HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

3 November 2010

**ISENTRESS 400 mg, film-coated tablet**
**B/60 (CIP code: 383 084-8)**

**Applicant: MSD-CHIBRET**

raltegravir
ATC code: J05AX08

List I
Initial annual hospital prescription limited to "doctors experienced in the management of HIV". Unrestricted renewal.

Date of initial Marketing Authorisation: 20/12/2007
Conditional centralised European Marketing Authorisation.

Amendments to the Marketing Authorisation:
- 14 July 2009: Change of status from a conditional Marketing Authorisation to a final Marketing Authorisation
- 9 September 2009: Amendment for “treatment-naïve patient”
- 26 March 2010: Amendment including data at 96 weeks for studies enrolling treatment-experienced patients.

Reason for request:
- Updating of raltegravir efficacy and tolerance data for treatment-experienced adult patients with a detectable viral load under treatment (initial Marketing Authorisation).
- Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use in the extension of indication to antiretroviral treatment-naïve adult patients with HIV-1 infection.

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

Raltegravir

## 1.2. Background

This is the first antiretroviral in the new integrase inhibitor class.

## 1.3. Indication

**New wording including the extension of the indication to treatment-naïve patients**

"ISENTRESS is indicated, in combination with other antiretroviral agents, in the treatment of human immunodeficiency virus infection (HIV-1) in adult patients.
This indication is based on tolerance and efficacy data from two double-blind, placebo-controlled studies conducted in treatment-experienced patients and one double-blind study versus an active comparator control, in treatment-naïve patients (see sections 4.4 and 5.1 of the SPC)."

## 1.4. Dosage

"Treatment must be initiated by a doctor specialising in the management of HIV infection.
ISENTRESS must be used in combination with other active antiretroviral agents (ARVs) (see sections 4.4 and 5.1 of the SPC). The use of raltegravir in treatment-naïve patients is based on data from a study in which it was administered in association with two NRTIs (see sections 4.4 and 5.1 of the SPC).

Dosage

*Adults*
The recommended dose of ISENTRESS is 400 mg twice daily to be taken with or without food. Food has a variable effect on absorption of raltegravir (see section 5.2 of the SPC). Patients should not crunch, crush or cut the tablets.

*Elderly patients*
Limited data are available on the use of ISENTRESS in elderly subjects (see section 5.2 of the SPC). ISENTRESS should therefore be used with caution in this population.

*Children and adolescents*
The safety and efficacy of this drug in children aged under 16 have not been established (see sections 5.1 and 5.2 of the SPC).

*Renal insufficiency*
No dose adjustment is necessary in patients with renal insufficiency (see section 5.2 of the SPC).

*Hepatic impairment*
No dose adjustment is required in patients with mild or moderate hepatic insufficiency. The safety and efficacy of ISENTRESS have not been established in patients with severe underlying hepatic disorders. ISENTRESS should therefore be administered with caution in patients with severe hepatic insufficiency (see sections 4.4 and 5.2 of the SPC).

Method of administration
For oral use."

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification

J : general antiinfectives for systemic use
J05 : antivirals for systemic use
J05A : direct-acting antivirals
J05AX : other antivirals
J05AX08 : raltegravir

### 2.2. Medicines in the same therapeutic category

There is no other antiretroviral in the integrase inhibitor class.

### 2.3. Medicines with a similar therapeutic aim

Other antiretrovirals used in combination in the treatment of HIV infection in treatment-naïve or treatment-experienced patients:

*Fusion inhibitor:*

- enfuvirtide 90 mg/ml: FUZEON, powder and solvent for injectable suspension (patients who failed to respond to at least one treatment including PIs, NNRTIs and NRTIs, or in cases of intolerability of the previously-mentioned treatments).

*Protease inhibitors (PIs):*

- amprenavir: AGENERASE capsules and oral solution
- atazanavir: REYATAZ gelatin-coated capsules or oral powder, indicated in adults
- darunavir: PREZISTA, film-coated tablets
- fosamprenavir: TELZIR film-coated tablets and oral solution
- indinavir: CRIXIVAN gelatin-coated capsules
- lopinavir / ritonavir: KALETRA tablets and oral solution
- nelfinavir: VIRACEPT film-coated tablets and oral powder
- ritonavir: NORVIR tablets and oral solution, increases the bioavailability of most protease inhibitors, which is why it is used only in combination with those drugs
- saquinavir mesylate: INVIRASE gelatin-coated capsules
- tipranavir 250 mg: APTIVUS soft capsules (very treatment-experienced patients).

