HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 May 2012

EVIPLERA, film-coated tablets
B/30 (CIP code: 219 473-5)

Applicant: GILEAD

rilpivirine 25 mg
emtricitabine 200 mg
tenofovir disoproxil 245 mg

ATC code (2012): J05AR (antivirals for treatment of HIV infections, combinations)

List I
Medicine requiring initial annual hospital prescription.
Unrestricted renewal.

Date of Marketing Authorisation (centralised procedure): 28 November 2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

EVIPLERA is a fixed combination of three antiviral medicines in a single tablet:

- rilpivirine 25 mg
- tenofovir disoproxil (as the fumarate) 245 mg
- emtricitabine 200 mg

1.2. Indications

"EVIPLERA is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml.
The demonstration of the benefit of the combination emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil fumarate in the treatment of HIV-1 infection is based on week-48 safety and efficacy analyses from two randomised, double-blind, controlled Phase III studies in antiretroviral treatment-naïve patients.

As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of EVIPLERA."

1.3. Dosage

"Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults: The recommended dose of EVIPLERA is one tablet, taken orally, once daily. EVIPLERA must be taken with a meal.

Where discontinuation of therapy with one of the components of EVIPLERA is indicated or where dose modification is necessary, separate preparations of emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil fumarate are available. Please refer to the Summary of Product Characteristics for these medicinal products.

Elderly:

EVIPLERA has not been studied in patients over the age of 65 years. EVIPLERA should be administered with caution to elderly patients.

Renal impairment:
Treatment with EVIPLERA resulted in an early small increase of mean serum creatinine levels which remained stable over time and is not considered clinically relevant.
Limited data from clinical studies support once daily dosing of EVIPLERA in patients with mild renal impairment (creatinine clearance 50-80 ml/min). However, long-term safety data for the emtricitabine and tenofovir disoproxil fumarate components of EVIPLERA have not been evaluated in patients with mild renal impairment. Therefore, in patients with mild renal impairment EVIPLERA should only be used if the potential benefits of treatment outweigh the potential risks.
EVIPLERA is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require a dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet.

Hepatic impairment:
There is limited information regarding the use of EVIPLERA in patients with mild or moderate hepatic impairment (Child-Pugh-Turcotte (CPT) Score A or B). No dose adjustment of EVIPLERA is required in patients with mild or moderate hepatic impairment. EVIPLERA should be used with caution in patients with moderate hepatic impairment. EVIPLERA has not been studied in patients with severe hepatic impairment (CPT Score C). Therefore, EVIPLERA is not recommended in patients with severe hepatic impairment (see sections 4.4 and 5.2 of the SPC).
If EVIPLERA is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation of hepatitis.

Paediatric population:
The safety and efficacy of EVIPLERA in children under the age of 18 years have not been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made."

1.4. Special warnings and precautions for use

"Virologic failure and development of resistance
EVIPLERA has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. EVIPLERA should be avoided in patients with HIV-1 harbouring the K65R mutation. The list of rilpivirine-associated mutations presented in section 5.1 of the SPC should only guide the use of EVIPLERA in the treatment-naïve population.
In the pooled analysis from the two Phase III clinical studies (C209 and C215), patients treated with emtricitabine/tenofovir disoproxil fumarate + rilpivirine with a baseline viral load > 100,000 HIV-1 RNA copies/ml had a greater risk of virologic failure (15.3% with rilpivirine versus 5.9% with efavirenz) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/ml (4.2% with rilpivirine versus 2.3% with efavirenz). Patients with a baseline viral load > 100,000 HIV-1 RNA copies/ml who experienced virologic failure exhibited a higher rate of treatment emergent resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class. More patients who failed virologically on rilpivirine than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance.
As with other antiretroviral medicinal products, resistance testing should guide the use of EVIPLERA."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2012)

J: Antiinfectives for systemic use
J05: Antivirals for systemic use
J05A: Direct-acting antivirals
J05AR: Antivirals for treatment of HIV infections, combinations
J05AR08: Emtricitabine, tenofovir disoproxil and rilpivirine

2.2. Medicines in the same therapeutic category

Individual formulations of the different active ingredients of EVIPLERA are available: EDURANT (rilpivirine), VIREAD (tenofovir disoproxil fumarate), EMTRIVA (emtricitabine) and TRUVADA (fixed combination of tenofovir disoproxil + emtricitabine).

It should be noted that the proprietary medicinal product ATRIPLA, fixed- combination in a single tablet of efavirenz, emtricitabine and tenofovir disoproxil, is indicated only in adults in whom the disease has been under virological control (with an HIV-1 RNA level < 50 copies/ml) through a combination of antiretrovirals for three months or longer, and is not indicated in treatment-naïve patients.

