HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

7 January 2009

INTELENCE 100 mg tablets
Box of 120 tablets (CIP: 387 426-0)

Applicant: JANSSEN-CILAG

etravirine

ATC Code: J05AG04

List I
Medicinal product for initial annual hospital prescription.
Unrestricted renewal

Date of European MA (centralised procedure): 28 August 2008
Conditional MA

Reason for request: Inclusion of the list of medicines reimbursed by National Insurance and approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

etravirine

1.2. Background

This is a new antiretroviral in the non-nucleoside reverse transcriptase inhibitor class.

1.3. Indication

"INTELENCE, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients (see sections 4.4, 4.5 and 5.1 of the SPC).

This indication is based on week 24 analyses from 2 randomised, double-blind, placebo-controlled phase III trials in highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors, where INTELENCE was investigated in combination with an optimised background regimen (OBR) including darunavir/ritonavir".

1.4. Dosage

"Treatment must be initiated by a doctor experienced in the management of HIV infection. INTELENCE must always be given in combination with other antiretroviral medicinal products.

Adults
The recommended dose of INTELENCE is 200 mg (two 100 mg tablets) taken orally twice daily following a meal.
Patients who are unable to swallow INTELENCE tablets whole may disperse the tablets in a glass of water.

Paediatric population
INTELENCE is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Elderly
There is limited information regarding the use of INTELENCE in patients over 65 (see section 5.2), therefore caution should be used in this population.

Hepatic failure:
No dose adjustment is required in patients with mild or moderate hepatic failure (Child-Pugh class A or B). INTELENCE must be used with caution in patients with moderate hepatic failure. The pharmacokinetic parameters of etravirine have not been studied in patients with severe hepatic failure (Child-Pugh class C).
Therefore, INTELENCE is not recommended in patients with severe hepatic failure.
Renal failure:
No dosage adjustment is necessary for patients with hepatic failure". See SPC

1.5. Interactions

"Medicinal products that affect etravirine exposure:
INTELENCE (etravirine) is metabolised by CYP3A4, CYP2C9 and CYP2C19.
Medicinal products that induce CYP3A4, CYP2C9 or CYP2C19 may increase the clearance of this drug, resulting in lowered plasma concentrations.

Co-administration of this drug with medicinal products that inhibit CYP3A4, CYP2C9 or CYP2C19 may decrease its clearance and may result in increased plasma concentrations.

Medicinal products that are affected by the use of etravirine:
INTELENCE is a weak inducer of CYP3A4. Its co-administration with medicinal products primarily metabolised by CYP3A4 may result in decreased plasma concentrations of such medicinal products, which could decrease or shorten their therapeutic effects.
INTELENCE is a weak inhibitor of CYP2C9 and CYP2C19. Its co-administration with medicinal products primarily metabolised by CYP2C9 or CYP2C19 may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect or alter their adverse effects profile".

See the interactions and dose recommendations with other medicinal products described in the SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

J : Antiinfectives for systemic use
J05 : Antivirals for systemic use
J05A : Direct acting antivirals
J05AG : Non-nucleoside reverse transcriptase inhibitors
J05AG04 : etravirine

2.2. Medicines in the same therapeutic category

Comparator medicines
Medicines in the same therapeutic category (non-nucleoside inhibitors: efavirenz (SUSTIVA) and nevirapine (VIRAMUNE)) do not have a comparable indication. In fact, contrary to INTELENCE, they can be used in treatment-naïve patients and have not been developed "in highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors".

2.3. Medicines with a similar therapeutic aim

- Antiretrovirals that are members of other classes of antiretroviral used in combination in patients for whom treatment has failed and who are on multiple treatments:

-Fusion inhibitor:
-enfuvirtide: FUZEON, powder and solvent for suspension for injection,
-Protease inhibitors:
-darunavir: PREZISTA, film-coated tablets,
-tipranavir: APTIVUS, soft capsules.
-Integrase inhibitor:
-raltegravir: ISENTRESS, tablets
-CCR5 receptor antagonist
-maraviroc: CELSENTRI film-coated tablets

- Other antiretrovirals used in combination treatment:

-Protease inhibitors (PI):
- amprenavir: AGENERASE capsules and oral solution
- atazanavir: REYATAZ gelatin-coated capsules or oral powder, indicated in adults
- fosamprenavir: TELZIR film-coated tablets and oral solution,
- indinavir: CRIXIVAN gelatin-coated capsules,
- nelfinavir: VIRACEPT film-coated tablets and oral powder
- 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.

