

The virological response (plasma HBV load ≤ 400 copies/ml), the biochemical response (normalisation of ALT levels) and the serological responses (HBeAg loss, HBe seroconversion in HBeAg-positive patients, HBsAg loss and HBs seroconversion) were maintained at 96 weeks in the patients treated with tenofovir in the 2 studies.

Indeed, the percentages of patients observed at 96 weeks were comparable (without statistical analysis) to those observed at 48 weeks for the patients treated with tenofovir in the 2 studies.

The histological response was not evaluated. Provision was made in the protocol for an additional biopsy between week 228 and 240.

Furthermore, among the HBeAg-positive patients (study GS 174-0103), a higher number of patients achieved HBsAg loss and HBs seroconversion at 96 weeks, notably in the adefovir followed by tenofovir treatment group, compared with the result observed at 48 weeks.

3.1.2 Phase II study GS-US-174-0106 in patients who had had an incomplete response to adefovir

The objective of this (unpublished) randomised, double-blind study was to compare monotherapy (tenofovir) with bitherapy (tenofovir combined with emtricitabine) in HBeAg-positive and HBeAg-negative patients who had had an incomplete response to treatment with adefovir (HEPSERA) over a period of more than 24 weeks.

The randomised patients (N=105) had chronic compensated hepatitis B, a viral load of ≥ 1,000 copies/ml and had been treated with adefovir for at least 24 weeks. 57% of the patients randomised to the tenofovir group compared with 60% of the patients randomised to the tenofovir combined with emtricitabine group had already been treated with lamivudine.

The primary efficacy endpoint was the percentage of patients with an HBV DNA load of < 400 copies/ml after 48 weeks of treatment.

Treatments:

- tenofovir group (N=53)
- tenofovir combined with emtricitabine group (N=52)

At 24 weeks, the patients in the tenofovir group with a viral load of > 400 copies/ml could receive open-label combination treatment with tenofovir /emtricitabine.

At week 24, 66% (35/53) of the patients treated with tenofovir had an HBV DNA load of < 400 copies/ml, compared with 69% (36/52) of the patients treated with the emtricitabine and tenofovir combination (with no significant difference between the monotherapy and bitherapy group).

The comparisons between the treatment groups beyond the 24th week of treatment are difficult to interpret because the investigators had the option of stepping up the treatment by combining emtricitabine with tenofovir under open-label conditions.
Long term studies evaluating the efficacy and safety of bitherapy with emtricitabine and tenofovir in patients infected with HBV are in progress.

3.1.3 Comparative study of tenofovir 245 mg / adefovir 10 mg in patients co-infected with HIV/HBV

The objective of a randomised, double-blind clinical study was to compare tenofovir 245 mg with adefovir 10 mg in patients co-infected with HIV/HBV who had been pretreated with lamivudine (study ACTG 5127[2]).
In this study, 52 patients were randomised: 27 patients to the tenofovir 245 mg group and 25 patients to the adefovir 10 mg group.
The results related to the data available at 48 weeks (n=18 patients in the tenofovir group; n=17 in the adefovir group).
The average HBV DNA load at baseline among the patients randomised to the tenofovir group was 9.45 $\log_{10}$ copies/ml (n = 27).
At 48 weeks:

- the average reduction in the HBV DNA load compared with baseline was 5.74 $\log_{10}$ copies/ml compared with 4.03 in the adefovir group
- 11/18 patients had a normal ALT level compared with 8/17 in the adefovir group

[2] Peters MG, Andersen J, Lynch P, Liu T, Alston-Smith B, Brosgart CL, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. Hepatology 2006; 44:1110-6

3.2. Resistance

No HBV mutation associated with resistance to tenofovir has been identified.
During tests on cells, HBV strains expressing the mutations rtV173L, rtL180M and rtM204I/V associated with resistance to lamivudine (ZEFFIX) and telbivudine (SEBIVO) exhibited 0.7-3.4 times greater sensitivity to tenofovir than the wild-type virus.
HBV strains expressing the mutations rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V associated with resistance to entecavir (BARACLUDE) exhibited 0.6-6.9 times greater sensitivity to tenofovir than the wild-type virus.
HBV strains expressing the mutations rtA181V and rtN236T associated with resistance to adefovir (HEPSERA) exhibited 2.9-10 times greater sensitivity to tenofovir than the wild-type virus.
Viruses with the mutation rtA181T remained sensitive to tenofovir with CE_{50} values corresponding to 1.5 times that of the wild-type virus.