2.3. Medicines with a similar therapeutic aim

Other antiretroviral medicines used in combination in the treatment of HIV infection in treatment-naïve adult patients.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):
- Efavirenz: SUSTIVA gelatin-coated capsules and oral solution
- Nevirapine: VIRAMUNE tablets and oral solution

Nucleoside reverse transcriptase inhibitors (NRTIs):
- Abacavir: ZIAGEN tablets and oral solution
- Didanosine: VIDEX hard capsules and powder for oral suspension
- Lamivudine: EPIVIR tablets and oral solution
- Stavudine: ZERIT hard capsules and oral solution
- Zidovudine: RETROVIR hard capsules, oral solution and solution for injection
- Abacavir/lamivudine: KIVEXA tablets
- Abacavir/lamivudine/zidovudine: TRIZIVIR tablets
- Zidovudine/lamivudine: COMBIVIR tablets

Protease inhibitors (PIs):
- Atazanavir: REYATAZ hard capsules or oral powder
- Darunavir: PREZISTA, film-coated tablets
- Fosamprenavir: TELZIR film-coated tablets and oral solution
- Indinavir: CRIXIVAN hard capsules
- Lopinavir with ritonavir: KALETRA soft capsules and oral solution
- Nelfinavir: VIRACEPT film-coated tablets and oral powder
- Saquinavir mesylate: INVIRASE hard capsules
- Ritonavir: NORVIR, soft capsules and oral solution, increases the bioavailability of most protease inhibitors, which is why it is used only in combination with those drugs.

Integrase inhibitor:
- Raltegravir: ISENTRESS film-coated tablets

3 ANALYSIS OF AVAILABLE DATA

The assessment of the efficacy and safety of the non-fixed combination of the components of EVIPLERA (rilpivirine 25 mg / emtricitabine 200 mg / tenofovir disoproxil fumarate 245 mg) is based on data from two randomised, double-blind, comparative phase III clinical studies (ECHO[1] and THRIVE[2]) versus efavirenz, carried out in antiretroviral treatment-naïve patients infected with HIV-1 and followed up for 96 weeks. These studies were also subjected to a planned a priori combined analysis so as to allow subgroup analyses.

A pharmacokinetics study (GS-US-264-0103) has also been submitted by the company. This open study in healthy subjects demonstrated the bioequivalence of a tablet of EVIPLERA with that of the three active ingredients administered individually in a single dose (one rilpivirine 25 mg tablet, one tenofovir disoproxil 245 mg tablet and one emtricitabine 200 mg capsule).

3.1. Efficacy

Objective:
The principal objective of the ECHO and THRIVE studies was to demonstrate the non-inferiority (delta threshold = 12%) of rilpivirine (25 mg once daily) versus efavirenz (600 mg once daily) in terms of virological response at 48 weeks when given as part of triple therapy in combination with optimised treatment in antiretroviral treatment-naïve patients infected with HIV-1.

Method:
The protocols of these two studies were similar: randomised, double-blind, controlled (with double placebo) phase III studies versus efavirenz, in antiretroviral treatment-naïve patients infected with HIV-1. These patients were followed up for 96 weeks.

Inclusion and exclusion criteria:
- Principal inclusion criteria: patients aged over 18 years, infected with HIV-1, antiretroviral treatment-naïve, HIV-1 viral load ≥ 5000 copies/ml, demonstrated sensitivity to NRTIs in optimised combination therapy.
- Principal exclusion criteria: mutation associated with resistance to NNRTIs, renal impairment (glomerular filtration rate < 50 ml/min), significant clinical pathology (including cardiac dysfunction, pancreatitis, significant psychiatric problems, hepatic impairment).

Treatments:
After stratification according to viral load (≤ 100,000 copies/ml; > 100,000 to ≤ 500,000 copies/ml and > 500,000 copies/ml) and according to optimised treatment (THRIVE study only), eligible patients were randomised to two groups (ratio 1:1) to receive rilpivirine 25 mg or efavirenz 600 mg once daily in combination with optimised treatment.

[1] Molina JM, Cahn P, Grinsztejn B et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet 2011; 378: 238-246.
[2] Cohen CJ, Andrade-Villanueva J, Clotet B et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet 2011; 378: 229-237.

