HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

11 June 2008

CELSENTRI 150 mg film-coated tablets
Aluminium and PVC blister pack(s) containing 60 tablets (CIP: 382 348-1)

CELSENTRI 300 mg film-coated tablets
Aluminium and PVC blister pack(s) containing 60 tablets (CIP: 382 349-8)

Applicant: PFIZER

maraviroc

ATC code: J05AX

List I
Medicinal product for hospital prescription only

Date of marketing Authorisation (MA): 17 September 2007

Reason for request: Inclusion on 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

maraviroc

1.2. Background

This is the first drug of a new class of antiretrovirals: CCR5 receptor antagonists.

1.3 Indication

"CELSENTRI, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced patients infected with only CCR5-tropic HIV-1 detectable.
This indication is based on safety and efficacy data from two double-blind, placebo-controlled trials in treatment-experienced patients."

1.4 Posology and method of administration

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

Before taking CELSENTRI it has to be confirmed that only CCR5-tropic HIV-1 is detectable (i.e. CXCR4 or dual/mixed tropic virus not detected) using an adequately validated and sensitive detection method on a newly drawn blood sample.

The Monogram Trofile assay was used in the clinical studies of CELSENTRI.

Other phenotypic and genotypic assays are currently being evaluated. The viral tropism cannot be safely predicted by treatment history and assessment of stored samples.

There are currently no data regarding the reuse of CELSENTRI in patients that currently have only CCR5-tropic HIV-1 detectable, but have a history of failure on CELSENTRI (or other CCR5 antagonists) with a CXCR4 or dual/mixed tropic virus.

There are no data regarding the switch from a medicinal product of a different antiretroviral class to CELSENTRI in virologically suppressed patients. Alternative treatment options should be considered.

Adults: The recommended dose of CELSENTRI is 150 mg, 300 mg or 600 mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products (see Table 2 in Section 4.5). CELSENTRI can be taken with or without food.

Children: CELSENTRI is not recommended for use in children due to lack of data on safety, efficacy and pharmacokinetics (see section 5.2 of the SPC).

Elderly: There is a limited experience in patients >65 years of age (see section 5.2) therefore CELSENTRI should be used with caution in this population.

Renal impairment: dosage adjustment is only recommended in patients with renal impairment who are receiving potent CYP3A4 inhibitors such as:

- protease inhibitors (except for tipranavir/ritonavir)
- ketoconazole, itraconazole, clarithromycin, telithromycin.

** Dual tropism: used to describe a virus that can penetrate host cells by using either CXCR4 or CCR5 as coreceptor.*
Mixed tropism: used to describe a virus population that includes viruses that use CCR5 as a coreceptor and viruses that use CXCR4 as a coreceptor and/or viruses with dual tropism

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2007)

J: General anti-infectives for systemic use
J05: Antivirals for systemic use
J05A: Direct-acting antivirals
J05AX: Other antivirals

2.2. Medicines in the same therapeutic category

There is no other CCR5 receptor antagonists in the antiviral class.

2.3. Medicines with a similar therapeutic aim

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

Protease inhibitors:
- darunavir: PREZISTA, film-coated tablets
- tipranavir: APTIVUS, soft capsules.

Fusion inhibitor:
- enfuvirtide: FUZEON, power and solvent for suspension for injection

Integrase inhibitor:
- raltegravir: ISENTRESS, tablets (proceedings currently underway)

Other antiretrovirals used in combination treatment:

Protease inhibitors:
- amprenavir: AGENERASE, capsules and oral solution
- atazanavir: REYATAZ capsules and oral powder, indicated for adults
- fosamprenavir: TELZIR, film-coated tablets and oral solution
- indinavir: CRIXIVAN capsules
- nelfinavir: VIRACEPT, film-coated tablets and oral powder
- ritonavir: NORVIR, soft capsules and oral solution, increased bioavailability of most protease inhibitors, for which reason it is used only in combination with these medicinal products.
- saquinavir mesylate: INVIRASE capsules
- lopinavir/ritonavir: KALETRA, soft capsule and oral solution