- saquinavir mesylate: INVIRASE gelatin-coated capsules
- lopinavir / ritonavir: KALETRA soft capsule and oral solution

- Non-nucleoside reverse transcriptase inhibitors (NNI) (etravirine is in the same therapeutic category):
- efavirenz: SUSTIVA gelatin-coated capsules and oral solution
- nevirapine: VIRAMUNE tablets and oral solution
- Nucleotide reverse transcriptase inhibitors:
- tenofovir: VIREAD tablets
- Nucleoside reverse transcriptase inhibitors (NI):
- 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
- Nucleoside and nucleotide reverse transcriptase inhibitors (NI)
- emtricitabine / tenofovir: TRUVADA tablets

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The clinical dossier comprises in particular:

- 1 phase IIb open-label exploratory study (study TMC125-C227) comparing the efficacy of INTELENCE with that of a protease inhibitor (combined with 2 nucleoside inhibitors).

This study was conducted on patients with HIV-1 infection in whom treatment had failed, who were resistant to at least one non-nucleoside inhibitor and who had never been treated with a protease inhibitor (N=59).

- 2 double-blind phase III clinical studies (studies DUET-1 and DUET-2**)** comparing the efficacy after 48 weeks of INTELENCE with that of a placebo (combined with a boosted protease inhibitor, darunavir/ritonavir and an optimised background regimen (OBR).

These two studies were conducted on patients with HIV-1 infection in whom treatment had failed, who were resistant to at least one non-nucleoside inhibitor and who had at least 3 major mutations to protease inhibitors:

. Study DUET-1 (N=612)
. Study DUET-2 (N=591)

The protocols for the two studies were identical. The combined results of these 2 studies were presented to EMEA.

3.1.1 Study TMC125-C227

This open-label study was conducted on patients with HIV-1 infection in whom treatment had failed, who were resistant to at least one non-nucleoside inhibitor and who had never been treated with a protease inhibitor.

It compared INTELENCE (in combination with two nucleoside inhibitors) to a ritonavir-boosted protease inhibitor (in combination with two nucleoside inhibitors). This study was

terminated prematurely in week 12 of treatment because the virological response in terms of reduction of viral load compared to baseline viral load was higher in the comparator group (-2.2 log10 copies/ml N=53) than in the INTELENCE group (-1.4 log10 copies/ml N=40). This difference between the treatment groups was statistically significant.
In the light of the results of this study, practitioners are advised not to combine this drug only with nucleoside inhibitors in patients with a history of virological failure under treatment involving NNIs and NIs. The therapeutic indication which was accepted specifies that INTELENCE must be combined with a ritonavir-boosted protease inhibitor and other antiretrovirals.

3.1.2 Studies DUET-1 and DUET-2

Objective:
The principal objective of the two studies was to compare the virological and immunological efficacy of this drug with that of a placebo at 24 weeks.
All the patients in both groups received a combination of a background regimen comprising the boosted protease inhibitor (darunavir/ritonavir) and an optimised background regimen (OBR).
The OBR (nucleoside inhibitors selected by the investigator with or without enfuvirtide) was determined on the basis of the patient's treatment history and the results of baseline genotype and phenotype resistance tests, in line with the recommendations in force at the time.

Method: both studies were conducted according to the same protocol: versus placebo, randomised, double-blind, on patients in whom treatment had failed, who had at least one mutation associated with resistance to non-nucleoside inhibitors and who had at least 3 major mutations to protease inhibitors. The protocol provided for a pooled analysis of the two studies.
The scheduled duration of treatment was 48 weeks, with a four-week follow-up after the end of treatment.
- 612 patients in the DUET-1 study (INTELENCE group N= 304; placebo group N = 308),
- 591 patients in the DUET-2 study (INTELENCE group N= 295; placebo group N = 296)

Stratification: randomisation was stratified according to:
- whether or not enfuvirtide (FUZEON) was included in the optimised background regimen (OBR) (reintroduction of enfuvirtide, absence of enfuvirtide or administration of enfuvirtide for the first time),
- previous use of darunavir
- viral load on selection.

Inclusion criteria:
- Male or female, aged 18 or over
- Documented HIV-1 infection
- HIV-1 plasma viral load > 5000 copies/ml
- Antiretroviral treatment stable for at least 8 weeks.
- 1 (or more) documented mutation(s) associated with resistance to non-nucleoside inhibitors present on selection or on the basis of a previous genotype analysis (documented resistance)
- 3 or more major mutations to protease inhibitors present on selection

Exclusion criteria:
- Patients not previously treated for HIV-1 infection
- HIV-2 infection

- Patients with a life expectancy of less than 6 months
- Patients with a pathology categorised as evolutive AIDS (CDC, category C) excluding Kaposi's sarcoma and cachexia syndrome
- Patients with a clinically active pathology (pancreatitis, cardiac function disorders, acute hepatitis, etc.)
- Chronic hepatitis with ASAT and/or ALAT values more than five times the normal level

Treatments:

- INTELENCE group 200mg twice a day + darunavir/ritonavir 600/100mg twice a day + OBR (at least 2 antiretrovirals (≥ 1 non-nucleoside inhibitor with or without enfuvirtide)
- Placebo group + darunavir/ritonavir 600/100mg twice a day + OBR (at least 2 antiretrovirals (≥ 1 non-nucleoside inhibitor with or without enfuvirtide)

The systematic use of darunavir/ritonavir allowed the investigators to ensure that most of the patients taking part in both studies would receive at least one active substance.

