HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 July 2011

Examination of the file of proprietary medicinal products registered for a period of 5 years as of 15 December 2005 (*Journal Officiel* of 15/12/2005)

TRUVADA 200 mg/245 mg, film-coated tablets
B/30 (CIP code: 365 656-3)

Applicant: GILEAD SCIENCES

Emtricitabine 200 mg
Tenofovir disoproxil fumarate 245 mg
ATC code (2010): J05AR03

List I
Medicine subject to annual initial hospital prescription
Unrestricted renewal

Date of Marketing Authorisation (centralised procedure): 21/02/2005

Reasons for the request:

- Renewal of inclusion in the list of medicines refundable by National Health Insurance.
- Request for re-assessment of the IAB in a sub-population (patients with a viral load ≥ 100 000 copies/ml) versus KIVEXA following the submission of new data.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Emtricitabine
Tenofovir disoproxil fumarate

1.2. Indications

"TRUVADA is a fixed combination of emtricitabine and tenofovir disoproxil (as a fumarate), indicated in combination with other antiretrovirals for the treatment of adults infected with HIV-1.
Demonstration of the benefit offered by the combination of emtricitabine and tenofovir disoproxil fumarate in the treatment of HIV infection relies solely on studies conducted in patients naïve to any previous antiretroviral treatment (see section 5.1)."

1.3. Dosage (cf. SPC)

"The treatment should be initiated by doctors experienced in the management of HIV infection.

Adults: The recommended dose of TRUVADA is one tablet to be taken orally once a day. In order to optimise the absorption of tenofovir, it is recommended to take TRUVADA with food. Even a light meal is sufficient to improve the absorption of tenofovir (see section 5.2).
If stopping the administration of one of the components of TRUVADA is indicated or if it is necessary to modify the dose, separate formulations of emtricitabine and tenofovir disoproxil fumarate are available. Please consult the Summary of Product Characteristics for these medicinal products.

Children and adolescents: TRUVADA should not be used in children below the age of 18 years owing to there being insufficient data concerning its safety and efficacy (see section 5.2).

Elderly persons: There are no data available that would allow a dosage recommendation to be made for patients over the age of 65 years. However, in the absence of renal impairment, no adjustment of the daily dose recommended in adults should be necessary.

Renal impairment: Emtricitabine and tenofovir are eliminated by renal excretion and exposure to emtricitabine and tenofovir is increased in renally impaired patients. Limited data are available concerning the tolerance and efficacy of TRUVADA in patients presenting moderate or severe renal impairment (creatinine clearance < 50 ml/min) and the long-term tolerance data have not been evaluated in cases of mild renal impairment (creatinine clearance of 50 to 80 ml/min). Therefore, in patients with renal impairment, TRUVADA should only be used if it is judged that the potential benefits of the treatment outweigh the potential risks. Close monitoring of kidney function may be necessary in patients with renal impairment (see section 4.4). It is recommended to adjust the interval between administrations in patients with a creatinine clearance of 30 to 49 ml/min. These dosage adjustments have not been confirmed in a clinical study setting and the clinical response to the treatment should be closely monitored in these patients (see sections 4.4 and 5.2).

Mild renal impairment (creatinine clearance of 50 to 80 ml/min): Data from clinical studies supporting the administration of a single daily dose of TRUVADA in patients with mild renal impairment are limited (see section 4.4).

Moderate renal impairment (creatinine clearance of 30 to 49 ml/min): It is recommended to administer TRUVADA every 48 hours, relying on modelling of the pharmacokinetic data obtained for emtricitabine and tenofovir disoproxil fumarate after administration of a single dose in non-HIV subjects presenting various degrees of renal impairment (see section 4.4).

Severe renal impairment (creatinine clearance < 30 ml/min) and patients on haemodialysis: TRUVADA is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients needing haemodialysis, as the reductions in the doses of emtricitabine and tenofovir necessary in these patients cannot be obtained with the fixed combination.

Hepatic impairment: The pharmacokinetics of TRUVADA and emtricitabine has not been studied in patients with hepatic impairment. The pharmacokinetics of tenofovir, on the other hand, has been studied in these patients and no adjustment of the dose of tenofovir disoproxil fumarate has proved necessary. Owing to the poor hepatic metabolism and the renal route of elimination of emtricitabine, it is unlikely that any adjustment of the dose of TRUVADA is necessary in hepatically-impaired patients (see section 4.4 and 5.2).
If TRUVADA is suspended in HIV/HBV co-infected patients, these patients should be closely monitored for any signs of exacerbation of the hepatitis (see section 4.4)."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

J: Anti-infectives for systemic use
J05: Antivirals for systemic use
J05A: Direct acting antivirals
J05AR: Antivirals for treatment of HIV infections, combinations
J05AR03: Tenofovir disoproxil and emtricitabine

2.2. Medicines in the same therapeutic category

Separate formulations of the two active ingredients of TRUVADA are available:
- tenofovir disoproxil: VIREAD 245 mg, film-coated tablets
- emtricitabine: EMTRIVA 200 mg, hard capsules

Every tablet of TRUVADA contains 245 mg tenofovir and 200 mg emtricitabine.