Clinical resistance:
In 426 HBeAg-negative (GS-US-174-0102, N= 250) and HBeAg-positive (GS-US-174-0103, N= 176) patients, the genotypic changes in HBV polymerase were evaluated by comparison with the baseline values.
All the patients included in studies GS-US-174-0102 and GS-US-174-0103 who had HBV DNA levels of > 400 copies/ml at week 48 (n = 39) and at week 96 (n = 24) were evaluated on the basis of genotypic resistance testing. No mutation associated with resistance to tenofovir was identified.

3.3. Adverse effects (from SPC)

The evaluation of safety derived from clinical study data is based primarily on experience in two double-blind comparative controlled studies (GS-US-174-0102 and GS-US-174-0103) in which 641 patients with chronic hepatitis B and compensated liver disease received treatment with tenofovir 245 mg daily (n = 426) or with adefovir 10 mg daily (n = 215).

The common adverse effects (≥ 1/100, < 1/10) with a suspected (at least possible) relationship to the treatment are as follows:

- headaches
- diarrhoea, vomiting, abdominal pain, nausea, abdominal distension, flatulence
- elevated ALT levels
- fatigue

The safety profile at 48 weeks in studies GS-US-174-0102 and GS-US-174-0103 for the patients in the tenofovir groups was comparable with that of the patients in the adefovir groups with the exception of nausea (5.4% compared with 0.9%), diarrhoea (1.4% compared with 0.5%) and abdominal pain (1.6% compared with 0.9%).
Continuation of treatment with tenofovir for up to 96 weeks did not reveal any new adverse effects or any change in the safety profile (nature or severity of the adverse effects).

<u>Post-marketing experience</u>
In addition to the reports of adverse effects from clinical studies, the following possible adverse effects have also been identified since the launch of tenofovir:

- Rare adverse effects (< 1/1,000 to ≥ 1/10,000):
Lactic acidosis – pancreatitis – raised transaminase levels – rash.
Acute renal failure, renal failure, proximal renal tubulopathy (including Fanconi syndrome), increased creatinine.

Renal impairment, renal failure, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir in clinical practice. Renal safety with tenofovir has only been studied to a very limited degree in patients with impaired renal function (CrCl < 80 ml/min).

It is recommended that creatinine clearance should be calculated in all patients prior to the instigation of therapy with tenofovir fumarate, and renal function (creatinine clearance and serum phosphate) should also be monitored every 4 weeks during the first year of treatment, and then every 3 months.
In patients at risk of renal impairment, and notably those who have previously experienced renal effects during administration of adefovir, more frequent monitoring of renal function should be considered.

- *Very rare adverse effects (<1/10,000)*:
Dyspnoea – hepatitis – asthenia – acute tubular necrosis.

- *Adverse effects of undetermined frequency*:
Hypokalaemia – hepatic steatosis – rhabdomyolysis, osteomalacia (manifesting as bone pain and capable of predisposing to fractures in rare cases), muscle weakness, myopathy - nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.

Exacerbations of the disease during treatment*:* Spontaneous exacerbations of chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After the instigation of antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline. Among tenofovir-treated patients, on-treatment exacerbations typically occurred after 4-8 weeks of therapy. In patients with compensated liver disease, these increases in serum ALT are not generally accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk of hepatic decompensation following hepatitis exacerbation, and should therefore be monitored closely during therapy.

Exacerbations of the disease after treatment discontinuation*:* Acute exacerbations of hepatitis have also been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with an increase in HBV DNA, and most appear to be self-limiting. Cases of severe exacerbation, some of them fatal, have been reported, however.
Hepatic function should be monitored regularly with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy.
Resumption of hepatitis B therapy may be imposed if necessary. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may cause hepatic decompensation.

3.4. Conclusion

In mainly treatment-naive patients (590 treatment-naive patients / 51 pretreated patients) who were HBeAg-negative carriers of a mutant hepatitis B virus (study GS-US-174-0102) and HBeAg-positive carriers of a wild-type hepatitis B virus (study GS-US-174-0103), the efficacy of tenofovir was superior after 48 weeks of treatment to that of adefovir in terms of complete response (defined as an HBV DNA level of < 400 copies/ml and an improvement in the Knodell necroinflammatory activity score of at least 2 points without any worsening of the Knodell fibrosis score): 71% compared with 49% in the HBeAg-negative patients ($p < 0.001$) and 67% compared with 12% in the HBeAg-positive patients ($p < 0.001$).