Primary endpoint:

The primary endpoint was the percentage of patients with a plasma viral load ≤50 copies/ml after 24 weeks of treatment (intention-to-treat population)

In view of the significant effect of enfuvirtide on treatment, the principal analysis was conducted on:

- patients using enfuvirtide who had used it before (as part of a previous treatment regimen) or who did not use it
- patients using enfuvirtide for the first time

Secondary endpoints, in particular:

- Percentage of patients with a plasma viral load ≤ 400 copies/ml
- Mean change in viral load relative to baseline
- Mean change in the CD4 level relative to baseline.
- Percentage of patients with a pathology classed as AIDS and/or who died
- Quality of life criteria (FAHI (Functional Assessment of Human Immunodeficiency virus infection) questionnaire)

Sub-group analyses of virological response were performed primarily in respect of:

- baseline viral load and CD4 level
- the number of mutations associated with resistance to INTELENCE present at baseline

Baseline characteristics of patients in the DUET-1 and DUET-2 studies according to treatment group:

	INTELENCE+darunavir/ritonavir +OBR	**Placebo+darunavir/ritonavir +OBR**

	N=599	N=604
Plasma HIV-1 RNA (median)	4.8 $\log_{10}$ copies/ml	4.8 $\log_{10}$ copies/ml
CD4 level (median)	99 x 10^6 cells/l	109 x 10^6 cells/l
Patients at stage C of the AIDS classification (disease not progressing or under control)	57.8%	59.4%
Co-infection hepatitis C and/or B	12.7%	11 .9%
Prior use of antiretrovirals: - 10-15 antiretrovirals - NNI - darunavir/ritonavir	65.6% 91.8% 4.2%	 64.7% 92.1% 5%
Detectable mutations: - ≥ 2 NNI mutations - ≥ 4 major PI mutations - ≥ 4 DRV/r mutations(%)	 68.2% 62.3% 23.5%	 68.7% 62.3% 24.5%
Background treatment: - Use of enfuvirtide - Sensitivity to DRV/r FC≤10 - No active antiretroviral - Only one active antiretroviral	 45.7% 63.5% 17 % 36.5%	 46.9% 64 % 16.2% 38.7%

NNI: non-nucleoside inhibitors PI: protease inhibitors DRV/r: darunavir and ritonavir

The subjects taking part in the studies were at an advanced stage of HIV-1 infection: high viral load (median around 70,000 copies/ml) and low CD4 level (median around 100 x 10^6 cells/l).
The patients had been highly pre-treated with antiretrovirals; approximately:
- 65% of patients had taken between 10 and 15 different antiretrovirals
- 68% of patients had at least 2 mutations to non-nucleoside inhibitors which were detectable at baseline
- 24% of patients had 4 major PI resistance mutations
- 17% of patients had no active antiretroviral in their optimised background regimen (OBR)
- 38% of patients had only one active antiretroviral in their optimised background regimen (OBR)

Pooled results of the two studies at 24 weeks (DUET-1 and DUET-2 studies)

The data from the two studies was pooled (intention-to-treat population)
Pooled results after 24 weeks of treatment (DUET-1 and DUET-2)

	INTELENCE	**Placebo +darunavir/ritonavir**	**Difference between treatments**

	+darunavir/ritonavir +OBR N=599	**+OBR** N=604	**(95% CI)**
Primary endpoint			
Confirmed undetectable viral load (HIV-1 RNA < 50 copies/ml)[a] n (%) **Total**	**353 (58.9%)**	**248 (41.1%)**	**17,8% (12.3%; 23.4%)[d]**
enfuvirtide taken for the first time	102 (66.7%)	99 (61.9%)	4.8% **(NS)** (5.8%; 15.4%)[f]
enfuvirtide (taken after having taken before, or not taken)	251 (56.3%)	149 (33.6%)	22,7% (16.4%; 29.1%)[f]
Secondary endpoints			
HIV RNA < 400 copies/ml [a] n (%)	445 (74.3 %)	317 (52.5 %)	21,8 % (16.5%; 27.1 %)[d]
Mean variation in HIV RNA compared to baseline (log_{10} copies/ml)[b]	-2.37	-1.69	-0,54 (-0.71; -0.37)[c]
Mean variation in CD4 level compared to baseline (x 10^6/l)[b]	+85.6	+66.8	+ 19,6 (8.4 ; 30.7)
Pathology (probable or confirmed)* classified as AIDS and/or death n (%)	22 (3.7%)	41 (6.8%)	-3.1% **(NS)** (-5.6%; -0.6%)[e]

[a] Defined according to the TLOVR (Time to Loss of Virological Response) algorithm.