Fixed combinations of nucleoside reverse transcriptase inhibitors:
- abacavir - lamivudine: KIVEXA tablets
- abacavir - lamivudine - zidovudine: TRIZIVIR tablets
- lamivudine - zidovudine: COMBIVIR tablets

Nucleoside reverse transcriptase inhibitors (NRTIs) within the framework of a treatment combining antiretrovirals:
- abacavir: ZIAGEN tablets and oral solution
- didanosine: VIDEX capsules and powder for oral suspension
- emtricitabine: EMTRIVA capsules and oral solution
- lamivudine: EPIVIR tablets and oral solution
- stavudine: ZERIT capsules and oral solution
- zidovudine: RETROVIR capsules and oral solution and solution for injection

Nucleotide reverse transcriptase inhibitor (NRTI) within the framework of a treatment combining antiretrovirals:
- tenofovir disoproxil: VIREAD film-coated tablets

2.3. Medicines with a similar therapeutic aim

This refers to other antiretrovirals used in combination in the treatment of HIV infection in both treatment-naïve and previously-treated adult patients:

Protease inhibitors:
- atazanavir: REYATAZ capsules or oral powder
- darunavir: PREZISTA, film-coated tablets
- fosamprenavir: TELZIR film-coated tablets and oral solution,
- indinavir: CRIXIVAN capsules,
- lopinavir combined with ritonavir: KALETRA soft capsules and oral solution
- nelfinavir: VIRACEPT film-coated tablets and oral powder
- saquinavir mesylate: INVIRASE capsules
- tipranavir: APTIVUS soft capsules (heavily treatment-experienced patients)
- ritonavir: NORVIR soft capsules and oral solution, increases the bioavailability of the majority of protease inhibitors, which explains its use exclusively in combination with these medicines.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):
- efavirenz: SUSTIVA capsules and oral solution
- nevirapine: VIRAMUNE tablets and oral solution
- etravirine: INTELENCE tablets

Combination of 2 NRTIs and 1 NNRTI:
- emtricitabine – tenofovir – efavirenz: ATRIPLA tablets

Integrase inhibitors:
- raltegravir: ISENTRESS film-coated tablets

Fusion inhibitor:
- enfuvirtide: FUZEON powder and solvent for suspension for injection (patients who have had a failed treatment comprising at least one drug from three classes of antiretrovirals)

CCR5 receptor antagonist:
- maraviroc: CELSENTRI, tablet.

3 REMINDER OF THE TRANSPARENCY COMMITTEE'S OPINIONS

OPINION of the Committee of 21 September 2005 (registration)

Improvement in actual benefit
Compared to the separate administration of the two currently available proprietary medicinal products – emtricitabine (EMTRIVA) and tenofovir (VIREAD) – one capsule and one film-coated tablet in one daily intake, the TRUVADA fixed combination (emtricitabine + tenofovir DF) in one daily intake does not provide an improvement in actual benefit (IAB V) in adult patients not requiring any dosage adjustment.

OPINION of the Committee of 23 January 2008 (submission of new data)

Improvement in actual benefit:

Compared to the separate administration of the two currently available proprietary medicinal products – emtricitabine (EMTRIVA) and tenofovir (VIREAD) – one capsule and one film-coated tablet in one daily intake, the TRUVADA fixed combination (emtricitabine and tenofovir) in one daily intake does not offer provide an improvement in the actual benefit (IAB V) in adult patients not requiring any dosage adjustment.

4 PRESCRIPTION DATA

- IMS data:

According to the EPPM-IMS data (cumulative annual growth rate, November 2010), there were 18,000 primary care prescriptions for TRUVADA. The small number of prescriptions does not permit a qualitative analysis of the data.

- French hospital database on HIV infection[1] (FHDH):

According to available data for the year 2008, 72.2% of patients (both naïve and pre-treated) under antiretroviral treatment were receiving a triple therapy comprising 2 NRTIs (combined with a protease inhibitor (PI) in 45.8% of cases and an NNRTI in 26.4% of cases).
Among the patients receiving an antiretroviral combination, 38.4% were receiving a treatment comprising at least emtricitabine and tenofovir. This amounted to a frequency of 74.9% if only treatment-naïve patients were taken into account, i.e. first-line.
It should be pointed out that this database does not reveal whether emtricitabine and tenofovir are administered as a fixed combination (TRUVADA) or as two separate proprietary medicinal products (EMTRIVA + VIREAD).