Non-nucleoside reverse transcriptase inhibitors:
- efavirenz: SUSTIVA, capsules and oral solution
- nevirapine: VIRAMUNE, tablets and oral solution

Nucleotide analogue reverse transcriptase inhibitors:
- tenofovir: VIREAD tablets

Nucleoside analogue reverse transcriptase inhibitors:
- abacavir: ZIAGEN, tablets and oral solution
- didanosine: VIDEX, capsules and powder for oral suspension
- emtricitabine: EMTRIVA, capsules and oral solution
- lamivudine: EPIVIR, tablets and oral solution
- stavudine: ZERIT, capsules and oral solution
- zidovudine: RETROVIR, capsules, oral solution and solution for injection
- abacavir/lamivudine: KIVEXA tablets
- abacavir/lamivudine/zidovudine: TRIZIVIR tablets
- zidovudine/lamivudine: COMBIVIR tablets

Nucleoside analogue and nucleotide analogue reverse transcriptase inhibitors
- emtricitabine/tenofovir: TRUVADA tablets

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The clinical trial data includes:

- 2 double-blind phase IIb/III clinical trials comparing effectiveness of CELSENTRI at 48 weeks (associated with optimised background therapy/OBT) with placebo in treatment-experienced patients for whom treatment has failed, and who are infected with only CCR5-tropic HIV-1 detectable.

. MOTIVATE 1 study (A4001027)
. MOTIVATE 2 study (A4001028)

The combined results of these studies were presented to, and accepted by, EMEA. Sub-group analyses were carried out.

- 1 exploratory double-blind phase IIb/III clinical trial comparing effectiveness of CELSENTRI (associated with optimised background therapy/OBT) in treatment-experienced patients infected with non-CCR5-tropic (CXCR4 or dual/mixed tropism*) HIV-1 at 24 weeks.

** Dual tropism: used to describe a virus that can penetrate host cells by using either CXCR4 or CCR5 as coreceptors.*
Mixed tropism: used to describe a virus population that includes viruses that use CCR5 as a coreceptor and viruses that use CXCR4 as a coreceptor and/or viruses with dual tropism.

3.1.2 MOTIVATE 1 (A4001027) and MOTIVATE 2 (A4001028) studies

Objective:

The objective of these two studies was to evaluate the virological and immunological efficacy of CELSENTRI at 48 weeks for 2 dosage regimens (150 mg or 300 mg** once or twice daily) in combination with optimised background therapy (OBT) *versus* placebo in combination with OBT (ratio 2:2:1) in patients with HIV-1 (with CCR5 tropism detected) for whom treatment has failed.

CCR5 tropism was identified using the Trofile phenotype test, carried out by Monogram Bioscience (this is the only test currently available). According to the Manufacturer, there must be a detectable (> 1000 copies/mL) viral load before this viral tropism test can be carried out. CELSENTRI can only be given after the test. The sensitivity of this test as used in clinical trials is 96% if the viral load is ≥ 1000 copies/mL, 94% if the viral load is between 500 and 1,000 copies/mL and 77% if the viral load is between 100 and 500 copies/mL. In addition, the maximum period between drawing a blood sample and receiving results at the test centre appears to be 4 weeks.

OBT was 3-6 antiretroviral drugs, selected by the investigator on the basis of genotype and phenotype resistance testing carried out during selection, medical history and tolerance.

In order to assess the antiretroviral activity of each patient's OBT, resistance scores were calculated using the result of genotype and phenotype testing carried out at inclusion, in particular the genotype sensitivity score (number of active ingredients in the background therapy was optimised according to the results of genotypic testing).

In addition, sub-group analysis was carried out on patients with an HIV-1 viral load of <50 copies/mL, based on the viral load, CD4 count at inclusion and the number of active antiretroviral agents in the optimised background therapy.

*** Dose was adjusted depending on the protease inhibitor used in the optimised background therapy (CYP3A4 inhibitors or inducers).*

Design:

Both studies were carried out using the same protocol: a placebo-controlled, double-blind study combined with OBT carried out on patients with treatment failure. The planned treatment duration was 48 weeks.
Data were analysed at 48 weeks or at treatment discontinuation.
An interim analysis was planned at 24 weeks.