The optimised treatment, which consisted of two NRTIs, was different in the two studies:
- ECHO study: fixed combination of tenofovir 245 mg/emtricitabine 200 mg (TRUVADA), one tablet daily,
- THRIVE study, at the discretion of the investigator:
    - tenofovir 245 mg + emtricitabine 200 mg, once daily, in a fixed combination (TRUVADA) or taken separately.
    - zidovudine 300 mg + lamivudine 300 mg, twice daily, in a fixed combination (COMBIVIR) or taken separately
    - abacavir 600 mg + lamivudine 300 mg, once daily, in a fixed combination (KIVEXA) or taken separately.

The patients who received the treatment rilpivirine 25 mg + tenofovir 245 mg + emtricitabine 200 mg were treated with the active ingredients separately and not in a single tablet of EVIPLERA.

Primary efficacy endpoint:
The primary efficacy endpoint was the virological response defined as the proportion of patients with an HIV-1 viral load < 50 copies/ml at week 48, calculated according to the *Time to Loss of Virologic Response* algorithm[3] (ITT-TLOVR analysis).

Statistical analysis:
Non-inferiority was demonstrated if the lower level of the 95% confidence interval (CI) for the difference in the percentage of patients with a viral load < 50 copies/ml at week 48 was ≥ -12%. If non-inferiority was demonstrated, a superiority test was provided for in the protocol.
Since the ECHO and THRIVE studies had similar protocols, analyses were carried out both on the two studies individually and on the combined data of the two studies[4] so as to achieve the necessary statistical power and to allow subgroup analyses. A subgroup analysis for the virological response primary endpoint was carried out as a function of the stratification factors optimised treatment and baseline viral load.

Principal secondary endpoints:
- Immune response (change in CD4+ count relative to baseline),
- Resistance analysis in patients with virological failure.

Study populations:
A total of 1368 patients were included in these studies, of whom 686 received rilpivirine and 682 received efavirenz (ITT population). The distribution of the patients included as a function of the treatments received in the THRIVE and ECHO studies is presented in Table 1.
In the overall population included in these studies, approximately 80% (1096/1368) of patients received optimised treatment consisting of the combination tenofovir/emtricitabine.

Table 1: Distribution of optimised treatment received by patients in the ECHO and THRIVE studies

	ECHO N = 690		**THRIVE N = 678**		**Combined data N = 1368**	
OT combination* n (%)	**Rilpivirine N' = 346**	**Efavirenz N' = 344**	**Rilpivirine N' = 340**	**Efavirenz N' = 338**	**Rilpivirine N' = 686**	**Efavirenz N' = 682**
Tenofovir/emtricitabine	690 (100)		204 (60.0)	202 (59.8)	550 (80.2)	546 (80.1)
Zidovudine/lamivudine	-	-	101 (29.7)	103 (30.5)	101 (14.7)	103 (15.1)
Abacavir/lamivudine	-	-	35 (10.3)	33 (9.8)	35 (5.1)	33 (4.8)

**OT: Optimised treatment consisting of two NRTIs*

[3] TLOVR: Time to Loss of Virologic Response algorithm
[4] The relevance of the performance of this combined analysis was validated by heterogeneity tests.

The characteristics of the patients included were comparable between the rilpivirine group and the efavirenz group (Table 2), with 50% of patients overall having a baseline viral load ≤ 100,000 copies/ml (subpopulation specified in the Marketing Authorisation).

Table 2: Baseline characteristics of the patients (combined data of the ECHO and THRIVE studies, ITT)

	Overall study populations*	
Characteristics	**RPV + OT** **N = 686**	**EFV + OT** **N = 682**
Men [%]	75.5	76.1
Age [years] **	36 [18-78]	36 [19-69]
Duration of infection [years] **	1.4 [0-24]	1.3 [0-28]
Viral load [log_{10} copies/ml] **	5.0 [2-7]	5.0 [3-7]
Viral load **≤ 100,000 copies/ml** > 100,000 copies/ml	 **53.6%** 46.4%	 **48.4%** 51.6%
CD4 [cells/mm^3] **	249 [1-888]	260 [1-1137]
AIDS-defining pathology	5.1%	5.7%
Co-infection with HCV/HBV [%]	7.3%	9.5%

RPV: rilpivirine (EDURANT), EFV: efavirenz (SUSTIVA), OT: optimised treatment

** Not subdivided according to associated optimised treatment or baseline viral load*

*** Median [min – max]*

In the subgroup of patients with a viral load ≤ 100,000 copies/ml who received tenofovir/emtricitabine as optimised treatment, the patient characteristics in each of the groups were comparable: the median age in each group was 36 years, the patients were mostly men (78% and 79%), the median baseline viral load (HIV-1 RNA) was 5.0 log_{10} copies/ml in the two groups and the median baseline CD4+ count was 247 [1-888] $\times 10^6$ cells/l in the rilpivirine group and 261 [1-857] $\times 10^6$ cellules/l in the efavirenz group.