5 ANALYSIS OF AVAILABLE DATA

In support of the application for renewal of registration and IAB re-assessment, the applicant has submitted the following efficacy data:

- Data at 144 weeks of the pivot study GS-01-934, whose results at 48 weeks were taken into consideration by the Transparency Committee in its Opinion of 23 January 2008.
- New clinical studies:

Studies in treatment-naïve patients

- Results of a controlled study (study ACTG A5202) aimed at comparing the efficacy of the fixed combinations emtricitabine/tenofovir (TRUVADA) and abacavir/lamivudine (KIVEXA), as an adjunct to efavirenz or atazanavir/ritonavir, in treatment-naïve patients.
- Results of a controlled study (HEAT study) aimed at comparing the efficacy and tolerance at 96 weeks of the fixed combinations emtricitabine/tenofovir (TRUVADA) and abacavir/lamivudine (KIVEXA), as an adjunct to liponavir/ritonavir (KALETRA), in treatment-naïve patients.
- Results of a controlled study (ASSERT study) aimed at comparing, at 48 weeks, the renal tolerance (primary endpoint) and virological efficacy (secondary endpoint) of the fixed combinations emtricitabine/tenofovir (TRUVADA) and abacavir/lamivudine (KIVEXA), as an adjunct to efavirenz, in treatment-naïve patients.

Treatment simplification studies (treatment-experienced patients)

- Results of a controlled study (BICOMBO study[2]) aimed at assessing the efficacy at 48 weeks of the substitution of two NRTIs (including lamivudine) with the fixed combination of emtricitabine/tenofovir (TRUVADA) or abacavir/lamivudine (KIVEXA), in patients with a VL of < 200 copies/ml for over six months. The third agent remained unchanged (a PI or a NNRTI).

[1] U943 INSERM. Clinical-Epidemiological Information Returns No. 16 (FHDH data). COREVIH Ile-de-France, October 2009.
[2] Martínez E, Arranz JA, Podzamczer D, et al. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. J Acquir Immune Defic Syndr 2009; 51: 290-7.

- Results of a controlled study (STEAL study[3]) aimed at assessing the efficacy at 96 weeks of substituting two NRTIs with KIVEXA or TRUVADA in patients under virological monitoring (viral load < 50 copies/ml for over 12 weeks).
- Results of the SWITCHMRK studies 1 and 2. These studies were conducted in patients infected with HIV-1 and subject to virological monitoring (viral load of < 50 copies/ml for at least three months), with a treatment protocol including liponavir/ritonavir (KALETRA). They aimed to demonstrate that replacing the lopinavir/ritonavir with raltegravir (situation not covered by the Marketing Authorisation) would help improve the lipid profile while maintaining a comparable antiretroviral efficacy.

5.1. Efficacy

5.1.1. Reminder of the previous opinion

Reminder of the Transparency Committee's conclusions in its Opinion of 23 January 2008 following the submission of new data (data at 48 weeks in the GS-01-934 pivot study)

The aim of this study was to compare the combination of tenofovir DF and emtricitabine (not fixed up to 96 weeks, then TRUVADA thereafter) with the fixed lamivudine/zidovudine combination (COMBIVIR) in a triple therapy setting with efavirenz, in treatment-naïve patients.

Committee's conclusions:
"The Committee does not have any specific clinical data relating to the administration of TRUVADA.
Clinical experience in the combined use of the two active ingredients is based on studies conducted with different formulations of emtricitabine and tenofovir disoproxil fumarate in combinations with antiretrovirals.

Compared to the COMBIVIR fixed combination (zidovudine and lamivudine) in two daily intakes, the virological response of the non-fixed combination (emtricitabine and tenofovir DF) made up of the two components of TRUVADA in a single daily dose was greater at 48 weeks than that of COMBIVIR in terms of the percentage of patients having a viral load of < 400 copies/ml".

5.1.2. Follow-up data from GS-01-934 pivot study[4]

The applicant has submitted the results at 144 weeks of the GS-01-934 pivot study.
Analysis of the data after 144 weeks of treatment was in favour of maintaining immunological and virological response (Table 1).

[3] Martin A, Bloch M, Amin J, Baker D, Cooper DA, Emery S, Carr A. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial. Clin Infect Dis 2009; 49: 1591-601.
[4] Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. J Acquir Immune Defic Syndr 2008; 47: 74-8.