Table 1: Number of treated patients in the MOTIVATE 1 and MOTIVATE 2 studies

	MOTIVATE 1			**MOTIVATE 2**		
	CELSENTRI once/day+OBT	CELSENTRI twice/day+OBT	Placebo+OBT	CELSENTRI once/day+OBT	CELSENTRI twice/day +OBT	Placebo+ OBT
Number of patients treated	**232**	**235**	**118**	**182**	**191**	**91**

A limited number of patients of ethnic origins other than Caucasian were included in these clinical studies, and as a result the available data are limited in these patient populations.

Inclusion criteria:
The main inclusion criteria were:
- Patients infected with HIV-1 with only CCR5 tropism detected
- aged ≥16,
- HIV-1 plasma viral load ≥ 5000 copies/mL
- Stable pre-study antiretroviral regimen, or on no antiretroviral treatment for at least the past 4 weeks
- Prior antiretroviral therapy with at least three of the four classes of antiretrovirals: [≥ 1 nucleoside reverse transcriptase inhibitor, ≥ 1 non-nucleoside reverse transcriptase inhibitor, ≥ 2 protease inhibitors] and/or enfuvirtide for 6 months or more.
  or
  a documented genotypic or phenotypic resistance to three of the four antiretroviral drug classes (nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, protease inhibitors or fusion inhibitors)

Treatments:
The three treatment groups were as follows:
- CELSENTRI 150 mg or 300 mg (depending on interactions with other therapies) once daily + OBT
- CELSENTRI 150 mg or 300 mg (depending on interactions with other therapies) twice daily + OBT
- Placebo + OBT

As maraviroc (CELSENTRI) is a substrate of cytochrome P450 CYP3A4, CELSENTRI dose adjustment was recommended if CELSENTRI was administered in combination with CYP3A4 inhibitors or inductors. In particular, the recommended dose when co-administered with a protease inhibitor (apart from tipranavir/ritonavir and fosamprenavir/ritonavir) was 150 mg.

Primary endpoint:
Change of the HIV-1 plasma viral load (log_{10} copies/mL) from baseline to 48 weeks.

Secondary judgement criteria, in particular:
- Percentage of patients with a HIV-1 plasma viral load < 400 copies/mL
- Percentage of patients with a plasma viral load < 50 copies/mL
- Change in CD4 count from baseline.

Population analysed:
Intention-to-treat population: randomised subjects who have received at least one dose of the therapy.

Statistical method:
Superiority hypothesis on the primary endpoint: the superiority of CELSENTRI to placebo was confirmed if the two bounds of the 97.5% confidence interval of the difference between the CELSENTRI group and the placebo group were below 0.

Results at 48 weeks: Only results from dosage given in the marketing authorisation (administration twice daily) are mentioned :

Optimised background therapy

Table 2: The most commonly used antiretrovirals in optimised background therapy were in the CELSENTRI (twice daily) and placebo groups as follows:

Number of patients	**MOTIVATE 1**		**MOTIVATE 2**	
	CELSENTRI twice/day +OBT N=235	Placebo+OBT N=118	CELSENTRI twice/day + OBT N=191	Placebo+OBT N=91
	n	n	n	n
Low-dose ritonavir	204 (87.5)	101 (86)	167 (87.5)	81 (89)
Tenofovir	207 (88)	107 (91)	148 (77.5)	69 (76)
Enfuvirtide	**107 (45.5)**	**49 (41.5)**	**75 (39.5)**	**41 (45)**
Emtricitabine	114 (48.5)	53 (45)	59 (31)	35 (38.5)
Lamivudine	90 (38)	43 (36.5)	92 (48)	38 (42)
Lopinavir	94 (40)	38 (32)	61 (32)	22 (24)
Abacavir	60 (25.5)	39 (33)	56 (29.5)	29 (32)
Didanosine	45 (19)	37 (31.5)	38 (20)	19 (21)
Amprenavir	52 (22)	34 (29)	53 (27.5)	32 (35)
Zidovudine	37 (16)	23 (19.5)	48 (25)	14 (15.5)
Atazanavir	37 (16)	20 (17)	33 (17.5)	19 (21)
Saquinavir	22 (9)	12 (10)	25 (13)	13 (14.5)
Tipranavir	**25 (11)**	**13 (11)**	**39 (20.5)**	**16 (17.5)**

