HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

9 May 2012

EDURANT 25 mg film-coated tablets
B/30 (CIP code: 219 472-9)

Applicant: JANSSEN-CILAG

rilpivirine
ATC code (2012): J05AG05 (non-nucleoside reverse transcriptase inhibitor)

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

Rilpivirine

1.2. Background

New antiretroviral belonging to the non-nucleoside reverse transcriptase inhibitors class.

1.3. Indications

"EDURANT, in combination with other antiretroviral medicinal products, 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.
This indication is based on week 48 tolerance and efficacy analyses from two randomised, double-blind, controlled, Phase III trials in treatment-naïve patients and week 96 tolerance and efficacy analyses from a Phase IIb trial in treatment-naïve patients.

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

1.4. Dosage

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

EDURANT must always be given in combination with other antiretroviral medicinal products.

Posology
Adults
The recommended dose of EDURANT is one 25 mg tablet taken once daily.
EDURANT must be taken with a meal**.**

Elderly
There is limited information regarding the use of EDURANT in patients > 65 years of age. No dose adjustment of EDURANT is required in elderly patients. EDURANT should be used with caution in this population.

Paediatric population
The safety and efficacy of EDURANT in children aged < 18 years have not yet been established. No data are available.

Hepatic impairment
There is limited information regarding the use of EDURANT in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). No dose adjustment of EDURANT is required in patients with mild or moderate hepatic impairment. EDURANT should be used with caution in patients with moderate hepatic impairment. EDURANT has not been studied in patients with severe hepatic impairment (Child-Pugh score C). Therefore, EDURANT is not recommended in patients with severe hepatic impairment.

Renal impairment
EDURANT has mainly been studied in patients with normal renal function. No dose adjustment of EDURANT is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, EDURANT should be used with caution. In patients with severe renal impairment or end-stage renal disease, the combination of EDURANT with a strong CYP3A inhibitor (e.g. ritonavir-boosted HIV protease inhibitor) should only be used if the expected benefit outweighs the potential risk.
Treatment with EDURANT resulted in an early small increase of mean serum creatinine levels which remained stable over time and is not considered clinically relevant (see section 4.8 of the SPC)."

1.5. Special warnings and precautions for use

"Virologic failure and development of resistance

EDURANT has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. The list of rilpivirine resistance-associated mutations presented in section 5.1 of the SPC should only guide the use of EDURANT in the treatment-naïve population.

In the pooled analysis from the Phase III trials, patients treated with EDURANT with a baseline viral load > 100,000 HIV-1 RNA copies/ml had a greater risk of virologic failure (15.1% with EDURANT versus 6.3% in the efavirenz arm) compared with patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/ml (3.8% with EDURANT versus 3.3% in the efavirenz arm). 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 EDURANT than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance.

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

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2012)

J: Antiinfectives for systemic use
J05: Antivirals for systemic use
J05A: Direct-acting antivirals
J05AG: Non-nucleoside reverse transcriptase inhibitors
J05AG05: Rilpivirine

2.2. Medicines in the same therapeutic category

Other non-nucleoside reverse transcriptase inhibitors (NNRTIs).

- Efavirenz: SUSTIVA gelatin-coated capsules and oral solution
- Nevirapine: VIRAMUNE tablets and oral solution
- Etravirine: INTELENCE tablets

Only efavirenz (SUSTIVA) and nevirapine (VIRAMUNE) are indicated in antiretroviral treatment-naïve patients (adults, adolescents and children over 3 years).
Etravirine (INTELENCE) is indicated only in antiretroviral-experienced patients.

2.3. Medicines with a similar therapeutic aim

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

Nucleoside reverse transcriptase inhibitors (NRTIs):

- Abacavir: ZIAGEN tablets and oral solution
- Didanosine: VIDEX hard capsules and powder for oral suspension
- Emtricitabine: EMTRIVA hard capsules and oral solution
- 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

Nucleotide reverse transcriptase inhibitor (NtRTI):

- Tenofovir: VIREAD tablets

Combination of two NRTIs:

- Emtricitabine/tenofovir: TRUVADA 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 tolerance of EDURANT is based primarily 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.