Table 1: Efficacy results at weeks 48 and 144

	48 weeks		144 weeks	
	Emtricitabine + tenofovir DF + efavirenz	**Lamivudine + zidovudine + efavirenz**	**Emtricitabine + tenofovir DF + efavirenz***	**Lamivudine + zidovudine + efavirenz**
Viral load < 400 copies/ml (TLOVR)	84% (206/244)	73% (177/243)	71% (161/227)	58% (133/229)
p	0.002		0.004	
Difference (%) (95% CI)	11% (4% to 19%)		13% (4% to 22%)	
Viral load < 50 copies/ml (TLOVR)	80% (194/244)	70% (171/243)	64% (146/227)	56% (130/231)
p	0.021		0.082	
Difference (%) (95% CI)	9% (2% to 17%)		8% (-1% to 17%)	
Mean variation in the level of CD4 cells compared to study entry (cells/mm^3)	+190	+158	+312	+271
p	0.002		0.089	
Difference (95% CI)	32 (9 to 55)		41 (4 to 79)	

*Patients in the emtricitabine + tenofovir + efavirenz group received TRUVADA + efavirenz in weeks 96 to 144.
TLOVR = Time to Loss of Virological Response

5.1.3. New clinical data

Only randomised controlled studies versus an active comparator (KIVEXA) in naïve patients (HEAT study, study ACTG A5202 and ASSERT study) will be taken into account.
The clinical studies assessing the “switch" treatment simplification strategies (BICOMBO and STEAL) will not be taken into account in this analysis because the patient inclusion and/or assessment criteria do not conform to the recommendations currently in force (YENI Report, 2010). SWITCHMARK studies 1 and 2 will likewise not be taken into account because the main objective was to assess raltegravir.

5.1.3.1. HEAT study[5]

Objective and method
This was a 96-week, phase IV, controlled, randomised double-blind study, the main objective of which was to demonstrate the noninferiority (delta threshold = 12%) in terms of the virological efficacy of the abacavir/lamivudine fixed combination (KIVEXA) versus emtricitabine/tenofovir (TRUVADA) in a triple therapy setting with the combination lopinavir/ritonavir (KALETRA) in antiretroviral treatment-naïve HIV-1 patients.
The patients were aged under 18 years, with an HIV-1 RNA viral load of ≥ 1000 copies/ml. HLA-B*5701 allele screening was not required[6]. In addition, the genotypic resistance status was unknown on inclusion[7].

Treatments
Eligible patients were randomised, after stratification according to their initial viral load (viral load of < or ≥ 100 000 copies/ml) to receive either KIVEXA (one tablet/day) or TRUVADA (one tablet/day, in combination with KALETRA.
The proposed duration of the study was 96 weeks.

[5] Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS 2009; 23: 1547-56.
[6] The presence of the HLA-B*5701 allele threatens the risk of the onset of the abacavir hypersensitivity syndrome, which contraindicates its being prescribed to carriers of this allele.
[7] It is recommended to carry out a genotypic resistance test when HIV infection is diagnosed and to base the choice of initial treatment taking these data into account. This test should be repeated when starting the treatment in case of possible re-exposure. This recommendation should be taken particularly seriously given that the initial treatment will include an NNRTI (cf. YENI 2010 Report).

Efficacy endpoint
The primary efficacy endpoint was the percentage of patients with a viral load of < 50 copies/ml at 48 weeks.

Statistical analysis
The analyses were performed in the ITT population (ITT-E).[8] The noninferiority of KIVEXA versus TRUVADA was demonstrated if the lower limit of the 95% confidence interval ($CI_{95\%}$) of the difference in the percentage of patients with a viral load of < 50 copies/ml in week 48 was ≥ -12%.

Results
A total of 688 patients were included, 343 of whom were in the KIVEXA group and 345 in the TRUVADA group. The proportion of patients with a viral load of ≥ 100 000 copies/ml was 45% in the KIVEXA group and 41% in the TRUVADA group.
The results as regards the primary efficacy endpoint are presented in Table 2.

The noninferiority of KIVEXA with respect to TRUVADA was demonstrated in terms of the percentage of patients with a viral load of < 50 copies/ml (primary endpoint) in week 48, whether in the overall population or in the strata of patients with a VL < or ≥ 100 000 copies/ml. This noninferiority was confirmed in week 96.
This publication is open to criticism on the grounds that it does not present the results in the per-protocol population.

Table 2: Results for the virological response (viral load of < 50 copies/ml) as a function of the viral load stratum on inclusion. (ITT-E population)

Virological response (primary efficacy endpoint)	**KIVEXA +KALETRA (n = 343)**		**TRUVADA +KALETRA (n = 345)**		**Difference (%) (IC_{95} of the difference)**	
	Week 48	Week 96	Week 48	Week 96	W48	W96
Overall response	**231/343 (68%)**	**205/343 (60%)**	**232/345 (67%)**	**200/345 (58%)**	**0.39% (-6.63; 7.40)**	**(-5.41; 9.32)**
Response in patients with a viral load of < 100 000 copies/ml on inclusion	134/188 (71%)	118/188 (63%)	141/205 (69%)	119/205 (58%)	-	
Response in patients with a viral load of ≥ 100 000 copies/ml on inclusion	97/155 (63%)	87/155 (56%)	91/140 (65%)	81/140 (58%)	-	