*Non-nucleoside reverse transcriptase inhibitors (NNRTIs):*

- efavirenz: SUSTIVA gelatin-coated capsules and oral solution
- nevirapine: VIRAMUNE tablets and oral solution

*Nucleotide reverse transcriptase inhibitor (NtRTI):*

- tenofovir: VIREAD tablets

*Nucleoside reverse transcriptase inhibitors (NRTIs):*

- abacavir: ZIAGEN tablets and oral solution
- didanosine: VIDEX gelatin-coated capsules and powder for oral suspension
- emtricitabine: EMTRIVA gelatin-coated capsules and oral solution
- lamivudine: EPIVIR tablets and oral solution
- stavudine: ZERIT gelatin-coated capsules and oral solution
- zidovudine: RETROVIR gelatin-coated capsules and oral and injectable solution
- abacavir / lamivudine: KIVEXA tablets
- abacavir / lamivudine / zidovudine: TRIZIVIR tablets
- zidovudine / lamivudine: COMBIVIR tablets

*Reverse transcriptase nucleoside and nucleotide inhibitor:*

- emtricitabine / tenofovir: TRUVADA tablets

*Combination of 2 NRTIs and 1 NNRTI:*

- emtricitabine – tenofovir – efavirenz: ATRIPLA tablets

*CCR5 receptor antagonist:*

- maraviroc: CELSENTRI tablets.

## 3 ANALYSIS OF AVAILABLE DATA

The file includes the following data:

- Data at 48 and 96 weeks from the *BENCHMRK 1* and *BENCHMRK 2* studies *(Protocols 018* and *019)*, the 24-week results for which were submitted with the application for registration for the initial indication restricted to the treatment of treatment-experienced patients.
- Data at 48 and 96 weeks from a new study (STARTMRK study), used as the basis for the extension of indication to treatment-naïve patients. The main objective of this study was to demonstrate the efficacy and tolerance of raltegravir *versus* efavirenz (SUSTIVA), in the context of triple therapy with a fixed combination of emtricitabine/tenofovir (TRUVADA), in treatment-naïve patients with HIV-1 infection.
- Complementary studies (*SWITCHMRK 1* and *2, Protocols 032* and *033)* evaluating the replacement of lopinavir/ritonavir with raltegravir in patients in whom virological control was achieved with a lopinavir/ritonavir combination (KALETRA) (indication not included in the Marketing Authorisation).

### 3.1. Efficacy

#### 3.1.1. Updating of efficacy data in treatment-experienced patients

##### 3.1.1.1. Review of data at 24 weeks from the BENCHMRK 1 and BENCHMRK 2 studies (TC Conclusion dated 2 April 2008)[1]

"The efficacy and safety of ISENTRESS 400 mg twice a day in combination with optimised treatment (OT) in patients with HIV-1 infection who had previously been treated with antiretrovirals and who were resistant to at least one product in the antiretroviral classes (PI, NI, NNI) have been assessed by two phase III studies (BENCHMRK 1 and BENCHMRK 2). A combined analysis of these two studies after 24 weeks has been performed.

After 24 weeks of treatment, virological efficacy in terms of the percentage of patients with a viral load below 400 copies/ml (primary endpoint) was higher in the ISENTRESS + OT group than in the placebo + OT group:
- BENCHMRK 1 study (P0018): 76.1% versus 46.39%, $p < 0.001$
- BENCHMRK 2 study (P0019): 76.1% versus 41.2%, $p < 0.001$
- Combined analysis (BENCHMRK 1 and 2): 75% versus 40%, $p < 0.001$.

Analysis of the secondary virological and immunological endpoints (especially the percentage of patients with a viral load < 50 copies/ml and the change in the CD4 count compared to the number on inclusion) confirms the results observed for the primary endpoint.

The only longer-term virological efficacy data available (48 weeks) came from the P005 phase II study, and suggested that virological response was maintained at 48 weeks. However, in view of the methodology used in the study (dose-finding study) and the small number of patients treated at the marketing authorisation dosage (n=30), these results need to be interpreted cautiously while awaiting the 48-week results of the BENCHMRK 1 and BENCHMRK 2 pivotal studies.

The adverse events most frequently observed (>10% of patients) were diarrhoea, nausea, headache and fever.

A higher rate of cancers was observed in the ISENTRESS group than in the placebo group: 19/758 patients (2.5%) versus 5/323 (1.5%), RR 1.2 [0.4; 4.1]. This data is insufficient to rule out the possibility that administration of ISENTRESS might be associated with the risk of developing cancer.

[1] See Opinion of the Transparency Committee dated 2 April 2008 relating to the initial application for registration for ISENTRESS in treatment-experienced patients (ISENTRESS 400 mg_avis 2_CT 5359).