Results for the primary efficacy endpoint:

- Virological response

At 48 weeks, the non-inferiority (lower limit of the 95% CI for the difference between treatments ≥ -12%) of rilpivirine 25 mg once daily versus efavirenz 600 mg once daily was demonstrated in terms of virological response (HIV-1 RNA < 50 copies/ml) in the per-protocol analysis, both in each of the two studies (ECHO and THRIVE) individually and in the combined analysis of the data (combined analysis: 85.1% in the rilpivirine group versus 82.8% in the efavirenz group; difference 2.3% 95% CI [-1.7; 6.2]). These results are confirmed by the ITT analysis (results presented in Table 3). Analysis of the combined data according to a logistic regression model, with adjustment for the stratification factors, also confirms the non-inferiority of rilpivirine 25 mg versus efavirenz in the overall population (ITT and per-protocol analyses).

In the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml, defined a posteriori but corresponding to the indication in the Marketing Authorisation, who received as optimised treatment the combination tenofovir/emtricitabine, the non-inferiority of rilpivirine 25 mg versus efavirenz 600 mg was likewise demonstrated in terms of 48-week virological response (results presented in Table 4).

- Virological failure (see Table 3)

In the overall population of the studies, regardless of the baseline viral load and optimised treatment received, the reasons for absence of virological response varied according to treatment group (combined data). For the patients in the rilpivirine group, the most common

reason was virological failure[5] (9%), whereas for those in the efavirenz group it was adverse events (6.7%).
Post-hoc analysis of these cases of virological failure according to baseline viral load showed that the higher number of patients with virological failure seen in the rilpivirine group (9% versus 4.8%) was due primarily to the subgroup of patients with a plasma HIV-1 RNA viral load > 100,000 copies/ml. Indeed, in this subpopulation virological failure was observed in 15.1% (48/318) of patients in the rilpivirine group, compared with 6.3% (22/352) in the efavirenz group. This high risk of virological failure explains why this subpopulation of patients with a viral load > 100,000 copies/ml was excluded from the Marketing Authorisation. On the other hand, in the population with a baseline viral load ≤ 100,000 copies/ml, these proportions are much lower, with virological failure after 48 weeks of treatment observed in 3.8% (14/368) of patients in the rilpivirine group and 3.3% (11/330) of patients in the efavirenz group.
In the patients with a viral load ≤ 100,000 copies/ml who received as optimised treatment the combination tenofovir/emtricitabine, virological failure was observed in 4.2% of patients in the rilpivirine group and 2.3% in the efavirenz group.

Table 3: 48-week efficacy data in the ECHO and THRIVE studies (combined data; ITT-TLOVR)

	Overall population		**Patients who received emtricitabine/tenofovir as optimised treatment**	
	RPV + OT N = 686	**EFV + OT N = 682**	**EVIPLERA N = 550**	**EFV + OT N = 546**
Responders: HIV-1 RNA < 50 copies/ml, n [%]	578 (84.3)	561 (82.3)	459 (83.5)	450 (82.4)
Difference [95% CI] *	2.0% [-2.0; 6.0]		1.0% [-3.4; 5.5]	
Nonresponders				
Virological failure	9%	4.8%	9.5%	4.2%
≤ 100,000 copies/ml	3.8%	3.3%	4.2%	2.3%
> 100,000 copies/ml	**15.1%**	**6.3%**	**15.3%**	**5.9%**
Death	0.1%	0.4%	0	0.2%
Withdrawal due to adverse event	2.0%	6.7%	2.2%	7.1%
Withdrawal for other reason	4.5%	5.7%	4.9%	6.0%

OT: optimised treatment
** Based on a normal approximation of the difference in response*

Table 4: 48-week virological response (viral load < 50 copies/ml) as a function of viral load (combined data; ITT-TLOVR)

	Rilpivirine + OT N = 686	**Efavirenz + OT N = 682**	**Observed difference [95% CI]**
Overall population, N = 1368			
≤ 100,000 copies/ml	90.2% (332/368)	83.6% (276/330)	6.6% [1.6; 11.5]
> 100,000 copies/ml	77.4% (246/318)	81.0% (285/352)	-3.6% [-9.8; 2.5]
Patients who received tenofovir/emtricitabine as optimised treatment, N = 1096			
≤ 100,000 copies/ml	89.6% (258/288)	84.8% (217/256)	4.8% [-0.8; 10.5]
> 100,000 copies/ml	76.7% (201/262)	80.3% (233/290)	-

OT: optimised treatment

[5] According to the definition of virological failure for the analysis of efficacy (TLOVR method): included subjects with rebound (confirmed viral load ≥ 50 copies/ml after having been responders) and those who had not been responders in the first place (no confirmed viral load < 50 copies/ml, treatment ongoing or stopped on account of lack or loss of efficacy), and subjects who ended the study prematurely.