5.1.3.2. Study ACTG A5202

Objective and method
This was a phase IIIb, controlled, randomised study whose principal objective was to demonstrate the equivalence at 96 weeks of the two fixed combinations: emtricitabine/tenofovir (TRUVADA) and abacavir/lamivudine (KIVEXA) in a triple therapy setting with atazanavir (REYATAZ) boosted by ritonavir (NORVIR) or efavirenz (SUSTIVA), in patients infected with HIV-1 naïve to antiretroviral treatment.
The patients were aged under 16 years and had an HIV-1 RNA viral load of > 1000 copies/ml. HLA-B*5701 allele screening was not required. Besides, the genotypic resistance status was not known in the case of 57% of the patients

Treatments
Eligible patients were randomised, after stratification according to their initial viral load (viral load < or ≥ 100,000 copies/ml) to receive one of the following four treatments:
- emtricitabine/tenofovir (TRUVADA 1 tablet/day) with efavirenz as adjunct (SUSTIVA) 600 mg
- abacavir/lamivudine (KIVEXA 1 tablet/day) with efavirenz as adjunct (SUSTIVA) 600 mg

[8] ITT-E for ITT-Exposed: randomised patients who have had at least one dose of treatment.

- emtricitabine/tenofovir (TRUVADA 1 tablet/day) with atazanavir as adjunct (REYATAZ) 300 mg boosted by ritonavir (NORVIR) 100 mg
- abacavir/lamivudine (KIVEXA 1 tablet/day) with atazanavir as adjunct to (REYATAZ) 300 mg boosted by ritonavir (NORVIR) 100 mg

The treatments were received in double-blind mode in the case of the nucleoside analogues (TRUVADA and KIVEXA) and in open mode as regards the third agent (efavirenz or atazanavir).

The proposed duration of the study was 96 weeks.

Efficacy endpoints

The primary efficacy endpoint was the time of onset of virological failure, failure being defined as:[9]

- a viral load ≥ 1000 copies/ml between week 16 and week 24,
- or a viral load of ≥ 200 copies/ml as from week 24.

The secondary endpoints included in particular the percentage of patients with a viral load of < 50 copies/ml in week 48.

Statistical analysis

The analyses were performed in the ITT population. The two treatments were considered to be equivalent if the 95% confidence interval ($CI_{95\%}$) of the difference in the relative risk of virological failure was included in the interval [0.71-1.40].

Results

An interim analysis provided for by the protocol, after a median follow-up duration of 60 weeks (0 to 112 weeks), showed that the abacavir/lamivudine combination (KIVEXA) was associated with a statistically greater risk of virological failure in the stratum of patients with a viral load (VL) of ≥ 100 000 copies/ml on inclusion. In light of these data, the DSMB (Data Safety Monitoring Board) recommended lifting the blinding in the case of patients with a VL of ≥ 100 000 copies/ml on inclusion and to consider a change in the therapeutic management of patients receiving abacavir/lamivudine (KIVEXA). Patients with a VL of < 100 000 copies/ml have continued to receive the treatment in accordance with the initial protocol.

The results presented therefore are from an interim analysis in a sub-group according to the viral load (VL < or ≥ 100 000 copies/ml). The published data[10] relate to the patient population with a VL of ≥ 100 000 copies/ml.

A total of 1858 patients were included, 797 of whom had a viral load of ≥ 100,000 copies/ml on inclusion, n = 398 in the KIVEXA group and n = 399 in the TRUVADA group.
The only results presented are those from a post hoc combined analysis of the two groups receiving the abacavir/lamivudine combination (KIVEXA) and the two groups receiving emtricitabine/tenofovir (TRUVADA). The impact of the third agent in the combination (efavirenz or atazanavir) was not taken into account in this analysis.

In patients with a viral load of ≥ 100 000 copies/ml, the risk of virological failure was greater in the KIVEXA group than in the TRUVADA group (Hazard Ratio: 2.33; $CI_{95\%}$ [1.46; 3.72]). However, no difference was observed between the two groups in their virological response (VL ≤ 50 copies/ml) in week 48 (Table 3).
This publication is open to criticism because it does not present the results in the per-protocol population.

[9] The YENI Report of 2010 defines initial failure as the persistence of a detectable plasma viral load (> 200 copies/ml confirmed after 6 months and > 50 copies/ml confirmed 12 months after the commencement of the treatment).
[10] Sax PE, Tierney C, Collier AC, Fischl MA, et al; AIDS Clinical Trials Group Study A5202 Team. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. N Engl J Med 2009; 361: 2230-40.