[b] Defined on the basis of patients not completing the study being regarded as failures (NC = F)

[c] The differences between the treatments are based on the least squares method (LSM) of an ANCOVA model which included the stratification factors. Mean reduction in HIV RNA: p<0.0001; mean variation in CD4 level: p=0.0060.

[d] Confidence interval of the difference observed between the response rates: p<0.0001 derived from a logistic regression model which included the stratification factors.

[e] Confidence interval of the difference observed between the rates of response; p=not significant

[f] Confidence interval of the difference observed between the response rates: p (derived from the CMH test taking the stratification factors into account) = 0.427 for subjects taking the substance for the first time, and <0.0001 for those who had taken it before or who did not take it.

* the (probable or confirmed) pathologies classified as AIDS are listed in the CDC classification, appendices C and D: either a definitive diagnosis (appendix C: definitive diagnostic methods) or a presumed diagnosis (appendix D: suggested guidelines for presumptive diagnostic)

After 24 weeks of treatment, the virological efficacy (percentage of patients with a confirmed undetectable viral load (HIV-1 RNA < 50 copies/ml)) was higher for all patients taken together in the INTELENCE group than in the placebo group (58.9 % versus 41.1%, p<0.0001).
This superiority was not demonstrated in the sub-group of patients who took enfuvirtide for the first time.

The results observed in respect of the secondary virological and immunological endpoints (percentage of patients with a viral load <400 copies/ml and variation in the viral load and CD4 count compared to baseline) were higher for all patients taken together in the INTELENCE group than in the placebo group.

The boosted protease inhibitor, darunavir/ritonavir, which was given to all subjects in both the treatment group and the placebo group, had been very little used on patients in previous treatments. No analysis of the virological response according to whether or not darunavir had

previously been taken was carried out in view of the small number of patients.

Taking account of
-the efficacy of INTELENCE administered in association with the protease inhibitor, darunavir/ritonavir,
-and the known pharmacokinetic interactions between INTELENCE and other protease inhibitors (metabolised by CYP304, CYP2C9 and CYP2C19),
it was accepted that co-prescription of this drug could be extrapolated to other protease inhibitors in addition to darunavir/ritonavir (except for tipranavir/ritonavir) in the context of the indications laid down in the marketing authorisation.
However, EMEA has asked the company to provide additional data assessing the combination of INTELENCE with other protease inhibitors (except for tipranavir/ritonavir).

Virological response after 24 weeks according to:
- baseline viral load
- baseline CD4 count

Pooled results of the two studies after 24 weeks treatment (DUET-1 and DUET-2)		
Sub-groups	Proportion of subjects with HIV-1 RNA < 50 copies/ml after 24 weeks	
	INTELENCE +darunavir/ritonavir +OBR N=599	**Placebo +darunavir/ritonavir +OBR** N=604
Baseline HIV-1 RNA		
< 30,000 copies/ml	76.4%	62.1%
≥ 30,000 and < 100,000 copies/ml	61.2%	39.4%
≥ 100,000 copies/ml	44.3%	25.8%
Baseline CD4 count (x 10^6/l)		
< 50	39.0%	23.4%
≥ 50 and < 200	66.8%	46.6%
≥ 200 and < 350	70.6%	54.4%
≥ 350	79.3%	55.7%

Note: Defined according to the TLOVR (Time to Loss of Virological Response) algorithm.

- the number of mutations associated with resistance to INTELENCE at baseline

An analysis was performed in order to identify the mutations involved in the development of resistance to INTELENCE; 13 mutations were identified: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V and G190A/S[1].

Virological response (percentage of patients with HIV-1 RNA < 50 copies/ml) according to the number of mutations associated with resistance to INTELENCE at baseline and according to whether or not the patient took enfuvirtide (ENF)

[1] Vingerhoets et al. : Impact of baseline NNRTI mutations on the virological response to TMC125 in the Phase III clinical trials DUET-1 and DUET-2; Antiviral Therapy 2007; 12:S34

Pooled results of the two studies at 24 weeks (DUET-1 and DUET-2):

Number of INTELENCE mutations at baseline*	**INTELENCE +darunavir/ritonavir +OBR N=549**		**Placebo +darunavir/ritonavir +OBR N=569**	
	Took ENF again / did not take ENF	Took ENF for the first time	Took ENF again / did not take ENF	Took ENF for the first time
Overall response	**62% (251/406)**	**71% (102/143)**	**36%(149/414)**	**64%(99/55)**
0	75% (121/161)	83% (39/47)	/	/
1	60% (73/121)	75% (39/52)	/	/
2	58% (37/64)	63% (17/27)	/	/
≥ 3	33% (20/60)	41% (7/17)	/	/

* Mutations associated with resistance to INTELENCE = V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S

The fall in the viral load was greater in patients who had fewer mutations to INTELENCE at baseline; the best results were obtained in those with fewer than 3 mutations to etravirine.