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 EDURANT 25 mg or efavirenz 600 mg once daily in combination with optimised treatment.
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 planned duration of the study was 96 weeks.

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).

[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.
[3] TLOVR: Time to Loss of Virologic Response algorithm

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.

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 (%)	**EDURANT N' = 346**	**Efavirenz N' = 344**	**EDURANT N' = 340**	**Efavirenz N' = 338**	**EDURANT 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*

In the combined analysis of the studies, the characteristics of the patients included were comparable between the EDURANT 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 patients (ITT population)

	ECHO		**THRIVE**		**Combined data**	
Characteristics	**RPV + OT n = 346**	**EFV + OT n = 344**	**RPV + OT n = 340**	**EFV + OT n = 338**	**RPV + OT n = 686**	**EFV + OT n = 682**
Men [%]	77.5	79.9	73.5	72.2	75.5	76.1
Age [years] *	36 [18-78]	36 [19-67]	36 [19-62]	35.5 [19-69]	36 [18-78]	36 [19-69]
Duration of infection [years] *	1.2 [0-22]	1.3 [0-25]	1.7 [0-24]	1.3 [0-28]	1.4 [0-24]	1.3 [0-28]
Viral load [log_{10} copies/ml]	5.0 [2-7]	5.0 [3-7]	4.9 [3-7]	5.0 [3-7]	5.0 [2-7]	5.0 [3-7]
Viral load						
≤ 100,000 copies/ml	**52.3%**	**47.4%**	**55.0%**	**49.4%**	**53.6%**	**48.4%**
>100,000 copies/ml	47.7%	52.6%	45.0%	50.6%	46.4%	51.6%
CD4 [cells/mm^3] *	240 [1-888]	257 [1-757]	263 [2-744]	263 [1-1137]	249 [1-888]	260 [1-1137]
AIDS-defining pathology	4.0%	6.7%	6.2%	4.7%	5.1%	5.7%
Co-infection with HCV/HBV [%]	5.7%	9.0%	8.9%	9.9%	7.3%	9.5%

RPV: rilpivirine (EDURANT), EFV: efavirenz (SUSTIVA), OT: optimised treatment
** Median [min-max]*

[4] The relevance of the performance of this combined analysis was validated by heterogeneity tests.

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 EDURANT 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 EDURANT 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, the non-inferiority of EDURANT 25 mg once daily versus efavirenz 600 mg once daily was likewise demonstrated in terms of virological response (results presented in Table 4).

- Virological failure (results in Table 3)

In the overall population of the studies, regardless of the baseline viral load, the reasons for absence of virological response varied according to treatment group (combined data). For the patients in the EDURANT 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 EDURANT 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 EDURANT 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 EDURANT group and 3.3% (11/330) of patients in the efavirenz group.

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

	ECHO		**THRIVE**		**Combined data**	
	RPV + OT N = 346	**EFV + OT N = 344**	**RPV + OT N = 340**	**EFV + OT N = 338**	**RPV + OT N = 686**	**EFV + OT N = 682**
Responders: HIV-1 RNA < 50 copies/ml, n [%]	287 (82.9)	285 (82.8)	291 (85.6)	276 (81.7)	578 (84.3)	561 (82.3)
Difference [95% CI] *	0.1% [-5.5; 5.7]		3.9% [-1.6; 9.5]		**2.0% [-2.0; 6.0]**	
Nonresponders	17.1%	17.2%	14.4%	18.3%	15.7%	17.7%
Virological failure **	11.0%	4.4%	7.1%	5.3%	**9%**	**4.8%**
Death	0%	0%	0.3%	0.9%	0.1%	0.4%
Withdrawal due to adverse event	1.7%	7.3%	2.4%	6.2%	2.0%	6.7%
Withdrawal for other reason	4.3%	5.5%	4.7%	5.9%	4.5%	5.7%

OT: optimised treatment

** Based on a normal approximation of the difference in response*

*** The incidence of virological failure was 15.1% in the EDURANT group versus 6.3% in the efavirenz group for patients with a viral load > 100,000 copies/ml and 3.8% versus 3.3%.for patients with a viral load ≤ 100,000 copies/ml.*

[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).