Table 3: Interim results in ITT, median follow-up at week 60 (0 to 112 weeks)

Primary efficacy endpoint	KIVEXA + efavirenz or azatanavir/r n = 398	TRUVADA + efavirenz or azatanavir/r n = 399	
Time to virological failure (number of cases)	**57**	**26**	Hazard Ratio = 2.33 $CI_{95\%}$: [1.46; 3.72] p = 0.0003
• VL of ≥ 1000 copies/ml between week 16 and week 24 and never of < 200 copies/ml	19	9	
• VL of ≥ 200 copies/ml after week 24 and never of < 200 copies/ml	9	2	
• VL of ≥ 200 copies/ml after week 24 and already having a VL of < 200 copies/ml	29	15	
Secondary endpoints % of patients with a VL of ≤ 50 copies/ml (95% CI at week 48	75% (69-80%)	80% (74-84%)	p = 0.2

In the patients with a viral load of < 100,000 copies/ml the interim statistical analysis of the data showed no difference between the two groups in terms of virological failure (unpublished data).

5.1.3.3. ASSERT study[11]

Objective and method

The ASSERT study is a 96-week randomised, controlled, open-label study to compare the renal tolerance (primary endpoint) and efficacy (secondary endpoint) of the abacavir/lamivudine fixed combination (KIVEXA) versus emtricitabine/tenofovir (TRUVADA), in a triple therapy setting with efavirenz 600 mg, in patients with HIV-1 naïve to antiretroviral treatment.
The patients were at least 18 years of age, had a viral load of > 1000 copies/ml and were not to be carriers of the HLA-B*5701 allele.

Endpoints

The primary endpoint related to the renal tolerability, in terms of the variation in glomerular filtration estimated by the MDRD (Modified Diet in Renal Disease) score at 48 weeks.
The secondary endpoints included an assessment of the efficacy in terms of the percentage of patients with a viral load of < 50 copies/ml at 48 weeks.

Results

In total, 392 patients were randomised, 385 of whom received at least one dose of treatment.
At 48 weeks, 63 patients (33%) in the KIVEXA group and 44 patients (23%) in the TRUVADA group withdrew from the treatment, mainly due to adverse effects.
The analysis showed no difference in terms of renal tolerability between the two groups.

The results at 48 weeks (study in progress) as regards the criterion of virological response (secondary endpoint) are presented in Table 4.
At week 48, the proportion of patients with a viral load of < 50 copies/ml was higher in the TRUVADA group than in the KIVEXA group, in combination with efavirenz (difference between the treatments: 11.6%, $CI_{95\%}$ [2.2; 21.1]). However, the experimental plan of this study was not designed to compare the efficacy (secondary endpoint) of the two treatments, which limits the scope of the results.

[11] Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. J Acquir Immune Defic Syndr 2010 Sep 1; 55(1): 49-57.

Table 4: Virological response (viral load of < 50 copies/ml) at 48 weeks in the ITT population (TLOVR analysis).

	KIVEXA + efavirenz (n = 192)	TRUVADA + efavirenz (n = 193)
Overall response	114/192 (59%)	137/193 (71%)
Difference (%) ($CI_{95\%}$)	11.6% (2.2; 21.1)	
Response in patients with a VL of < 100 000 copies/ml	61/95 (64%)	62/83 (75%)
Response in patients with a VL of ≥ 100 000 copies/ml	53/97 (55%)	75/110 (68%)

A final analysis is planned to be carried out at 96 weeks.

5.1.3.4. Other clinical data

The applicant also presented the results of a meta-analysis[12] whose aim was to compare the efficacy of the fixed combinations emtricitabine/tenofovir (TRUVADA) and abacavir/lamivudine (KIVEXA) in a triple therapy setting together with a boosted PI in treatment-naïve patients. The primary efficacy endpoint was the percentage of patients with a plasma HIV-1 RNA viral load of < 50 copies/ml at 48 weeks. This meta-analysis included 12 clinical studies in a total of 5168 patients. HLA-B*5701 allele screening was not required.
The authors concluded that the results suggested that TRUVADA had a greater virological response than KIVEXA. However, the results of this meta-analysis do need to be confirmed, given that the various studies analysed are rather mixed from a methodological point of view.