3.2. Resistance

In the DUET-1 and DUET-2 studies, the mutations which developed most often in patients in virological failure to the treatment were: V108I, V179F, V179I, Y181C and Y181I. These mutations normally appeared along with several other mutations associated with resistance to non-nucleoside inhibitors.

The emerging mutations most frequently found in the other studies were: L100I, E138G, V179F, V179I, Y181C and H221Y.

The mutation to non-nucleoside inhibitors, K103N, which was the most common mutation at baseline in the DUET-1 and DUET-2 studies, was not identified as being associated with resistance to INTELENCE when present alone.

The presence of this mutation alone did not affect the response observed. Additional data is needed to conclude on the influence of the mutation K103N when associated with other mutations to non-nucleoside inhibitors.

The efficacy of INTELENCE according to resistance to non-nucleoside inhibitors present at baseline was analysed primarily in the context of association with darunavir/ritonavir (DUET-1 and DUET-2).

Boosted protease inhibitors, such as darunavir/ritonavir, offer a greater barrier to resistance than other classes of antiretrovirals. The efficacy reduction thresholds (> 2 mutations among those associated with resistance to INTELENCE at baseline) apply when this drug is associated with a boosted protease inhibitor.

Cross-resistance

Practitioners are advised not to administer efavirenz and/or nevirapine to patients who have experienced virological failure of etravirine treatment.

3.3. Tolerance

The most frequently reported adverse effects (incidence ≥ 10% in the INTELENCE group), of any degree of severity, during the DUET-1 and DUET-2 studies were:

- skin rash (17.0% versus 9.4% in the placebo group),

- diarrhoea (15.0% versus 20.4% in the placebo group),
- nausea (13.9% versus 11.1% in the placebo group).
The skin rashes were usually slight to moderate, generally macular to maculopapular or erythematous, occurred mainly in the second week of treatment, and were uncommon after the fourth week. In most cases, the skin rashes usually abated and disappeared in one or two weeks even though the subject was continuing with the treatment.

The following adverse events were reported as common (≥ 1/100, < 1/10) and of at least moderate intensity (≥ grade 2) among patients being treated with INTELENCE (versus the placebo group):
- thrombocytopenia 1.3% (vs 1.3%), anaemia 3.5% (vs 3.6%)
- peripheral neuropathy 2.8% (vs 1.8%), headache 2.7% (vs 4.1%)
- gastro-oesophageal reflux 1.5% (vs 1.0%), diarrhoea 5.2% (vs 9.6%), vomiting 2.3% (vs 2.0%), nausea 4.7% (vs 3.5%), abdominal pain 3.0% (vs 2.5%), flatulence 1.0% (vs 1.0%), gastritis 1.0% (vs 0.7%)
- renal failure 1.5% (vs 1.5%)
- skin rash 9.0% (vs 3.2%)
- diabetes mellitus 1% (versus 0.2%), hyperglycaemia 1.2% (vs 0.5%), hypercholesterolaemia 3.5% (vs 2.2%), hypertriglyceridaemia 4.7% (vs 3.0%), hyperlipidaemia 1.5% (vs 0.7%), dyslipidaemia 1.0% (vs 0.3%)
- hypertension 2.8% (vs 2.2%)
- fatigue 3.3% (vs 4.0%), anxiety 1.2% (vs 1.7%), insomnia 1.8% (vs 2.2%)

Biological abnormalities:
The biological abnormalities most frequently observed during treatment (grade 3 or 4), reported in ≥2% of patients versus the placebo arm, were as follows:
- increase in amylasaemia 7.5% (vs 7.9%), triglycerides 7.0% (vs 4.3%), total cholesterol 5.8% (vs 4.1%), LDL cholesterol 5.2% (vs 5.4%), glucose 2.5% (vs 2.0%), alanine aminotransferase (ALAT) 2.5% (vs 1.7%), aspartate aminotransferase (ASAT) 2.5% (vs 1.7%)
- a fall in the neutrophil count (3.7% versus 6.3%).

5.8% of patients discontinued treatment because of adverse effects, versus 4.5% in the placebo group. The adverse effect which most often caused patients to discontinue treatment was skin rash (2.0% versus 0% in the placebo group)

Lipodystrophy:
Combination antiretroviral therapy of patients with HIV infection has been associated with redistribution of body fat mass (lipodystrophy).
Immune reconstitution syndrome:
In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (immune reconstitution syndrome).
Osteonecrosis:
Cases of osteonecrosis have been reported, particularly in patients with generally known risk factors, in an advanced stage of the disease or who are on a long-term exposure to combination antiretroviral treatment. The frequency of this effect is unknown.