Results for the secondary endpoints (analysis of the combined data of the ECHO and THRIVE studies):

- Immune response at 48 weeks (change in CD4+ count relative to baseline)

In the overall population of the studies, the change in CD4+ count relative to baseline was $+192 \times 10^6$ cells/l in the rilpivirine group and $+176 \times 10^6$ cells/l in the efavirenz group (estimated difference 17.9 [2.1; 33.6]).
In the subgroup of patients with a viral load ≤ 100,000 copies/ml, the change in CD4+ count relative to baseline was comparable in the two groups: $+185.2 \times 10^6$ cells/l (95% CI [+171.82; +198.64]) in the rilpivirine group versus $+160.6 \times 10^6$ cells/l (95% CI [+144.78; +176.35]) in the efavirenz group.
In the subgroup of patients who received as optimised treatment the combination tenofovir/emtricitabine, irrespective of viral load, this change was $+193 \times 10^6$ cells/l in the rilpivirine group versus $+182 \times 10^6$ cells/l.

- Resistance analysis[6]

In the overall population, the resistance analysis carried out in the patients with virological failure showed that the patients with virological failure treated with rilpivirine who developed resistance to rilpivirine generally developed cross-resistance to other NNRTIs. Moreover, the emergence of mutations associated with resistance to NRTIs, in particular cross-resistance to lamivudine/emtricitabine, was more common in patients with virological failure in the rilpivirine group than in patients with virological failure under efavirenz.
In the patients with a baseline viral load ≤ 100,000 copies/ml who received as optimised treatment the combination tenofovir/emtricitabine, virological failure was observed in 16/288 (5.6%) of patients in the rilpivirine group and 6/255 (2.4%) in the efavirenz group.
Among these patients, 4/288 (1.4%) developed resistance to an NNRTI in the rilpivirine group and 2/255 (0.8%) in the efavirenz group. In the rilpivirine group, two patients developed resistance to rilpivirine, in one case crossed with etravirine and in the other crossed with efavirenz. No resistance to nevirapine was observed. In the efavirenz group, the patients who became resistant to efavirenz remained sensitive to etravirine and rilpivirine, but developed cross-resistance to nevirapine.
As regards NRTIs, more patients in the rilpivirine group developed resistance to at least one substance in this class: 5/288 developed cross-resistance to lamivudine and emtricitabine in the rilpivirine group, compared with none in the efavirenz group.

3.2. Adverse effects

Extract from the SPC:
"The most frequently reported adverse reactions considered possibly or probably related to rilpivirine hydrochloride and emtricitabine/tenofovir disoproxil fumarate (EVIPLERA) were nausea (9%), dizziness (8%), abnormal dreams (7%), headache (6%), diarrhoea (5%) and insomnia (5%) (pooled data from the Phase III clinical studies C209 [ECHO] and C215 [THRIVE]). The safety profile of emtricitabine and tenofovir disoproxil fumarate in these studies was consistent with the previous experience with these agents when each was administered with other antiretroviral agents."

The adverse effects associated with each of the antiretroviral agents of the combination EVIPLERA may occur with the fixed-combination tablet. In particular, treatment with tenofovir disoproxil fumarate has been associated with renal manifestations, in particular renal impairment, proximal tubulopathy (including cases of Fanconi syndrome), tubular necrosis and nephrogenic diabetes insipidus.
Refer to the SPC of EVIPLERA for adverse effects considered at least possibly linked to one of its components in clinical studies or since their market launch.

[6] For the analysis of resistance in the context of safety, the definition of virological failure was different to that used for the analysis of efficacy.

Comparative 48-week safety data of the ECHO and THRIVE studies

The comparative assessment of the safety of the non-fixed combination of the components of EVIPLERA is based primarily on the combined data of the ECHO and THRIVE studies. Approximately 80% (1096/1368) of patients included in these studies received optimised treatment with tenofovir/emtricitabine.

The safety data from these studies in the subgroup of patients who received as optimised treatment the combination tenofovir/emtricitabine and who had a baseline viral load ≤ 100,000 copies/ml have not been submitted by the company.