A high level of resistance was observed in the presence of two or more mutations of the following amino acids: 155 (N155 changed to H), 148 (Q148 changed to H, K or R), 143 (Y143 changed to H, C or R) and one or more additional integrase mutations.
These resistance data suggest that ISENTRESS may have a weak genetic barrier to the selection of mutations. This must be investigated in subsequent assessments, particularly with regard to the long term."

#### 3.1.1.2. Data at 48 weeks and 96 weeks from the BENCHMRK 1 and BENCHMRK 2 studies

Analysis of data after 48 and 96 weeks of treatment in the BENCHMRK 1 and BENCHMRK 2 studies shows that virological efficacy and immunological benefits are maintained.
The combined results of the BENCHMRK 1 and BENCHMRK 2 trials (week 48 and week 96) in patients treated at the recommended dose of ISENTRESS 400 mg twice daily are presented in Table 1. The primary efficacy endpoint was the virological response in terms of the percentage of patients with a viral load of less than 400 copies/ml.

**Table 1: Efficacy results at 48 and 96 weeks**

| **BENCHMRK 1 and 2 combined** | **48 weeks** | | **96 weeks** | |
|---|---|---|---|---|
| **Parameter** | **ISENTRESS 400 mg twice daily + OT (n = 462)** | **Placebo + OT (n = 237)** | **ISENTRESS 400 mg twice daily + OT (N = 462)** | **Placebo + OT (N = 237)** |
| **Patients with a viral load of < 400 copies/ml, % [95% CI]†** | **72 [68; 76]** | **37 [31; 44]** | **62 [57; 66]** | **28 [23; 34]** |
| **Patients with a viral load of < 50 copies/ml, % [95% CI]†** | **62 [57; 67]** | **33 [27; 39]** | **57 [52; 62]** | **26 [21; 32]** |
| Characteristics at inclusion‡ | | | | |
| HIV-RNA > 100 000 copies/ml | 48 [40; 56] | 16 [8; 26] | 47 [39; 55] | 13 [7; 23] |
| HIV-RNA ≤ 100 000 copies/ml | 73 [68; 78] | 43 [35; 52] | 70 [64; 75] | 36 [28; 45] |
| Sensitivity score (GSS) § | | | | |
| 0 | 45 [35; 54] | 3 [0; 11] | 41 [32; 51] | 5 [1; 13] |
| 1 | 67 [59; 74] | 37 [27; 48] | 72 [64; 79] | 28 [1; 39] |
| 2 and above | 75 [68; 82] | 59 [46; 71] | 65 [56; 72] | 53 [4; 66] |
| Change in the CD4 count vs inclusion: mean (cells/mm$^3$) [95% CI] | 109 [98; 121] | 45 [32; 57] | 123 [110; 137] | 49 [35; 63] |

† Withdrawals from the study were counted as failures: patients who stopped the study early were considered as failures as from the time they stopped treatment.
The percentage of patients responding with a 95% confidence interval (CI) is shown.

§ The Genotype Sensitivity Score (GSS) was defined as the total number of ARVs for the optimised basic treatment (OT) to which the patient's viral strain demonstrated genotype sensitivity on the basis of genotype resistance tests. The use of enfuvirtide in the OT of enfuvirtide-naïve patients was counted as 1 active molecule of OT.
Furthermore, the use of darunavir in darunavir-naïve patients was counted as 1 active molecule of OT.

In some patients, a viral rebound effect was observed between week 16 and week 96. Factors associated with failure included a high viral load at inclusion and optimised basic treatment (OT) not including at least one active antiretroviral agent (according to the GSS).

### 3.1.2. Efficacy in treatment-naïve patients (extension of indication)

The clinical file is based on data at 48 and 96 weeks from a phase III study (*STARTMRK study – Protocol 021*)[2] used to obtain a Marketing Authorisation for the treatment of infection with the human immunodeficiency virus (HIV-1) in antiretroviral treatment-naïve adult patients.

Study design and objectives

This is a phase III, 240-week controlled study (study in progress), the main objective of which was to demonstrate non-inferiority (delta threshold = 12%) of raltegravir (ISENTRESS) *versus* efavirenz (SUSTIVA), in the context of triple therapy with a fixed combination of emtricitabine/tenofovir (TRUVADA), in treatment-naïve patients with HIV-1 infection with a viral load of more than 5 000 copies/ml.

Non-inferiority was established if the lower level of the 95% confidence interval (CI) for the difference in the virological response (proportion of patients with a viral load < 50 copies/ml at week 48) between ISENTRESS and efavirenz was more than -12%.

Inclusion criteria

ARV treatment-naïve adult patients (> 18 years) with HIV-1 infection, with HIV-1 RNA plasma viral load ≥ 5 000 copies/ml.