Patients co-infected with hepatitis B and/or hepatitis C virus:
The incidence of hepatic events tended to be higher in co-infected subjects in the treatment group than in the placebo group. This drug must be used with caution in these patients.

The company submitted additional pooled data relating to longer-term tolerance derived from phase IIb and phase III studies during assessment of the dossier by EMEA (279 patients for at least 48 weeks and 277 patients for over 48 weeks).
In the light of all the data submitted by the company, the following observations were made:
- the incidence of adverse effects, including rashes, tended to fall over the longer term; however, an increased risk of skin reaction among patients with a history of skin rashes linked to other non-nucleoside inhibitors cannot be ruled out.
- no adverse psychiatric effect was observed in the DUET-1 and DUET-2 clinical studies; this is in contrast to efavirenz (another nucleoside inhibitor).
Monitoring requests were referred to in the risk management plan, relating in particular to possible adverse effects on the skin, liver and pancreas, hyperlipidaemia and coronary disorders.
(See SPC)

3.4. Conclusion
The virological and immunological efficacy and tolerance of INTELENCE (etravirine), in combination with a boosted protease inhibitor, darunavir/ritonavir, and an optimised background regimen (OBR) (including at least 2 antiretrovirals, with or without enfuvirtide) have been assessed in the context of two phase III studies, DUET-1 and DUET-2, versus a placebo in combination with a boosted protease inhibitor, darunavir/ritonavir, and an optimised background regimen (OBR) (including at least 2 antiretrovirals, with or without enfuvirtide).
These studies were carried out on highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

A pooled analysis of these two studies at 24 weeks was carried out.
After 24 weeks of treatment, the virological efficacy in terms of the percentage of patients with a viral load below 50 copies/ml (primary endpoint) was higher for all patients taken together in the INTELENCE than in the placebo group: 58.9 % (353 /599) versus 41.1% (248 /604) ($p<0.0001$).
This superiority was not demonstrated at 24 weeks for the primary endpoint in the sub-group of patients taking enfuvirtide for the first time.

The results observed in respect of the secondary virological and immunological endpoints (percentage of patients with a viral load <400 copies/ml and variation in the viral load and CD4 count compared to baseline) were higher for all patients taken together in the INTELENCE group than in the placebo group.

However, EMEA has asked the company to provide additional data assessing the combination of this drug with other protease inhibitors (except for tipranavir/ritonavir).

The following adverse events were most frequently reported (incidence: ≥ 1/100, < 1/10) and of at least moderate intensity (≥ grade 2) among patients being treated with INTELENCE (versus the placebo group):
- skin rash: 9.0% (vs 3.2%)
- diarrhoea: 5.2% (vs 9.6%),
- hypertriglyceridaemia: 4.7% (vs 3.0%),
- nausea: 4.7% (vs 3.5%),

5.8% of patients discontinued treatment because of adverse effects, versus 4.5% in the placebo group. The adverse effect which most often caused patients to discontinue treatment was skin rash (2.0% versus 0% in the placebo group).
In contrast to efavirenz (SUSTIVA), no psychiatric adverse effect was observed in the DUET-1 or DUET-2 clinical studies.

In the DUET-1 and DUET-2 studies, the mutations which developed most often in patients in virological failure to the treatment were: V108I, V179F, V179I, Y181C and Y181I. These mutations normally appeared along with several other mutations associated with resistance to non-nucleoside inhibitors.
The mutation to non-nucleoside inhibitors, K103N, which was the most common mutation at baseline in the DUET-1 and DUET-2 studies, was not identified as being associated with resistance to INTELENCE when present alone. The presence of this mutation alone did not affect the response observed.
This resistance data suggests that INTELENCE may have a weaker genetic barrier than other non-nucleoside inhibitors to the selection of mutations. This must be investigated in subsequent assessments, particularly with regard to the long term.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

HIV infection leads to severe reduction in quality of life and is life-threatening.

This drug aims to prevent and/or correct the immune deficiency resulting from HIV infection.
The efficacy/adverse effects ratio of this drug, administered in combination with other antiretrovirals to adult pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors, is high.

Public health benefit:
HIV-1 infection is a significant public health burden. In the population to which this indication is relevant (adult patients infected with HIV-1, highly pre-treated and with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors), the burden is moderate because the number of patients affected is lower than the total population of patients suffering from HIV in France.
There is a drug therapy need that has been identified as a priority in order to reduce AIDS-related morbidity and mortality (National programme to combat HIV-AIDS. DGS/DHOS 2005-2008).
The 24-week data available from clinical trials is insufficient to produce a direct estimate of the impact of INTELENCE on morbidity/mortality criteria or quality of life. However, in view of the biological data available (in particular, viral load efficacy at 24 weeks), the product is expected to have an impact on reducing HIV-1-releated morbidity and mortality. This impact would be, at best, low at the population scale.
In conclusion, in the light of the data available, INTELENCE is expected to have a public health benefit. This benefit is slight.