Table 3: Demographic characteristics of patients included in the MOTIVATE-1 and MOTIVATE-2 studies (combined data analysis)

Demographic characteristics at inclusion	**CELSENTRI (twice daily) + OBT N = 426**	**Placebo + OBT N = 209**
Age (years) (range)	46.3 (21-73)	45.7 (29-72)
Male	89.7 %	88.5 %
Mean viral load at baseline (log_{10} copies/ml)	4.85	4.86
Mean CD4+ cell count at baseline (cells/mm^3) (range, cells/mm^3)	166.8 (2.0-820.0)	171.3 (1.0-675.0)
Viral load ≥ 100,000 copies/mL at baseline	179 (42.0 %)	84 (40.2 %)
CD4+ cell count ≤ 200 cells/mm^3 at baseline	250 (58.7 %)	118 (56.5 %)
Number (percentage) of patients with a GSS score* of:		
0	102 (23.9%)	51 (24.4%)
1	138 (32.4%)	53 (25.4%)
2	80 (18.8%)	41 (19.6%)
≥ 3	104 (24.4%)	59 (28.2%)

* GSS score: genotypic sensitivity score (number of active ARV drugs in therapy optimised according to genotypic testing)

Table 4: Pooled data from MOTIVATE-1 and MOTIVATE-2 studies at 48 weeks, for the primary and secondary endpoints

Results	**CELSENTRI twice daily + OBT N = 426**	**placebo + OBT N = 209**	**Difference between treatments[1] (Confidence interval[2])**
Change from baseline of plasma HIV-1 viral load (log_{10} copies/ml) Primary endpoint	**-1.84**	**-0.78**	**-1.05 (-1.33 ; -0.78)**
Percentage of patients with a plasma HIV-1 viral load < 400 copies/mL n(%)	239 (56.1%)	47 (22.5%)	Odds ratio: 4.76 (3.24 ; 7.00)
Percentage of patients with a plasma HIV-1 viral load < 50 copies/mL n(%)	194 (45.5%)	35 (16.7%)	Odds ratio: 4.49 (2.96 ; 6.83)
Change from baseline in CD4+ count (cells/mm^3)	+124.07	+60.93	+63.13 (44.28 ; 81.99)

[1] p<0.0001 – [2] For all endpoints relating to efficacy, confidence intervals were 95%, with the exception of the endpoint relating to change from baseline in HIV-1 viral load, which was 97.5%.

At 48 weeks, virological efficacy (in terms of reduction of viral load from baseline) of CELSENTRI + OBT (twice daily) was superior to placebo + OBT.

Analysis of results relating to the secondary endpoints (percentage of patients with a viral load of < 400 copies/mL, percentage of patients with a HIV-1 viral load < 50 copies/mL and change from baseline of CD4+ count) confirms the results seen on the primary endpoint.

In patients with treatment failure in whom tropism has changed to dual/mixed or CXCR4 tropism, mean increase in CD4 count compared with baseline was greater in the CELSENTRI + OBT twice daily group (+56 cells/mm^3) than in the placebo + OBT group (+13.8 cells/mm^3).