Patients with chronic hepatitis B or C co-infection were able to take part in the trial if their clinical condition was stable and did not require treatment during the study period.

Treatments

Eligible patients were randomised after stratification according to viral load (≤ 50 000 and > 50 000 copies/ml) and co-infection with chronic hepatitis B and/or C, to receive double-blind treatment with:

- ISENTRESS 400 mg twice daily (with an interval of approximately 12 hours between doses, irrespective of meal times) or
- efavirenz (SUSTIVA) 600 mg tablet as a single dose, separate from meals, preferably at bed-time.

The treatments were associated with a fixed combination of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine as a single daily dose (TRUVADA 1 tablet daily).

Efficacy endpoint

The primary efficacy endpoint was virological response defined by the proportion of patients with a viral load < 50 copies/ml at 48 weeks.

The main secondary endpoints were:

- Proportion of patients with a viral load < 400 copies/ml
- Immune response (change to CD4+ count compared with inclusion)

Characteristics of patients included

A total of 566 patients were randomised, 282 in the ISENTRESS group and 284 in the efavirenz group. Of the patients randomised, 563 (99.5%) received at least one dose of treatment and were included in the ITT population (281 in the ISENTRESS group and 282 in the efavirenz group).

The demographic and medical characteristics of the patients were similar in the two treatment groups at inclusion. The mean age of the patients was 37.2 years (18-64 years: 99%; male: 81.3%). The majority (80%) of patients was infected with HIV-1 sub-type B and approximately 7% had chronic hepatitis B or C co-infection.

The mean plasma RNA HIV-1 viral load at inclusion was 5 $\log_{10}$ copies/ml (including 53% with a viral load > 100 000 copies/ml) and the median CD4+ count was 207.1 x $10^6$ cells/l.

[2] Lennox JL, Dejesus E, Lazzarin A, *et al*; for the STARTMRK investigators. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet 2009; 374: 796-806

Results at 48 and 96 weeks

In the *per protocol* analysis, the percentage of patients with a viral load < 50 copies/ml at week 48 (primary efficacy endpoint) was 87.1% (230/264) in the ISENTRESS group versus 81.8% (224/274) in the efavirenz group (difference = 5.3%; 95% CI [- 0.8; 11.5]). As the lower limit of the 95% CI for the difference in response between the two treatment groups was higher than the pre-defined non-inferiority threshold (-12%), it can be concluded that ISENTRESS is not inferior to efavirenz. The ITT analysis supports non-inferiority (Table 2). The results at 96 weeks show that virological and immunological efficacy was maintained.

**Table 2: Efficacy results at 48 and 96 weeks (ITT analysis)**

| **Primary efficacy endpoints** | **Treatment groups*** | | |
|---|---|---|---|
| | **ISENTRESS (N = 281)** | **Efavirenz (N = 282)** | **Difference [95% CI]** |
| **Analysis at 48 weeks**** | | | |
| **Patients with a VL < 50 copies/ml, n (%)** | **241 (86.1)** | **230 (81.9)** | **+4.2 (-1.92; +10.32)** |
| Patients with a viral load < 400 copies/ml, n (%) | 252 (90.0) | 241 (85.8) | 4.1 [-1.28; 9.68] |
| Mean change in CD4 count compared with inclusion (cells/$mm^3$) [95% CI] | 189.1 [173.9 – 204.3] | 163.3 [148.2 – 178.4] | 25.77 [4.37; 47.17] |
| **Analysis at 96 weeks** | | | |
| **Patients with a VL < 50 copies/ml, n (%)** | **228 (81.1)** | **222 (78.7%)** | **+4.2 (-1.92; +10.32)** |
| Patients with a viral load < 400 copies/ml, n (%) | 240 (85.4) | 229 (81.2) | 4.1 [- 2.0; 10.4] |
| Mean change in CD4 count compared with inclusion (cells/$mm^3$) [95% CI] | 239.6 [219.8; 259.4] | 224.8 [205.8; 243.9] | 14.8 [-12.7; 42.2] |

* Both groups received a basic treatment comprising a fixed combination of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine, as a single daily dose.
** the analysis was conducted on 280 patients in the ISENTRESS group and 281 in the efavirenz group.

Sub-group analyses according to prognostic factors (viral load and CD4 count at inclusion, co-infection with HBV/HCV) indicated similar response rates and support the non-inferiority of ISENTRESS compared to efavirenz.