5.2. Adverse effects

5.2.1 Clinical study data

- ASSERT study

The aim of this study was to compare the renal tolerability of the KIVEXA fixed combination versus the TRUVADA fixed combination in a triple therapy setting with efavirenz 600 mg in HIV-1 patients naïve to antiretroviral treatment. The primary tolerance endpoint was the variation in glomerular filtration estimated by the MDRD (Modified Diet in Renal Disease) score at 48 weeks.
On inclusion, patients were supposed to have a creatinine clearance of > 50 ml/min and only 32% had a creatinine clearance of < 90 ml/min,
At 48 weeks, the variation in the glomerular filtration was +0.22 ml/min/1.73 m^2 in the KIVEXA group versus +1.18 ml/min/1.73 m^2 in the tenofovir group (mean difference of 0.953 ml/min/1.73 m^2; $CI_{95\%}$ [-1.445; 3.351]; p = 0.435).
The incidence of treatment-related adverse events was 51% (98/192) in the KIVEXA group versus 47% (91/193) in the TRUVADA group. The incidence of Grade 2-4 treatment-related adverse events was 29% in the KIVEXA group versus 20% in the TRUVADA group, the most common being vertigo, abnormal dreams and hypersensitivity to the drug.

- HEAT study

At 96 weeks, the incidence of Grade 2-4 treatment-related adverse events was compared in the two groups: 50% (171/343) in the KIVEXA group versus 46% (157/345) in the TRUVADA group. The most common of these events was diarrhoea in 19% of the patients in each group.

[12] Hill A, Sawyer W. Effects of nucleoside reverse transcriptase inhibitor backbone on the efficacy of first-line boosted highly active antiretroviral therapy based on protease inhibitors: meta-regression analysis of 12 clinical trials in 5168 patients. HIV Med. 2009; 10: 527-35.

Treatment withdrawals linked to adverse events were 6% in each group. These withdrawals were due mainly to lipid anomalies in the KIVEXA group and gastrointestinal disorders in the TRUVADA group.
Proximal tubular damage was reported in 1% (5/343) of the patients in the TRUVADA group.

- Study ACTG A5202

Only the data relating to the patients with a viral load of ≥ 100,000 copies/ml are available and presented below.
The interim analysis of the tolerability at 48 weeks showed a shorter time to onset of a Grade 3-4 adverse event in the KIVEXA group than in the TRUVADA group. The incidence of these events (Grade 3-4) was 33% (130/397) in the KIVEXA group versus 20% (78/397) in the TRUVADA group. The most frequently reported Grade 3-4 adverse events in the TRUVADA group were pain or discomfort (14/397), gastrointestinal disorders (10/397) and asthenia (10/397). In the KIVEXA group, they consisted mainly of lipid balance anomalies (48/397), pain or discomfort (24/397) and fever (10/397).

5.2.2 Other tolerance data

One of the risks associated with the use of TRUVADA is the renal toxicity of tenofovir (rare reported cases of renal failure, renal damage and proximal renal tubulopathy). It is therefore recommended to monitor renal function during the treatment, especially in patients with renal failure (see SPC).
On the basis of the experience gained in the clinical trials and since the product was placed on the market, the most frequently reported adverse events (frequency ≥ 1/10) in patients receiving TRUVADA have been: hypophosphataemia, headache, vertigo, diarrhoea, vomiting, nausea, elevated creatine kinase, rash and asthenia.

The presented PSUR[13] data have not revealed any new signal with respect to the known tolerability profile of TRUVADA.

5.3. Conclusion

Since the Transparency Committee's previous opinion, TRUVADA (emtricitabine/tenofovir) has been the subject of three new comparative studies versus KIVEXA (abacavir/lamivudine) in treatment-naïve patients. These two products are combinations of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) preferentially recommended for the initial treatment of HIV infection in a triple therapy setting with a third agent, possibly a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI).

In one study (HEAT), the non-inferiority of KIVEXA compared to TRUVADA, in combination with KALETRA (lopinavir/ritonavir), was demonstrated at 48 weeks (ITT analysis) for virological response (% of patients with a viral load of < 50 copies/ml), in the overall population (68% vs 67%: difference 0.39%, $CI_{95\%}$ [-6.63; 7.40]) and in the sub-groups of patients with an initial viral load (VL) of < or ≥ 100,000 copies/ml. This non-inferiority was confirmed at 96 weeks.

One study (ACTG A5202), whose main aim was to demonstrate, at 96 weeks, the equivalence of TRUVADA and KIVEXA, both combined with REYATAZ (atazanavir/ritonavir) or SUSTIVA (efavirenz), was terminated early after the interim analysis results had revealed a higher risk of virological failure[14] (primary efficacy endpoint) in the KIVEXA group than in the TRUVADA group in the sub-group of patients with an initial VL of ≥ 100 000 copies/ml (Hazard Ratio: 2.33, $CI_{95\%}$ [1.46; 3.72]). In view of the interim analysis, this degree of effect is probably an overestimate.
On the other hand, this risk of virological failure was in fact the same for TRUVADA and KIVEXA in patients with an initial VL of <100 000 copies/ml.

[13] PSUR for 3 April 2008 to 2 April 2010.
[14] Failure defined as a VL > 1 000 copies/ml at week 16 or after week 16 and before week 24, or defined as a VL > 200 copies/ml at week 24 or later.