Sub-group analysis of pooled data from MOTIVATE-1 and MOTIVATE-2 studies, in terms of percentage of patients with an HIV-1 viral load < 50 copies/mL, according to:

- viral load at baseline (<1,000,000 copies/mL and ≥ 100,000 copies/mL)
- CD4 count at baseline
- the number of active antiretroviral agents in the optimised background therapy (see table below)

Table 5: Percentage of patients achieving HIV-1 viral load < 50 copies/mL at week 48 by sub-group (collected data from MOTIVATE-1 and MOTIVATE-2 studies, ITT population)

Sub-groups	**HIV-1 viral load < 50 copies/mL***	
	CELSENTRI twice daily + OBT N = 426	**Placebo + OBT N = 209**
Baseline HIV-1 viral load		
< 100,000 copies/mL	58.4 (142/243)	26.0 (32/123)
≥ 100,000 copies/mL	34.7 (61/176)	9.5 (8/84)
Baseline CD4+ count (cells/mm^3):		
< 50	**16.5 (14/85)**	**2.6 (1/38)**
50-100	36.4 (20/55)	12.0 (3/25)
101-200	56.7 (59/104)	21.8 (12/55)
201-350	57.8 (67/116)	21.0 (13/62)
≥ 350	72.9 (43/59)	38.5 (10/26)
Number of active ARV agents in the background treatment[1,2]:		
0	32.7 % (33/101)	2.0 % (1/50)
1	44.5 % (61/137)	7.4 % (4/54)
2	58.2 % (46/79)	31.7 % (13/41)
≥ 3	62.0 % (62/100)	38.6 % (22/57)

*** Statistical test not carried out**

[1] Patients who stopped treatment or who experienced viral escape are considered as failures.

[2] According to GSS score

Patients with a very low CD4 cells count (< 50 cells/mm^3) at baseline had less favourable results in both groups. This sub-group had markers of poor prognosis (significant resistance and high viral load at baseline).

3.1.3 Study A4001029

This study was carried out on 192 ARV-experienced patients infected with HIV-1 with non-CCR5 tropism (this patient population does not correspond to the therapeutic indication for CELSENTRI).

The exploratory study was carried out using a protocol that was similar to that used for the MOTIVATE-1 and MOTIVATE-2 studies, on patients infected with HIV-1 with non-CCR5 tropism (dual/mixed tropism or CXCR4 tropism).

This study on ARV-experienced patients infected with HIV-1 with non-CCR5 tropism, CELSENTRI + OBT was not demonstrated to be superior or non-inferior to placebo + OBT.

3.2 Resistance:

Viral escape to CELSENTRI may occur in 2 ways:

- selection of virus with detected CXCR4 tropism (coreceptor for the virus) or with dual tropism
- virus with detected CCR5 tropism with reduced sensitivity to CELSENTRI.

During the MOTIVATE-1 and MOTIVATE-2 studies: 7.6% of patients experienced a change in viral tropism (from CCR5 tropism to CXCR4 or dual/mixed tropism) between screening and inclusion (a 4-6 week period).

Changes in viral tropism were observed between inclusion and treatment failure (see table below).

Table 6: Patients in treatment failure: number and percentage of patients regardless to viral tropism detected at time of failure

Patients in treatment failure	CCR5 n (% failure)	CXCR4 or mixed n (% failure)	NR/NP n (% failure)
CELSENTRI once daily + OBT N=56/414	18(32%)	31 (55%)	7 (13%)
CELSENTRI twice daily + OBT N= 57/426	17 (30%)	32 (56%)	8 (14%)
Placebo + TFO N= 89/209	80 (90%)	4 (4%)	5 (6%)

At the time of failure, a virus using the CXCR4 coreceptor was detected in approximately 60% patients in treatment failure in the CELSENTRI + OBT groups, and in approximately 6% of patients in the placebo + OBT group. Approximately 30% of patients had CCR5 viral tropism detected.

Treatment failure was defined as one of the following virological criteria:

- increase in HIV-1 plasma viral load to a value that was at least 3 times the baseline level
- decrease in HIV-1 plasma viral load of < 0.5 $\log_{10}$ copies/mL
- a decrease in HIV-1 plasma viral load of < 1 $\log^{10}$ copies/mL in patients who had previously a reduction in plasma HIV-1 RNA of ≥ 2 $\log_{10}$ copies/mL from baseline
- an increase in plasma HIV-1 viral load of ≥ 5000 copies/mL in patients who had a plasma HIV-1 RNA level of < 400 copies/mL at two consecutive visits.