The percentages of patients with an HBV DNA load of < 400 copies/ml were higher in the tenofovir groups than in the adefovir groups.
However, no significant difference was observed between the 2 treatment groups in terms of histological response, defined as an improvement in the Knodell necroinflammatory activity score of at least 2 points without any worsening of the Knodell fibrosis score.
Among the HBeAg-positive patients (study GS-US-174-0103), the percentage of patients who achieved a normalised ALT and who achieved HBsAg loss was higher than in the adefovir group and no difference was observed between the 2 treatment groups in terms of HBeAg seroconversion.

Among the patients pretreated with a nucleoside (n = 51) at 48 weeks, the combined retrospective analysis of 2 subgroups from studies GS-US-174-0102 and GS-US-174-0103 showed the complete response at 48 weeks to be comparable with that observed in treatment-naive patients (n = 375).

After 96 weeks of treatment:

- the virological response (plasma HBV load ≤ 400 copies/ml)
- the biochemical response (normalisation of ALT levels)
- the serological responses (HBeAg loss, Hbe seroconversion in the HBeAg-positive patients, HBsAg loss and HBs seroconversion) were maintained in the tenofovir-treated patients in the 2 studies.

There were no data enabling the duration of treatment to be specified.

All the patients included in studies GS-US-174-0102 and GS-US-174-0103 who had an HBV DNA level of > 400 copies/ml at week 48 (n = 39) and at week 96 (n = 24) were evaluated on the basis of genotypic resistance testing.
No mutation associated with resistance to tenofovir was identified among the patients included in studies GS-US-174-0102 and GS-US-174-0103 and who had an HBV DNA level of > 400 copies/ml at week 48 and at week 96.

The safety profile at 48 weeks in studies GS-US-174-0102 and GS-US-174-0103 for the patients included in the tenofovir groups was comparable with that for patients in the adefovir groups with the exception of nausea (5.4% compared with 0.9%), diarrhoea (1.4% compared with 0.5%) and abdominal pain (1.6% compared with 0.9 %).
Continuation of treatment with tenofovir for up to 96 weeks did not reveal any new adverse effects or any change in the safety profile (nature or severity of the adverse effects).
Renal impairment, renal failure, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir in clinical practice.
Renal safety with tenofovir has only been studied to a very limited degree in patients with impaired renal function (CrCl < 80 ml/min). **Consequently, in patients with renal impairment, tenofovir should be used only if the potential benefits of treatment are considered to outweigh the potential risks.**

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hepatitis B is a common viral disease which can be life-threatening.

This medicinal product is intended as curative therapy.

The efficacy/adverse effects ratio for this medicinal product is high.

This is a first- or second-line therapy.

Alternative medicinal products exist.

> Public health benefit
> Hepatitis B represents a low public health burden in France (< 3,000 DALYs lost per year according to WHO estimates).
> Combating hepatitis B and C is a public health priority and improving the quality of care and the quality of life for people with chronic hepatitis B (or C) is one of the strategic focuses of the "Plan National de Lutte contre les Hépatites B et C, 2009 – 2012" (National Plan for Combating Hepatitis B and C, 2009 – 2012).
> In the light of the clinical data available and in view of the product's therapeutic use (the 2009 European guidelines of the EASL recommend interferon alfa - entecavir, ténofovir as first-line therapy for chronic hepatitis B), the medicinal product VIREAD can be expected to have a low impact in terms of morbidity and mortality.
> Consequently, it is expected that VIREAD will benefit public health in the treatment of chronic hepatitis B. This benefit can be quantified as low.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

In adult patients who are chronically infected with the hepatitis B virus and have compensated liver disease, tenofovir disoproxil (VIREAD) has the following characteristics compared with adefovir dipivoxil (HEPSERA):
- greater efficacy
- lower emergence of viral resistance
- a comparable safety profile with the exception of nausea, diarrhoea and abdominal pain

Consequently, the Committee considers that VIREAD provides a moderate improvement in actual benefit (level III) compared with HEPSERA.

4.3. Therapeutic use

The objective of antiviral treatment in chronic hepatitis B is to achieve a rapid and significant decrease in the viral load and arrest viral multiplication, and then to maintain this virological control in the long term. With virological control, it is possible to reduce the level of necroinflammatory activity in the liver.