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

	EDURANT + OT N = 686	**Efavirenz + OT N = 682**	**Observed difference [95% CI]**
Responders as a function of baseline viral load			
≤ 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]
Responders as a function of optimised treatment			
Tenofovir/emtricitabine	83.5% (459/550)	82.4% (450/546)	1.0% [-3.4; 5.5]
Zidovudine/lamivudine	87.1% (88/101)	80.6% (83/103)	6.5% [-3.6; 16.7]
Abacavir/lamivudine	88.6% (31/35)	84.8% (28/33)	3.7% [-12.7; 20.1]

OT: optimised treatment

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 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 overall population of the studies, irrespective of the baseline viral load, this change 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]).

- Resistance analysis

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 subgroup of patients with a baseline viral load ≤ 100,000 copies/ml, the percentage of patients with virological failure[6] was 5.2% (19/368) in the EDURANT group and 4.8% (16/330) in the efavirenz group.
Among these patients with virological failure who had a baseline viral load ≤ 100,000 copies/ml, 6/368 (1.6%) developed resistance to a NNRTI in the EDURANT group, compared with 5/330 (1.5%) in the efavirenz group. In the EDURANT group, two patients were resistant to rilpivirine, of whom one was also resistant to etravirine and one to 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, in patients with a viral load < 100,000 copies/ml with virological failure, resistance to at least one substance in this class was seen more often in the EDURANT group, in particular cross-resistance to emtricitabine and lamivudine in seven patients (1.9%) in the EDURANT group versus two patients (0.6%) in the efavirenz group. No resistance to tenofovir was observed.

3.2. Adverse effects

The assessment of the tolerance of EDURANT is based primarily on combined data from the ECHO and THRIVE studies, in which 1368 patients were included, carried out in antiretroviral treatment-naïve adult patients infected with HIV-1. Median exposure was 55.7 weeks in the EDURANT group (n = 686) and 55.6 weeks in the efavirenz group.

[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.

In the overall population, based on the combined data from the ECHO and THRIVE studies, the incidence of adverse events (AEs) at 48 weeks was similar in the two treatment groups: 89.8% (616/686) in the EDURANT group versus 92.2% (629/682) in the efavirenz group.
The most common AEs in the EDURANT group considered by the investigator to be at least possibly linked to the treatments were nausea (10.1%), dizziness (8.0%), headache (6.1%) and abnormal dreams (6.3%).
The frequency of AEs considered by the investigator to be at least possibly linked to the treatments was lower in the EDURANT group (46.4%) than in the efavirenz group (64.1%), notably central nervous system disorders (17.2% versus 36.7%) including dizziness (8.0% versus 26.2%), psychiatric disorders (14.9% versus 22.7%) and rash (2.5% versus 8.9%).
The frequency of grade 2-4 AEs considered to be at least possibly linked to the treatments was lower in the EDURANT group (15.9% versus 31.1%).

In the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml, the population corresponding to the Marketing Authorisation, the frequency of AEs possibly linked to the treatments was lower in the EDURANT 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 EDURANT group, the most common 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 EDURANT group (16.8% versus 30%).

Treatment discontinuation linked to an adverse event occurred less often in the EDURANT 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 EDURANT 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 overall population a lower incidence of grade 2-3 abnormalities in total cholesterol (5% versus 18%) and of LDL-C (6% versus 15%) was observed in the EDURANT group than in the efavirenz group. In the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml, the same trend was observed (4.1% versus 19.2% for grade 2-3 abnormalities of total cholesterol and 5.6% versus 13.9% in the case of LDL-C).
In the overall population as in the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml, a difference between the two treatment groups in favour of EDURANT 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.

3.3. Conclusion

The assessment of the efficacy and tolerance of EDURANT 25 mg once daily is based on data from two randomised, double-blind comparative phase III clinical studies (ECHO and THRIVE studies) versus efavirenz (600 mg once daily), carried out in antiretroviral treatment-naïve patients infected with HIV-1. The study treatments were given in combination with optimised background therapy consisting of two NRTIs, tenofovir/emtricitabine in the ECHO study and tenofovir/emtricitabine, zidovudine/lamivudine or abacavir/lamivudine in the THRIVE study.
The protocols of the two studies were similar and were subjected to individual analyses and a combined analysis.