3.2.1 Patients in CELSENTRI treatment failure with a CXCR4 tropism virus detected (CCR5 at time of inclusion)

To investigate the likely origin of the CXCR4-using virus emerging on-treatment, a detailed clonal analysis was conducted on virus from 20 representative subjects (16 subjects from the CELSENTRI arms and 4 subjects from the OBT alone arm) in whom CXCR4-using virus was detected at treatment failure.

This analysis indicated that CXCR4-virus emerged from a pre-existing CXCR4-using reservoir not detected at baseline, rather than from mutation of CCR5-tropic virus present at baseline.

An analysis of tropism following treatment failure with CELSENTRI with CXCR4-using emerging virus, has shown that the virus population reverted back to CCR5 tropism in the majority of patients during follow up after discontinuation of CELSENTRI.

Out of 44 patients studied, the virus population in 30 reverted back to exclusively CCR5-tropism during a median follow-up of 203 days; 14 patients continued to have detectable CXCR4-using virus. However, the follow-up period in these patients was shorter: median of 16 days" (extract from SPC).

At treatment failure, the resistance profile to other antiretroviral drugs in the population with detected CXCR4 tropism seemed similar to those in the population with CCR5 tropism detected at baseline, based on available data.

3.2.2 Patients in CELSENTRI treatment failure with a CCR5 tropism virus detected (CCR5 at time of inclusion)

Phenotypic resistance:
In patients with CCR5-tropic virus at time of treatment failure with CELSENTRI, 15 out of 36 patients had virus with reduced sensitivity to maraviroc.
In the remaining 21 patients, there was no evidence of virus with reduced sensitivity.

As a result, continuing CELSENTRI treatment after failure cannot be generally recommended, regardless of the viral tropism.

Genotypic resistance:
The resistance profile of viruses in treatment-experienced patients has not yet been completely defined. Specific mutations associated with reduced sensitivity to maraviroc have been identified in the viruses of 5 patients, but each patient had a unique profile of mutations (extract from SPC).

3.3 Adverse effects

Assessment of treatment related adverse reactions is based on pooled data at the recommended dose from two phase IIb/III studies (MOTIVATE 1 and MOTIVATE 2) in CCR5-tropic HIV-1 infected patients.

The number of treatment related adverse events was similar in both groups (50% in the CELSENTRI + OBT groups compared with 44.5% in the placebo + OBT group).
Rates of treatment discontinuation due to treatment related adverse events were similar in both groups (2.3% in the CELSENTRI + OBT group versus 2.4% in the placebo + OBT group).

The most frequently reported adverse effects during the phase IIb/III studies at the recommended dose were nausea, headache and diarrhea.

The adverse effects occurring more frequently in the CELSENTRI + OBT group than in the placebo +OBT group, with an incidence > 1% were as follows:
Incidence ≥ 1/100 and < 1/10:
- alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, weight decreased
- dizziness, paraesthesia, dysgeusia, somnolence
- cough
- vomiting, abdominal pain, abdominal distension, dyspepsia, constipation
- rash, pruritus
- muscle spasms, back pain
- asthenia
- insomnia

Incidence ≥ 1/10:
- nausea

Uncommon (< 1%) adverse effects occurring in patients in the CELSENTRI group during the phase III studies were as follows:
- myocardial infarction, myocardial ischaemia
- pancytopenia, neutropenia, lymphadenopathy
- loss of consciousness, epilepsy, petit mal epilepsy, convulsion, facial palsy, polyneuropathy, areflexia
- respiratory distress, bronchospasm
- pancreatitis, rectal haemorrhage
- renal failure, polyuria
- myositis
- pneumonia
- hepatic cirrhosis
- hallucination

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.