There are drug treatment alternatives to this drug for heavily pre-treated patients in the other classes of antiretrovirals.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

The efficacy and tolerance of INTELENCE in combination with darunavir/ritonavir and an optimised background regimen were compared after 24 weeks with the efficacy and tolerance of a placebo in combination with darunavir/ritonavir and an optimised background regimen in the treatment of human immunodeficiency virus infection (HIV-1) among highly

pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

The Committee considers that INTELENCE, administered in combination with the boosted protease inhibitor (darunavir/ritonavir) and optimised antiretroviral treatment, offers a moderate improvement in actual benefit (level III) in terms of virological efficacy in the management of a population limited to highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

In the absence of data relating to pre-treated patients whose characteristics are different from those observed at baseline in the DUET-1 and DUET-2 studies, INTELENCE offers no improvement in actual benefit (level V).

4.3. Therapeutic use

4.3.1 Management of people with HIV (Advanced failure and multiple regimen failure)
From: "Prise en charge médicale des personnes infectées par le VIH - Recommandations du groupe d'experts - Rapport 2008 sous la direction du Professeur Patrick YENI" [Medical management of individuals infected with HIV - Expert group recommendations - 2006 report produced under the guidance of Professor Patrick YENI] (www.sante.gouv.fr).

Key points*
(Reminder):
- Antiretroviral treatment should be started after multidisciplinary efforts to optimise compliance with treatment (AIII).
- The aim of antiretroviral therapy is to reach and maintain an undetectable viral load (< 50 copies/ml) and a CD4 lymphocyte count of > 500/mm^3 (A).
- There is no benefit in stopping an antiretroviral therapy. In patients successfully treated, temporarily discontinuing treatment results in an HIV rebound replication and a reduction in CD4 lymphocyte count, the speed of which is a function of the depth of the fall (AIIa).
- Persistent viral replication (viral load > 500 copies/ml) while on treatment exposes the patient to a risk of cumulative resistance mutations, which reduces the chances that a subsequent treatment will be effective (AIIb) and has a negative effect on CD4 lymphocyte count (AIIa).
- If a patient is in virological failure, multi-disciplinary discussions must take place (AIII). The opinion of an experienced HIV team is indispensable in situations in which there seem to be limited therapeutic options AIII).

In situations of virological failure, the expert group recommends:

- notwithstanding the type of failure (first-line, subsequent lines, including after multiple treatment failures), keep in mind the stated goal to maintain a plasma viral load of < 50 copies/ml (AIII);
- analysis of virological failure, with assessment of clinical situation, CD4 lymphocyte count and plasma viral load, compliance, toleration and any possible drug interactions (AIII);
- the patient's treatment history has to be analysed when choosing a new optimal antiretroviral therapy, and carrying out genotypic testing on treatment (AIIa). Results of any previous tests (AIII) and, if available, drug levels should also be taken into account (BIII);
- combining at least two new medicinal products, with ideally one from a therapeutic class that has not yet been used (AIIa);
- when no more than one drug remains active and the CD4 lymphocyte count is below 200/mm^3, attempting to optimise treatment using drugs that the patient is taking at the time or

has previously taken, in particular increasing dose levels of PI and/or ritonavir on the basis of pharmacological dose levels (AIII);
- not interrupting treatment for any period of time (AIa).

* Grading of the recommendations:

A: Data available justifies a strong recommendation
B: Data available justifies a moderate recommendation
C: Data available is insufficient to justify a recommendation
Levels of evidence: type of data used in the recommendations:
I a, b: At least one randomised clinical trial; meta-analysis of randomised trials
II a, b: Non-randomised clinical trials; cohort or case studies; meta-analysis of cohort or case studies
III: Expert analyses based on other data available

a: data published in a scientific journal with a review committee
b: data submitted to a scientific conference with a selection committee and available in the form of an abstract.

4.3.2. Therapeutic use of INTELENCE:

The efficacy and tolerance of INTELENCE combined with darunavir/ritonavir and optimised antiretroviral treatment have been assessed at 24 weeks in comparison with those of a placebo combined with darunavir/ritonavir and optimised antiretroviral treatment in the context of two phase III studies (-DUET-1 and DUET-2) conducted on highly pre-treated patients.

The results of these studies indicate that this drug can be used in combination with optimised treatment including a protease inhibitor on highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

INTELENCE administered in combination with other antiretrovirals of a different therapeutic class, including a protease inhibitor, is a new therapeutic alternative for highly pre-treated patients with viral strains harbouring mutations of resistance to non-nucleoside reverse transcriptase inhibitors and protease inhibitors for whom very few therapeutic options are available.