For information, in the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml (the indication of the Marketing Authorisation), irrespective of the background treatment given, the incidence of AEs at least possibly linked to the treatments was lower in the rilpivirine group (47.3%) than in the efavirenz group (62.7%), notably dizziness (9.5% versus 28.8%), rash (1.6% versus 8.8%) and drowsiness (3.5% versus 7.9%). In the rilpivirine group, the most common AEs at least possibly linked to the treatments were the same as those observed in the overall population, i.e. nausea, dizziness, headache and abnormal dreams. As in the overall population, the frequency of grade 2-4 AEs considered to be at least possibly linked to the treatments in this subgroup was lower in the rilpivirine group (16.8% versus 30%).

Treatment discontinuation linked to an adverse event occurred less often in the rilpivirine group than in the efavirenz group (2.2% versus 5.8% in the subgroup of patients with a viral load ≤ 100,000 copies/ml and 2.0% versus 6.7% in the overall population).

Five deaths occurred during the THRIVE and ECHO studies: one in the rilpivirine group and four in the efavirenz group. None of these deaths was considered to be linked to the study treatments.

As regards lipid abnormalities linked to treatment, in the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml a lower incidence of grade 2-3 abnormalities in total cholesterol (4.1% versus 19.2%) and LDL-C (5.6% versus 13.9%) was observed in the rilpivirine group than in the efavirenz group. However, a difference between the two treatment groups in favour of rilpivirine was observed at 48 weeks in the change relative to baseline in total cholesterol, LDL-C, HDL-C and triglycerides. No difference between the two groups was observed at 48 weeks in the change relative to baseline in the ratio total cholesterol/HDL-C.

In the population of patients with a viral load ≤ 100,000 copies/ml who received as optimised treatment the combination tenofovir/emtricitabine, the incidence of treatment discontinuation associated with an adverse event was 2.4% in the rilpivirine group versus 6.3% in the efavirenz group.

3.3. Conclusion

The assessment of the efficacy and safety of the non-fixed combination of the components of EVIPLERA (rilpivirine 25 mg / emtricitabine 200 mg / tenofovir disoproxil fumarate 245 mg) is based primarily on data from two randomised, double-blind, comparative phase III clinical studies (ECHO and THRIVE) versus efavirenz, carried out in antiretroviral treatment-naïve patients infected with HIV-1.

As the protocols of these two studies were similar, they were subjected to individual analyses and to a combined analysis so as to achieve the necessary statistical power and to allow subgroup analyses.

Approximately 80% (1096/1368) of patients included in these studies received optimised treatment consisting of the combination tenofovir/emtricitabine, of whom half (544/1096) had a baseline viral load ≤ 100 000 copies/ml.

In the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml (the indication of the Marketing Authorisation) who received as optimised treatment the combination tenofovir/emtricitabine, the non-inferiority (delta threshold = 12%) of rilpivirine 25 mg versus efavirenz 600 mg was demonstrated in terms of virological response at 48 weeks (per-protocol and ITT analyses). In the overall study population, the non-inferiority of the rilpivirine group was likewise demonstrated.

The safety profile of rilpivirine at 48 weeks was overall better than that of efavirenz in the two studies. In the population of patients with a baseline viral load ≤ 100,000 copies/ml who received as optimised treatment the combination tenofovir/emtricitabine, the incidence of treatment discontinuation associated with an adverse event was 2.4% in the rilpivirine group versus 6.3% in the efavirenz group.
Based on safety data from the ECHO and THRIVE studies, in the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml, irrespective of the background treatment given (of whom 544/698 received the combination tenofovir/emtricitabine), the incidence of AEs possibly linked to the treatments was lower in the rilpivirine group than in the efavirenz group 47.3% versus 62.7%), notably dizziness (9.5% versus 28.8%), rash (1.6% versus 8.8%) and drowsiness (3.5% versus 7.9%). The same trend in favour of rilpivirine was true of the change in total cholesterol, LDL-C, HDL-C and triglycerides at 48 weeks relative to baseline.
The AEs at least possibly linked to the treatment that were the most common in the rilpivirine group were similar to those observed in the overall population, i.e. nausea, dizziness, headache and abnormal dreams.
The adverse effects associated with each of the antiretroviral agents in the combination EVIPLERA may occur with the fixed-combination tablet.