Table 7: Laboratory abnormalities
Grade 3-4 abnormalities (ACTG Criteria) based on the maximum shift in laboratory test values without considering the baseline values.
(pooled analysis, up to 48 weeks)

Laboratory parameter	**Limit**	**CELSENTRI + OBT twice daily N = 421* (%)**	**Placebo + OBT N = 207* (%)**
Aspartate aminotransferase	> 5.0 x ULN	4.5	2.9
Alanine aminotransferase	> 5.0 x ULN	2.4	3.4
Total bilirubin	> 5.0 x ULN	5.7	5.3
Amylase	> 2.0 x ULN	5.5	5.8
Lipase	> 2.0 x ULN	4.9	6.3
Absolute neutrophil count	< 750/mm^3	3.8	1.9

ULN: Upper Limit of Normal
* Percentages based on total patients evaluated for each laboratory parameter

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors (advanced HIV disease or long-term exposure to combination antiretroviral therapy). The frequency of this is unknown.

Potential effect on immunity: CCR5 antagonists could potentially impair the immune response to certain infections. This should be taken into consideration when treating infections such as active tuberculosis and invasive fungal infection. The incidence of AIDS-defining infections was similar between CELSENTRI and placebo arms of the clinical trials.

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 and cause serious clinical conditions, or aggravation of symptoms.

A case of possible CELSENTRI-induced hepatotoxicity with allergic features has been reported in a study in healthy volunteers.Moreover, an increase in hepatic adverse reactions with CELSENTRI was observed during studies of treatment-experienced subjects with HIV infection, although there was no overall increase in ACTG grades 3-4 liver function test abnormalities.

Cardiovascular safety: limited data exist concerning the use of CELSENTRI in patients with severe cardiovascular disease. Therefore specific caution should be exercised when treating these patients with CELSENTRI.

3.2. Conclusion

The efficacy of CELSENTRI in combination with optimised background therapy in patients infected with CCR5-tropic HIV-1 in treatment failure was assessed in two phase IIb/III clinical trials (MOTIVATE 1 and MOTIVATE 2). A pooled analysis of both studies at 48 weeks was carried out.

Assessment of viral CCR5 tropism was carried out using the only currently available test.
According to the manufacturer, there must be a detectable (> 1000 copies/mL) viral load before this test can be carried out. CELSENTRI can only be given after the test. The sensitivity of this test as used in clinical trials is 96% if the viral load is ≥ 1,000 copies/mL, 94% if the viral load is between 500 and 1000 copies/mL and 77% if the viral load is between 100 and 500 copies/mL. Moreover, the maximum period between drawing a blood sample and receiving the results at the test centre appears to be 4 weeks.Accordingly, the Committee wishes to emphasise that viral tropism may change in some patients during the potential 4-week period between testing and results.

At 48 weeks, virological efficacy (in terms of reduction of viral load from baseline) of CELSENTRI + OBT (twice daily) was greater than that of placebo + OBT: the difference between the two therapies (log_{10} copies/mL): -1,05 [-1,33 ;-0,78].

At 48 weeks, analysis of results for the secondary endpoints (percentage of patients with a viral load of < 400 copies/mL, percentage of patients with a HIV-1 viral load < 50 copies/mL and change from baseline of CD4+ count) confirms the results seen on the primary endpoint.

CXCR4-tropic virus was detected in approximately 60% of subjects who failed treatment on CELSENTRI, as compared to 6% of subjects who experienced treatment failure in the placebo arm.

A detailed clonal analysis was conducted on virus from 20 representative subjects (16 subjects from the CELSENTRI arms and 4 subjects from the placebo arm), and showed that CXCR4-virus emerged from a pre-existing CXCR4-using reservoir not detected at baseline, rather than from mutation of CCR5-tropic virus present at baseline.

In 44 patients who failed CELSENTRI therapy with CXCR4-using virus, tropism analysis has shown that the virus population reverted back to CCR5 tropism in the majority of patients during follow up after discontinuation of CELSENTRI.

The resistance profile of viruses in treatment-experienced patients has not yet been completely defined.

The most frequently reported adverse effects during the phase IIb/III studies at the recommended dose were nausea, headache and diarrhoea.

Opportunistic infections, AIDS and cancer were equally frequent in both groups. CCR5 antagonists could potentially impair the immune response to certain infections. This must be taken into consideration when treating these infections.