Guidelines were issued recently in 2009 by the European Association for the Study of the Liver (EASL)[3]:

Extract from these guidelines:

Initial treatment: Tenofovir (VIREAD) may be used as first-line therapy, as may interferon (pegylated or non-pegylated) and entecavir (BARACLUDE).

Two treatment strategies are possible:

- treatment of limited duration with:
  - pegylated interferon alfa in those HBeAg-positive patients who are most likely to undergo HBe seroconversion and those HBeAg-negative patients who are most likely to have a sustained response on discontinuation of treatment.

These are patients who, before treatment, have raised ALT levels (> 3 x ULN) and an HBV DNA level of < 7 $\log_{10}$ copies/ml or

  - a nucleoside inhibitor (HBeAg-positive patients in whom HBe seroconversion occurs during treatment)

HBe seroconversion is more frequent in patients who have raised ALT levels (> 3 x ULN) and an HBV DNA level of < 7 $\log_{10}$ copies/ml before treatment.

The limited-duration treatment strategy necessitates preferably potent antiviral agents with the highest possible barrier to resistance such as entecavir (BARACLUDE) or tenofovir (VIREAD) such that serum virus levels are reduced rapidly to levels below the detectability threshold and virological rebounds related to HBV resistance are avoided.

- long-term treatment with a nucleoside inhibitor in patients in whom virological control cannot be achieved without treatment and who require long-term treatment, i.e. HBeAg-positive patients who have not achieved HBe seroconversion and HBeAg-negative patients

This strategy is also recommended in patients with cirrhosis, whatever their HBeAg status.

In cases of lack of a primary response (viral load reduction < 1 $\log_{10}$ at 12 weeks) to adefovir (HEPSERA), substitution with entecavir (BARACLUDE) or tenofovir (VIREAD) is recommended.

In cases of a partial virological response (viral load detectable with real-time PCR):

- In patients receiving lamivudine (ZEFFIX), adefovir (HEPSERA) or telbivudine (SEBIVO) with a partial virological response at 24 weeks, 2 strategies may be considered:
  - substitution with a more potent antiviral agent, entecavir (BARACLUDE) or tenofovir (VIREAD)
  - addition of a more potent antiviral agent which does not have cross-resistance: add tenofovir (VIREAD) to lamivudine (ZEFFIX) or telbivudine (SEBIVO); add entecavir (BARACLUDE) to adefovir (HEPSERA)
- In patients receiving entecavir (BARACLUDE) or tenofovir (VIREAD) with a partial virological response at week 48, some experts propose adding in the other antiviral agent in order to prevent the development of resistance in the long term. The long-term safety of tenofovir (VIREAD) and entecavir (BARACLUDE) is not known.

In cases of therapeutic failure, defined as resistance to antiviral treatment including lamivudine (ZEFFIX), adefovir (HEPSERA), entecavir (BARACLUDE) or telbivudine (SEBIVO), tenofovir (VIREAD) may be recommended as a substitute or in combination, although the long-term safety of certain combinations is not known.

[3] EASL Jury. EASL Clinical practice Guidelines: Management of chronic hepatitis B : *Journal of Hepatology* 2009; 50 : 242-540

4.3. Target population

The target population able to benefit from treatment with tenofovir disoproxil (as fumarate) is that of adult chronic hepatitis B patients with compensated liver disease with evidence of active viral replication, persistent elevation of serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and/or fibrosis.

The prevalence of the HBs antigen, a marker of chronic hepatitis B in mainland France in 2004, is estimated at 0.65%, or 280,821 people, only 44.8% of whom are aware of their status [4], i.e. 126,000 people who are liable to receive treatment.

Chronic hepatitis B treatment concerns only those patients in whom the disease is active (30% of patients according to experts), i.e. around 40,000 people.

4.4. Transparency Committee recommendations

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

4.4.1. Packaging: The packaging is appropriate for the prescription conditions

4.4.2. Reimbursement rate: 65 % *(in hepatitis B)*

[4] Meffre C. Prévalence des hépatites B et C en France en 2004. Saint-Maurice: Institut de Veille Sanitaire2007. Available at: http://www.invs.sante.fr/publications/2006/prevalence_b_c/vhb_france_2004.pdf (consulted on 19/06/2009).