3.1.3. Other data: Switch to raltegravir in virologically controlled patients

The SWITCHMRK 1 and 2 studies (Protocols 032 and 033) were designed to demonstrate, in patients with HIV-1 infection controlled with a treatment protocol including lopinavir/ritonavir (KALETRA), that the replacement of lopinavir/ritonavir by raltegravir (ISENTRESS) achieved an improvement in the lipid profile (superiority hypothesis) whilst maintaining comparable antiretroviral efficacy (non-inferiority hypothesis delta threshold = 12).
These studies were suspended after the primary efficacy analysis at 24 weeks since the non-inferiority of raltegravir versus lopinavir/ritonavir was not demonstrated (the lower level of the confidence interval for the difference between the two treatments was above -12% in both studies):

- In the SWITCHMRK 1 study, an RNA HIV viral load of less than 50 copies/ml was maintained in 139/172 (80.8%) patients in the raltegravir group and 152/174 (87.4%) patients in the lopinavir/ritonavir group. The difference between the two groups (raltegravir – lopinavir/ritonavir) was -6.6% [-14.4; 1.2].

- In the SWITCHMRK 2 study, an RNA HIV viral load of less than 50 copies/ml was maintained in 154/175 (88.0%) patients in the raltegravir group and 167/178 (93.8%) patients in the lopinavir/ritonavir group. The difference between the two groups was -5.8% [-12.2; 0.22].

The results of these two studies, which have been published[3], do not validate this therapeutic strategy.

### 3.2. Adverse effects (clinical experience)

The tolerance profile of ISENTRESS is based on combined tolerance data from two phase III clinical studies conducted in treatment-experienced patients and one phase III clinical study conducted in treatment-naïve patients.

In the two clinical studies conducted in treatment-experienced patients, the recommended dose of 400 mg twice daily was used in association with an OT in 462 patients versus 237 patients receiving a placebo in association with the OT. During the double-blind phase of the study, total follow-up amounted to 708 patient-years in the group treated with ISENTRESS 400 mg twice daily and 244 patient-years in the placebo group.

In the active comparator-controlled study conducted in treatment-naïve patients, the recommended dose of 400 mg twice daily was used in 281 patients *versus* 282 patients treated with efavirenz (EFV) 600 mg (at bed-time), in association with a fixed combination of emtricitabine 200 mg (+) tenofovir 245 mg. During the double-blind phase of the study, total follow-up amounted to 480 patients-years in the group taking ISENTRESS 400 mg twice daily and 463 patients-years in the group taking efavirenz 600 mg at bed-time.

In the combined analysis of treatment-experienced patients, rates for discontinuing treatment on account of adverse effects were 3.9% in patients treated with ISENTRESS + OT and 4.6% in patients treated with placebo + OT. In treatment-naïve patients, rates for discontinuing treatment on account of adverse effects were 3.6% in patients treated with ISENTRESS plus emtricitabine (+) tenofovir and 6.7% in patients treated with efavirenz plus emtricitabine (+) tenofovir.

The most frequent adverse effects (≥ 1% to < 10%) in patients taking ISENTRESS were:

- Psychiatric disorders: abnormal dreams, insomnia
- Nervous system disorders: dizziness, vertigo, headaches
- Gastrointestinal disorders: abdominal distension, abdominal pain, diarrhoea, flatulence, nausea, vomiting
- Skin and sub-cutaneous tissue disorders: rash
- General disorders: asthenia, fatigue, fever
- Laboratory tests: ASAT/ALAT elevation, atypical lymphocytes, elevated levels of triglycerides in the blood and lipases.

Cases of cancer have been reported in treatment-experienced patients and in treatment-naïve patients taking ISENTRESS in association with other antiretroviral agents. The types and incidence of specific cancers were as expected in a severely immunodepressed population. In these studies, the risk of a cancer developing was comparable in the ISENTRESS groups and the comparator treatment groups.

On a muscular level, grade 2-4 CPK laboratory abnormalities were observed in subjects treated with ISENTRESS. Cases of myopathy and rhabdomyolysis were reported. ISENTRESS should be used with caution in patients with a history of myopathy or rhabdomyolysis or with risk factors such as the use of medicinal products known to cause such effects (see section 4.4 of the SPC).

Cases of osteonecrosis have been reported, particularly in patients with known risk factors: advanced HIV disease or long-term treatment with associations of antiretroviral agents. The frequency of such cases has not been established (see section 4.4 of the SPC).