4.4. Target Population

Estimated target population

The target population has been estimated in the light of the product use indications, its therapeutic use and the data available on the basis of an estimate of the number of HIV-positive individuals who were receiving medical care and undergoing antiretroviral treatment in 2006. The target population estimate was produced for 2007.

The number of HIV-positive individuals in France at the end of 2005 has been estimated at 134,000 [100,000 to 170,000][2]. It is estimated at 140,000 in 2007[3]. It is thought that approximately 30% of HIV-positive individuals living in France are not aware of their status and cannot therefore receive medical care for their condition[4]. It can therefore be estimated that 98,000 people were diagnosed as HIV-positive in 2007. However, it is likely that some of these 98,000 people do not meet the criteria for starting antiretroviral treatment. Conversely, it can be assumed that some people with HIV infection have reached a stage of the disease that would justify antiretroviral treatment, but that they do not know that they are HIV-positive and so cannot receive treatment.

As of early 2005 the number of people with HIV infection receiving treatment was estimated at 88,000[5]. This figure increased by 2.8% between 2004 and 2005. Assuming that it continues to rise at the same rate of 2.8% a year, it can be estimated that 93,000 people were HIV-positive and receiving medical care in 2007.

82.8% of people who were HIV-positive and receiving medical care in 2006 were being treated with antiretrovirals, 11.3% were not being treated with antiretrovirals and 5.9% had previously been taking them but had stopped doing so[5]. It can therefore be estimated that 77,000 patients were undergoing treatment in 2007.

The aim of antiretroviral treatment must be to obtain and maintain a plasma viral load below 50 copies/ml[6]. The current therapeutic strategy recommends rapid therapeutic intervention in the event of virological failure when the viral load exceeds 500 copies/ml. In the event of "moderate" failure (viral load confirmed as between 50 and 500 copies/ml), practitioners are also advised to amend or intensify treatment.

In 2007, 12% of patients who had been on multiple therapy for more than 6 months had a viral load above 500 copies/ml, and 23% had a viral load above 50 copies/ml[5]. If these proportions are applied to the 77,000 patients being treated with antiretrovirals, it can be estimated that 9,200 patients have a viral load >500 copies/ml and that 8,500 have a viral load between 50 and 500 copies/ml.

The experts estimate that 50% of patients in treatment failure (viral load >500 copies/ml), are resistant to at least one NI, one NNI and more than one PI[7]. If this estimate is applied to

[2] Institut de veille sanitaire (Health Monitoring Institute). Lutte contre le VIH/sida et les infections sexuellement transmissibles en France – 10 ans de surveillance, 1996-2005 [The fight against HIV/AIDS and sexually transmitted infections in France - 10 years of monitoring]. March 2007. Available at http://www.invs.sante.fr/publications/2007/10ans_vih/index.html (consulted on 10/10/2008).

[3]UNAIDS. Report on the global HIV/AIDS epidemic 2008. Geneva: UNAIDS, 2008. Available at http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp (consulted on 05/02/2009).

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

[5] Ministry of Health. 2008 report. Prise en charge médicale des personnes infectées par le VIH » [Medical management of individuals with HIV infection] edited by Professor Patrick Yeni. Epidemiology. Available at: http://www.sante-jeunesse-sports.gouv.fr/IMG//pdf/03_Epidemiologie.pdf (consulted on 05/02/2009).

[6] Ministry of Health. 2008 report. Prise en charge médicale des personnes infectées par le VIH » [Medical management of individuals with HIV infection] edited by Professor Patrick Yeni. Antiretroviral treatment. Available at: http://www.sante-jeunesse-sports.gouv.fr/IMG//pdf/03_Epidemiologie.pdf (consulted on 05/02/2009).

7 Haute Autorité de Santé Transparency Committee Opinion. ISENTRESS 400 mg, film-coated tablet. Saint Denis : HAS. 2008. Available at: http://www.has-sante.fr/portail/jcms/c_657726/isentress (consulted on 05/02/2009).

patients in treatment failure, the target population for INTELENCE can be estimated at between **4,600 and 8,800** patients.

Future trends

This population is likely to increase over the next few years for two reasons:

- the total number of HIV-positive people is increasing as mortality among HIV-positive patients is declining thanks to better treatments, and this fall in mortality is not "offset" by a rise in the incidence of new cases.

- the number of HIV-positive patients receiving treatment is expected to increase because reducing the proportion of undiagnosed HIV-positive individuals through better targeted screening is one of the aims of public health legislation[8]

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the marketing authorisation's indications and dosages.

4.5.1. Packaging: appropriate for the prescription conditions

4.5.2. Reimbursement rate: 100 %

[8] Ministry of Health. Indicateurs de suivi de l'atteinte des 100 objectifs du rapport annexé à la loi du 9 août [Indicators used to monitor success in achieving the 100 objectives of the report appended to the Act of 9 August]