At 48 weeks, the non-inferiority (delta threshold = 12%) of rilpivirine 25 mg versus efavirenz was demonstrated in terms of virological response (HIV-1 RNA < 50 copies/ml) in each of the studies and in their combined analysis (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 for the per-protocol analyses are confirmed by the ITT analysis.

This non-inferiority of rilpivirine versus efavirenz was likewise demonstrated in terms of virological response in the subgroup of patients with a viral load (HIV-1 RNA) < 100,000 copies/ml, which corresponds to the population of the Marketing Authorisation: 90.2% (332/368) versus 83.6% (276/330); difference 6.6%, 95% CI [1.6; 11.5], ITT population.

The tolerance profile of rilpivirine at 48 weeks was overall better than that of efavirenz in the two studies. Treatment withdrawals linked with an adverse event were less common in the rilpivirine group than in the efavirenz group in the overall population (2.0% versus 6.7%).
In the subgroup of patients with a baseline viral load ≤ 100,000 copies/ml, the population corresponding to the Marketing Authorisation, treatment withdrawals linked to an adverse event (2.2% versus 5.8%) and AEs possibly linked to the treatments (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%), were less common in the rilpivirine group than in the efavirenz group. 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 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 were in virological failure:

- 6/368 patients in the rilpivirine group and 5/330 in the efavirenz group developed resistance to an NNRTI,
- resistance to at least one NRTI was seen more often with rilpivirine, notably cross-resistance to emtricitabine/lamivudine in seven patients in the rilpivirine group versus two patients 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 that of efavirenz. These data are too limited to draw any conclusions as regards the robustness of this genetic barrier and the consequences of cross-resistances and their possible reversibility, and this warrants further studies of this cohort on this point.

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

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 EDURANT is high in combination with other antiretrovirals in the population of the Marketing Authorisation restricted to patients for whom treatment with efavirenz is not appropriate.
The efficacy/adverse effects ratio of EDURANT is low in the other populations of the Marketing Authorisation due to its genetic barrier, 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 tolerance 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 in the NNRTI class.

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 EDURANT on morbidity and mortality or quality of life to be assessed directly. However, on the basis of the available data (non-inferiority of EDURANT 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 EDURANT 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 combination with other antiretrovirals in the population of the Marketing Authorisation restricted to patients for whom treatment with efavirenz 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 a tolerance profile which is more favourable overall than that of efavirenz, having taken into account the uncertainty regarding the genetic barrier to resistance and failure to demonstrate efficacy superior to efavirenz, the Committee considers that EDURANT offers no improvement in actual benefit (IAB V) over efavirenz in treatment-naïve adult patients with a viral load ≤ 100,000 copies/ml.

4.3. Therapeutic use

Therapeutic strategy:
According to the 2010 report on the clinical management of persons infected with HIV headed by Professor Patrick Yeni[8]:

- ***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 EDURANT:
The current NNRTI of choice in initial triple therapy in treatment-naïve patients, in combination with two NRTIs, is efavirenz. Because of the genetic barrier of rilpivirine, the superiority of which over that of efavirenz having not been demonstrated, its use in treatment-naïve patients with a viral load ≤ 100,000 copies/ml must be limited to situations where treatment with efavirenz is not appropriate, notably in patients with a history of neuropsychiatric disorders or drug intolerance.

4.4. Target population

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

[8] 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 recommendations] Available at www.sante.gouv.fr.
[9] Rilpivirine (EDURANT) is a new antiretroviral belonging to the non-nucleoside reverse transcriptase inhibitors class (NNRTI). 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 rilpivirine in therapeutic strategies.

As of 31 December 2010[10], the number of patients with the chronic condition HIV 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 chronic condition HIV infection 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 efavirenz was initiated in 24.8% 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 efavirenz can be estimated at approximately 1000 per year.

In practice, the number of patients likely to receive EDURANT as part of first-line triple therapy will be very limited. Taking into account its place in the therapeutic strategy, the target population of EDURANT 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 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