*Patients with hepatitis B and/or hepatitis C virus co-infection*

Treatment-experienced patients (n = 114/699 i.e. 16%, HBV = 6%, HCV = 9%, HBV + HCV = 1%) and treatment-naïve patients (n = 34/563 i.e. 6%, HBV = 4%, HCV = 2%, HBV + HCV = 0.2%) with active chronic (but not acute) hepatitis B and/or C were allowed to take part in the phase III clinical trials as long as the initial liver function test values were ≤ 5 times the upper normal limit. The ISENTRESS tolerance profile has been found to be generally similar in patients

[3] Eron JJ, Young B, Cooper DA et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet. 2010 Jan 30; 375(9712):396-407. Epub 2010 Jan 12.

co-infected with the hepatitis B and/or C virus as with those who are not co-infected with either of these viruses. However, in both treatment groups, ASAT/ALAT abnormality levels were slightly higher in the sub-group of patients with concomitant hepatitis B and/or C. Grade 2 or higher laboratory anomalies, representing a worsening in ASAT, ALAT or total bilirubinaemia values compared to the initial values, were reported more frequently in patients with concomitant hepatitis B and/or C.

### 3.3. Resistance

Most viruses isolated from patients failing raltegravir had a high level of resistance to raltegravir, arising from the emergence of two or more mutations. Most of them had a mutation of the amino acids 155 (N155 changed to H), 148 (Q148 changed to H, K or R), 143 (Y143 changed to H, C or R) and one or more additional integrase mutations (for example L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, S230R). These mutations reduce viral sensitivity to raltegravir and the presence of further mutations increases this effect. Factors which reduce the likelihood of developing resistance include a low viral load on inclusion and the use of other active antiretroviral agents. Preliminary data indicate that there is a potential risk of the appearance of cross-resistance between raltegravir and other integrase inhibitors.

Raltegravir has a relatively low genetic barrier to resistance. As a result, whenever possible, raltegravir should be used in association with two other active antiretroviral agents[4] in order to reduce the risk of virological failure and the development of resistance (see section 4.4 of the SPC. Special warnings and precautions for use).

### 3.4. Conclusion

Raltegravir efficacy and tolerance data for treatment-experienced patients with HIV-1 infection (initial Marketing Authorisation) have been updated. In antiretroviral treatment-naïve patients with HIV-1 infection (extension of indication) data at 96 weeks from a study currently being conducted have been analysed.

- In treatment-experienced patients with HIV-1 infection with a viral load detectable under treatment (initial Marketing Authorisation).

Two randomised, double-blind, placebo-controlled studies (BENCHMRK 1 and BENCHMRK 2, Protocols 018 and 019) have evaluated the efficacy of raltegravir (400 mg twice daily) versus placebo, in association with an optimised basic treatment (OT), in treatment-experienced patients with HIV infection, 16 years of age or older, with documented resistance to at least 1 product in each of the 3 classes of antiretroviral agents (NRTI, NNRTI, PI). The results at 24 weeks were analysed in the previous opinion of the Transparency Committee[5].

Analysis of new data at 48 and 96 weeks of treatment demonstrated maintained virological efficacy and immunological benefit. Treatment with raltegravir achieved plasma viral loads < 50 copies/ml in 62.1% of patients at week 48 and 57.0% at week 96 (missing data = failure).

In some patients, a viral rebound effect was observed between week 16 and week 96. Factors associated with failure included a high viral load at inclusion and an OT not including at least one active antiretroviral agent.

- In antiretroviral treatment-naïve adult patients with HIV-1 infection (extension of indication)

The clinical efficacy of raltegravir (400 mg twice daily) was evaluated in a phase III, randomised, double-blind, 240-week controlled study (*STARTMRK* study, protocol 021, currently being conducted), the main objective of which was to demonstrate non-inferiority (delta threshold = 12%) versus efavirenz (600 mg x 1 daily), in the context of triple therapy in a fixed combination

[4] Any antiretroviral treatment belonging to a class not yet used or belonging to a class already used but where the current (and cumulative) resistance genotype(s) demonstrate the absence of resistance or possible resistance to this antiretroviral agent must be considered as active (see report by Yéni 2010).

[5] See Opinion of the Transparency Committee dated 2 April 2008 (ISENTRESS _Avis 2 _CT 5359)

of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine (TRUVADA 1 tablet daily), in treatment-naïve patients with HIV-1 infection (> 18 years of age), with a viral load of more than 5 000 copies/ml.

The non-inferiority of raltegravir compared to efavirenz in terms of virological response defined by the percentage of patients with a viral load < 50 copies/ml at week 48 of treatment (primary efficacy endpoint) was demonstrated: 86.1% (241/281) in the raltegravir group *versus* 81.9% (230/282) in the efavirenz group (difference = +4.2 [-1.92; +10.32]).

The immune response (median increase in the CD4+ count) was 189.1 [173.9– 204.3] $10^6$ cells/l versus 163.3 [148.2 – 178.4] cells/l (difference = 25.77 [4.37; 47.17]).