The combined analysis of the ECHO and THRIVE studies showed that the incidence of virological failure was higher when the baseline HIV-1 RNA viral load was > 100,000 copies/ml (15.1% with rilpivirine versus 6.3% with efavirenz)[7] than when it was ≤ 100,000 copies/ml (3.8% with rilpivirine versus 3.3% with efavirenz). In the overall population of these two studies, the patients with virological failure treated with rilpivirine who developed resistance to rilpivirine generally developed cross-resistance to other NNRTIs. In these patients with virological failure, the emergence of mutations associated with resistance to NRTIs (particularly cross-resistance to lamivudine/emtricitabine) was more common with rilpivirine than with efavirenz.
In the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml who received as optimised treatment the combination tenofovir/emtricitabine, the proportion of patients with virological failure[8] was 5.6% (16/288) in the rilpivirine group versus 2.4% (6/255) in the efavirenz group. Among these patients

- 4/288 in the rilpivirine group and 2/255 in the efavirenz group developed resistance to an NNRTI,
- more patients developed resistance to at least one NRTI in the rilpivirine group: 5/288 developed cross-resistance to lamivudine and emtricitabine in the rilpivirine group, compared with none in the efavirenz group.

On the basis of the available data, it is not possible to establish whether the genetic barrier to resistance of rilpivirine is higher than efavirenz. These data are too limited to draw any conclusions about the robustness of this genetic barrier, the consequences of cross-resistances and possible reversibility of them. This warrants further study cohort on this point.

[7] According to the definition of virological failure for the analysis of efficacy.
[8] According to the definition of virological failure for the analysis of resistances.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

HIV infection is a serious pathology that is life-threatening.

This proprietary medicinal product aims to prevent and/or correct the immune deficiency caused by HIV infection in adult patients.

The efficacy/adverse effects ratio of EVIPLERA is high in the population of the Marketing Authorisation restricted to patients for whom treatment with efavirenz as the third agent in triple therapy including emtricitabine and tenofovir is not appropriate.
The efficacy/adverse effects ratio of EVIPLERA is low in the other populations of the Marketing Authorisation due to the genetic barrier of rilpivirine, the superiority of which at 48 weeks over that of efavirenz having not been demonstrated, despite virological efficacy being non-inferior to that of efavirenz and a safety profile which is more favourable overall than that of efavirenz.

For treatment-naïve patients with a viral load ≤ 100,000 copies/ml, there are treatment alternatives to this proprietary medicinal product.

Public health benefit

The public health burden of HIV-1 infection is substantial. For treatment-naïve patients starting first-line treatment the burden is small on account of the limited number of such patients.

Reducing HIV-associated morbidity and mortality is a public health need that is an established priority*.

There is no available information that allows the impact of the proprietary medicinal product EVIPLERA on morbidity and mortality or quality of life to be assessed directly. However, on the basis of the available data (non-inferiority of rilpivirine versus efavirenz on the viral load at 48 weeks in treatment-naïve patients, failure to demonstrate a higher genetic barrier), this proprietary medicinal product is not expected to have an impact on reducing morbidity and mortality in treatment-naïve patients compared with other existing treatments.

Consequently, on the basis of the available data, it is not expected that the proprietary medicinal product EVIPLERA will benefit public health in this indication.

*National programme against HIV-AIDS. Directorate-General for Health/Hospital and Organisation of Care Directorate 2005-2008 and Public Health Law 2004 (Law No. 2004-806 of 9 August 2004 relating to Public Health Policy)

The actual benefit of this proprietary medicinal product is substantial in the population of the Marketing Authorisation restricted to patients for whom treatment with efavirenz as third agent in triple therapy including emtricitabine and tenofovir is not appropriate.
The actual benefit of this proprietary medicinal product is insufficient in the other populations of the Marketing Authorisation.

4.2. Improvement in actual benefit (IAB)

Despite the simplification of the dose regimen and despite rilpivirine having a overall safety profile more favourable than efavirenz, having taken into account the uncertainty regarding the genetic barrier to resistance of rilpivirine and failure to demonstrate efficacy superior to the combination efavirenz plus emtricitabine/tenofovir, the Committee considers that EVIPLERA

offers no improvement in actual benefit (IAB V) in the management strategy of antiretroviral treatment-naïve patients infected with HIV-1 with a viral load ≤ 100,000 copies/ml.

4.3. Therapeutic use

Therapeutic strategy:
EVIPLERA is a new fixed combination of antiretroviral medicines containing one NNRTI and two NRTIs which allows simplification of the dose regimen (one tablet per day). The 2010 report on the clinical management of persons infected with HIV predates the publication of the results of the ECHO and THRIVE studies and does not therefore include EVIPLERA in therapeutic strategies.

According to the 2010 report on the clinical management of persons infected with HIV headed by Professor Patrick Yeni:[17]

- ***In treatment-naïve patients***

4.3.1. Management of persons infected with HIV[9]

Numerous antiretrovirals, in six drug categories, are available:

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Fusion inhibitors (FIs)
- CCR5 receptor antagonists
- Integrase inhibitors (INIs)

First-line triple therapy remains a combination of two NRTIs with a third agent.