In patients with an initial VL of ≥ 100 000 copies/ml, the virological response (VL of < 50 copies/ml at week 48) did not show any difference between TRUVADA and KIVEXA (80% in the TRUVADA group versus 75% in the KIVEXA group).
Based on this interim analysis carried out in an equivalence study on a sub-group of patients it is not possible to conclude with a sufficient level of proof that TRUVADA is superior to KIVEXA.

One study (ASSERT), whose main aim was to compare the renal tolerability at 48 weeks of TRUVADA with that of KIVEXA, both combined with efavirenz, failed to show any difference between the two treatments in the variation in the glomerular filtration estimated by the MDRD (Modified Diet in Renal Disease) score. However, only 32% (125/325) of the patients had a creatinine clearance of < 90 ml/min on inclusion (lower limit 50 ml/min). The percentage of patients with a VL of < 50 copies/ml at 48 weeks (secondary endpoint) was higher with TRUVADA than with KIVEXA (71% versus 59%, difference 11.9%, $CI_{95\%}$ [2.2; 21.1]).

The contradictory results of these studies are difficult to interpret on account of their different methodology, especially as regards their efficacy endpoints and the choice of the third agent of the triple therapy. Furthermore, neither screening for the HLA-B*5701 allele nor genotypic resistance testing[15] were required[16] in the HEAT study or study ACTG A5202, which limits the transferability of the results into actual practice.

However, these new studies do confirm the efficacy of these two fixed combinations – TRUVADA and KIVEXA – which are the treatments of choice in cases of HIV infection. These data were taken into account when updating the guidelines currently in force (YENI Report, 2010).[17]

The new tolerance data from the periodic international pharmacovigilance reports[18] and those from clinical experimentation do not alter the known tolerance profile of TRUVADA.

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Actual benefit

HIV infection is a serious and life-threatening condition.

This proprietary medicinal product seeks to prevent and/or correct immune deficiencies caused by HIV in adult patients.

Used in combination with other antiretroviral agents, its efficacy/tolerance ratio is considerable.

Alternative drugs do exist.

The actual benefit offered by this proprietary medicinal product as part of an antiretroviral combination remains substantial.

[15] It is recommended to carry out a genotypic resistance test when HIV infection is diagnosed and to base the choice of initial treatment taking these data into account. This test should be repeated when starting the treatment in case of possible re-exposure. This recommendation should be taken particularly seriously given that the initial treatment will include an NNRTI (cf. YENI 2010 Report).
[16] The presence of the HLA-B*5701 allele threatens the risk of the onset of the abacavir hypersensitivity syndrome, which contraindicates its being prescribed to carriers of this allele.
[17] Yeni P. Report 2010. Medical management of persons with HIV infection. Recommendations by a group of experts. Available from www.sante.gouv.fr.
[18] PSUR of 3 April 2008 to 2 April 2010.

6.2. Improvement in actual benefit

In light of the available data the Committee considers that the proprietary medicinal product TRUVADA does not offer any improvement in actual benefit (IAB V) by comparison with KIVEXA.

The committee takes note of the recommendations by the group of experts (Yéni Report, 2010) on the management of persons infected with HIV which state that TRUVADA should be given preference over KIVEXA if the plasma viral load is ≥ 100 000 copies/ml, especially when combined with atazanavir/ritonavir (REYATAZ) or efavirenz (SUSTIVA), on account of the greater risk of virological failure with KIVEXA in this sub-population (interim results from study ACTG A5202).

6.3. Therapeutic use

According to the 2010 report on the medical management of persons infected with HIV, under the direction of Prof. Patrick Yeni:[17]

- **In treatment-naïve patients**

Choice of the first antiretroviral treatment

Many antiretrovirals are available in six drug classes:

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors (PI)
- Fusion inhibitors (FI)
- CCR5 receptor antagonists
- Integrase inhibitors (INI)

A first-line triple therapy remains a combination of two NRTI with a third agent.

The choice of the two NRTI of the triple therapy rests preferentially on the fixed combinations of tenofovir/emtricitabine (TRUVADA) or abacavir/lamivudine (KIVEXA).
TRUVADA should be given preference if the plasma viral load is ≥ 100 000 copies/ml, especially when combined with atazanavir/ritonavir (REYATAZ) or efavirenz (SUSTIVA), on account of the greater risk of virological failure with KIVEXA in this sub-population (interim results from study ACTG A5202).
When the VL is < 100 000 copies/ml, the choice between KIVEXA and TRUVADA may be made on a case-by-case basis and should take account of factors such as HBV co-infection and renal impairment.
TRUVADA should be used with caution in cases of renal failure or if there is a risk of renal failure occurring. KIVEXA may only be used in subjects who are not carriers of the HLA B*5701 allele.

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

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

6.4. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance.

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 100%