The results at 96 weeks demonstrated maintained virological and immunological efficacy.

- Tolerance

The updated tolerance data for raltegravir indicate a satisfactory tolerance profile, including in particular the cancellation of the warning on the carcinological risk. The adverse effects reported in studies were essentially of moderate to low intensity and rarely led to suspension of treatment.

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

HIV infection is a serious condition and has an impact on life expectancy.

This medicinal drug aims to prevent and/or correct the immune deficiency resulting from HIV infection.

The efficacy/adverse effects ratio is high when used in association with other antiretrovirals.

This medicinal product is of benefit when used in association for patients resistant to treatment with other antiretrovirals. In this context, the long-term efficacy and safety data submitted (96 weeks) are reassuring.

With regard to treatment-naïve patients, on account of the risk of selection of resistant variants and as superiority has not been demonstrated in terms of immunovirological efficacy compared to therapeutic alternatives available, its use should be limited to a small number of patients for whom it is not possible to use other first-line treatments.

Alternative medicinal products exist.

Public health benefit:

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

There is a drug therapy need that has been identified as a public health priority in order to reduce AIDS-related morbidity and mortality*.

No information allowing the direct impact of ISENTRESS on morbidity, mortality or quality of life criteria is available. However, in view of the data available (non-inferiority of ISENTRESS compared to efavirenz on the viral load at 48 weeks in treatment-naïve patients, relatively low genetic resistance barrier of ISENTRESS), compared to other existing treatments, this product is not expected to have an impact on reducing total morbidity and mortality (associated with HIV-1 infection, cardiovascular disorders) in treatment-naïve patients.

In conclusion, in the light of the data available, ISENTRESS is not expected to have a public health benefit for this extension of indication (to treatment-naïve patients).

**National programme against HIV-AIDS. Ministry of Health 2005-2008 and Public Health Law 2004 (Law* n°2004-806 of 9 August 2004 relating to Public Health Policy)

The actual benefit of this medicinal product is substantial.

### 4.2. Improvement in actual benefit (IAB)

- **In treatment-naïve patients**

As superiority has not been demonstrated in terms of immunovirological efficacy compared to alternative treatments available and given the relatively low genetic barrier to the development of resistance (risk of selection of resistant variants) which would limit its use as a first-line treatment in this population, the Committee considers that ISENTRESS does not provide an improvement in actual benefit (ASMR V) in the management of treatment-naïve adult patients with HIV-1 infection.

- **In treatment-experienced patients**

The new data submitted do not affect the assessment of the improvement in actual benefit compared to the previous opinion of the Transparency Committee[6].

ISENTRESS continues to be of benefit used in association with an optimised antiretroviral treatment, in the management of a small population of treatment-experienced adult patients who have a detectable viral load under their current antiretroviral treatment and who have been confirmed by genotype and phenotype tests to be resistant to at least one nucleoside inhibitor (NI), one non-nucleoside inhibitor (NNI) and more than one protease inhibitor (PI).

### 4.3. Therapeutic use

- From: "Prise en charge médicale des personnes infectées par le VIH - Recommandations du groupe d'experts" [Medical management of individuals infected with HIV - Expert group recommendations] - 2010 report produced under the guidance of Professor Patrick YENI] (www.sante.gouv.fr)[7]

- **In treatment-naïve patients**

Choice of the first antiretroviral treatment

Many antiretrovirals are available in 6 classes of medicinal product:
- 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 continues to be an association of 2 NRTIs with a third agent.
The choice of the 2 NRTIs for triple therapy should preferably involve fixed associations of tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC).
The third agent should preferably be a PI/r or a NNRTI. There is no conclusive argument for favouring the use of one or other of these two classes.

Raltegravir is not recommended as the preferred third agent for the following reasons:
- Raltegravir has not been compared to a PI/r and has not been evaluated with NRTIs other than the TDF/FTC association.
- The risk of selection of resistant variants in case of virological failure is higher and faster than with a treatment including a PI/r.
- Furthermore, no data are yet available on long-term tolerance.

[6] See opinion of the Transparency Committee dated 2 April 2008 relating to the initial application for registration for ISENTRESS in treatment-experienced patients (ISENTRESS 400 mg_avis 2_CT 5359).
[7] Yéni P. Prise en charge médicale des personnes infectées par le VIH. Recommandations du groupe d'experts (www.sante.gouv.fr). Preliminary version of the 2010 report (Special Edition "AIDS 2010 (Vienna, 18-23 July 2010)").

It can be used in certain situations, particularly in patients with a high cardiovascular risk or to reduce the risk of interactions with other medicinal products in patients receiving other treatments.