The choice of the two NRTIs for triple therapy should preferably involve fixed combinations of tenofovir/emtricitabine (TRUVADA) or abacavir/lamivudine (KIVEXA).
TRUVADA should be preferred if the plasma viral load is ≥ 100,000 copies/ml, particularly in the case of combination with atazanavir/ritonavir (REYATAZ) or efavirenz (SUSTIVA), owing to the greater risk of virological failure with KIVEXA in this subpopulation (interim results of study ACTG A5202).
When the viral load is < 100,000 copies/ml, the choice between KIVEXA and TRUVADA can be made on a case-by-case basis, taking account of factors such as HBV co-infection and renal impairment.
TRUVADA must be used with caution in patients with renal impairment or who are at risk of this occurring. KIVEXA must only be used in patients who are not carriers of allele HLA B*5701.

The third agent should preferably be a PI/ritonavir or an NNRTI. There is no conclusive argument in favour of the use of one or these two classes over the other. It is recommended to use preferentially:

- if a PI/ritonavir is chosen as the third agent: atazanavir/r, darunavir/r or lopinavir/r
- if an NNRTI is chosen as the third agent: efavirenz

Therapeutic use of EVIPLERA:
Efavirenz is the current NNRTI prefered choice in an initial triple therapy in treatment-naïve patients, in combination with two NRTIs.
Because of the genetic barrier of rilpivirine which superiority over of efavirenz has not been demonstrated, when triple therapy including emtricitabine and tenofovir is being considered (particularly in patients who are carriers of allele HLA B*5701, who cannot be treated with abacavir), use of EVIPLERA in treatment-naïve patients with a viral load ≤ 100,000 copies/ml must be limited to situations where use of efavirenz as third agent in the regimen is not appropriate, especially in patients with a history of neuropsychiatric disorders or drug intolerance.

[9] Yeni P. 2010 report. Prise en charge médicale des personnes infectées par le VIH. Recommandations du groupe d'experts [Medical management of persons infected with HIV – expert group guidelines] Available at www.sante.gouv.fr.

4.4. Target population

Regarding the indications for use of the product and its restricted role in the treatment strategy, the estimation of the maximum target population of EVIPLERA was based on the number of treatment-naïve patients starting an antiretroviral treatment with an efavirenz/emtricitabine/tenofovir combination in whom the viral load at the start of treatment is < 100,000 copies/ml. The target population was estimated for 2010.

As of 31 December 2010,[10] the number of patients with HIV infection chronic condition in the general scheme was 96,963. Extrapolating the data from the general scheme, which covers approximately 88% of the population, to the whole of the population in France, the number of persons in 2010 classed as having the HIV infection chronic condition can be estimated at 110,000.

According to the FHDH database,[11] the percentage of treatment-naïve patients starting first-line treatment was 5.4% (2144/39,819) of patients monitored in 2010. Applying this percentage to the 110,000 persons being treated for HIV infection at the end of 2010, the number of treatment-naïve adult patients starting first-line treatment in 2010 can be estimated at approximately 6000.
According to this same database, approximately 65% of treatment-naïve patients had a viral load < 100,000 copies/ml and the efavirenz/emtricitabine/tenofovir combination was initiated in 23.7% of treatment-naïve patients starting first-line treatment. If these percentages are applied to the above figure of 6000, the number of treatment-naive patients with a viral load < 100,000 copies/ml starting first-line treatment with the efavirenz/emtricitabine/ tenofovir combination can be estimated at approximately 1000 per year.

In practice, the number of patients likely to receive EVIPLERA as part of first-line triple therapy will be very limited. Taking into account its place in the therapeutic strategy, the target population of EVIPLERA will be well below 1000 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 in the management of treatment-naïve patients infected with HIV-1 with a viral load ≤ 100,000 copies/ml in whom the use of efavirenz is not appropriate.
The transparency Committee does not recommend inclusion on the list of medicines refundable by National Insurance and on the list of medicines approved for use by hospitals in the other populations of the Marketing Authorisation.

The transparency Committee notes the observational cohort study instituted as part of the risk management plan for assessment of the emergence of resistance linked to treatment with rilpivirine and would like to re-evaluate the dossier within a maximum period of two years from now in the light of additional data arising from this study.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 100%

[10] CNAMTS [French National Salaried Workers' Health Insurance Fund] data.
[11] FHDH - ANRS CO4. Retour d'informations Clinico-Épidémiologiques [Return of clinico-epidemiological information.] June 2011. http://www.ccde.fr