- **In treatment-experienced patients**

In the event of virological failure (particularly in the case of multi-resistance), raltegravir is one of the treatments of choice. It should be considered as a product which is fully active in all integrase inhibitor-naïve patients. On account of the high risk of resistant mutations emerging in cases of virological failure, it is essential to use raltegravir with at least 2 active antiretroviral agents[8].

- **Switch to raltegravir in virologically-controlled patients**

This strategy should be used only in special circumstances as it cannot be validated with the data available.
With regard to the simplification of initial triple therapy comprising a PI/r in virologically-controlled patients, the replacement of the PI/r with raltegravir should be considered only in the event of complications (metabolic disorders) or to manage drug interactions. In such situations, it should also be ensured that products used in association are fully active considering the patient's complete treatment history.

### 4.4. Target population

- Estimate of the target population of treatment-naïve adult patients with HIV-1 infection

On the basis of the indications for use of the product and its role in the treatment strategy, on the one hand, and the data available, on the other, the target population has been estimated on the basis of the number of treatment-naïve patients starting treatment for HIV infection. The target population was estimated for 2008.

The number of seropositive people living in France in 2008 was estimated at 152 000 (between 135 000 and 170 000) at the end of 2008. It is estimated that approximately 30% of these people are unaware that they are seropositive as a result of which their condition cannot be managed[9]. It can therefore be estimated that in 2008, 106 000 people had been diagnosed as seropositive. It is however probable that some of these 106 000 seropositive people will not meet the criteria for starting antiretroviral treatment. On the other hand, it can be assumed that a number of HIV-infected people have reached a stage of the disease which would justify antiretroviral treatment but as they are unaware of their seropositivity, they cannot benefit from treatment.

Furthermore, 89 911 people were classified as having a chronic condition due to HIV infection at the end of 2008 under the general sickness insurance system[10]. Taking account of the fact that the general system covers approximately 88% of the population living in France, it can be estimated that the number of people treated for HIV infection at the end of 2008 was 102 000.

According to the French hospital database[11] the percentage of treatment-naïve patients starting first-line treatment was 3.7% (1430/38481) of patients monitored in 2008. By applying this percentage to the 102 000 people treated for HIV infection at the end of 2008, the number of treatment-naïve adult patients starting first-line treatment in 2008 can be estimated at approximately 3 800.

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[8] Any antiretroviral treatment belonging to a class not yet used or belonging to a class already used but where the current (and cumulative) resistance genotype(s) demonstrate the absence of resistance or possible resistance to this antiretroviral agent must be considered as active.

[9] Hamers FF, Phillips AN. Diagnosed and undiagnosed HIV-infected populations in Europe. HIV Med. 2008;9 Suppl 2:6-12.

[10] Païta M, Weill A. Les personnes en affection de longue durée au 31 décembre 2007. Points de repère 2008;20:1-8. Available at: http://www.ameli.fr/fileadmin/user_upload/documents/Points_de_repere_n__20.pdf (consulted on 14/05/2009).

[11] Costagliola D. Epidémiologie clinique et traitement de l'infection à VIH. Retour d'informations clinico-épidémiologiques. N°16, October 2009. Paris : Inserm . Available at: http://www.ccde.fr/_fold/fl-1Z56586820-617.pdf (consulted 2/08/2010).

In practice, the number of patients who could be treated with raltegravir in the context of first-line triple therapy will be very small taking account of the limited number of patients eligible for this treatment according to recommendations currently in force[12].

- Updating of the target population of treatment-experienced patients

The target population for the proprietary product ISENTRESS is qualitatively identical to the enrolment criterion. It corresponds to treatment-experienced adult patients who have a detectable viral load under their current antiretroviral treatment and who have been confirmed by genotype and phenotype tests to be resistant to at least one nucleoside inhibitor (NI), one non-nucleoside inhibitor (NNI) and more than one protease inhibitor (PI).

The target population for ISENTRESS has been adjusted to approximately 8500 patients on the basis of the new epidemiological data published[12]:

| | |
|---|---|
| Seropositive subjects living in France | 152 000 |
| Subjects managed | 102 000 |
| Patients treated (85%) | 86 700 |
| Patients treated with VL > 50 copies/ml (17%) | 14 739 |
| Patients resistant to one NRTI, NNRTI and more than one PI (58%) | 8 548 |

### 4.5. Transparency Committee recommendations

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

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 100%

[12] Yéni P. Prise en charge médicale des personnes infectées par le VIH - Recommandations du groupe d'experts - [Medical management of individuals infected with HIV - Expert group recommendations] (www.sante.gouv.fr). Preliminary version of the 2010 report (Special edition "AIDS 2010 (Vienna, 18-23 July 2010)")