A higher frequency of hepatic adverse reactions was observed in the CELSENTRI arm, although there was no overall increase in grade 3-4 liver function test abnormalities.

Limited data exist concerning the use of CELSENTRI in patients with severe cardiovascular disease.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

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

This medicinal product aims to prevent and/or correct the immune system deficit caused by HIV infection.

This product has a high efficacy/adverse effect ratio, when administered in combination with other antiretrovirals in ARV-experienced adult patients in treatment failure and infected with detected CCR5-tropic HIV-1.

Public health benefit:

HIV infection is a significant public health burden. The population for whom CELSENTRI is indicated (ARV-experienced adult patients with CCR5-tropic HIV-1), represents only a modest burden, because of small number of patients concerned in comparison with the total population of patients living with HIV in France.

A reduction in morbidity and mortality caused by AIDS, in particular through the provision of new effective therapies in case of resistance or failure of existing therapies.

The available data do not make it possible directly to assess the impact of CELSENTRI on morbidity, mortality or quality-of-life criteria.

Nevertheless,considering the results on the reduction of viral load and CD4 count increase, a low impact theory can be expected on the reduction of morbidity and mortality related to HIV infection. It is not certain that this impact would be translated into real life, given:

- some incertainties in the identification of patients eligible for treatment only in view of possible changes in viral tropism during the period necessary to obtain results from the only currently available test tropism (period for up to 4 weeks);
- the lack of long-term follow-up data for patients treated with CELSENTRI.

With our current knowledge, it is not possible to assume from the response obtained that CELSENTRI could meet a public health need.

Accordingly, CELSENTRI is not expected to benefit public health.

Alternative medicinal products exist to these drugs for ARV-experienced patients in treatment failure infected with only CCR5-tropic HIV-1.

The actual medical benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit

In the treatment of infection with HIV-1 in adult patients in antiretroviral treatment failure with CCR5-tropic HIV-1, the efficacy and safety of CELSENTRI (in combination with optimised background antiretroviral therapy) were compared to placebo (in combination with optimised background antiretroviral therapy) at 48 weeks.

Bearing in mind on the one hand:
- the benefit of the availability of a drug in a new antiretroviral class: CCR5 receptor antagonists
- the fact that it was virologically more effective than the comparator

but on the other hand:
- some uncertainties in the identification of patients eligible for treatment
- the lack of long-term follow-up data of patients in treatment failure with CELSENTRI, in particular concerning the viral escape mechanisms and their consequences.

The Committee considers that CELSENTRI, in combination with OBT, provides a minor improvement in actual benefit (IAB level IV) in terms of virological efficacy in management of a limited population of adult patients in treatment failure with a viral load of ≥ 1000 copies/mL,
- who had antiretroviral-class experience greater than or equal to 6 months with at least three of the four classes of antiretrovirals: [≥ 1 nucleoside reverse transcriptase inhibitor, ≥ 1 non-nucleoside reverse transcriptase inhibitor, ≥ 2 protease inhibitors] and/or enfuvirtide
- or documented genotypic or phenotypic resistance to three of the four antiretroviral drug classes (nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, protease inhibitors or fusion inhibitors).

4.3. Therapeutic use

Recommendations relating to the management of people infected with HIV (the YENI report) were published in 2006; these recommendations are currently being updated for 2008.

4.3.1 Management of people with HIV (Advanced failure and multiple regimen failure)

From: “Treatment for adult HIV infection – Recommendations of the group of experts – 2006 report, led by Professor Patrick Yeni” (www.sante.gouv.fr).

STRENGTHS[1]

- Antiretroviral treatment should be started after multidisciplinary efforts to optimise compliance with treatment (AIII).
- The aim of antiretroviral therapy is to achieve 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 antiretroviral therapy. In patients with successful treatment, temporarily discontinuing treatment results in a rebound replication of HIV 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 treatment failure, multi-disciplinary discussions must take place (AIII). The opinion of an experienced HIV team is indispensable in situations where therapeutic options appear limited (AIII).

In situations of virological failure, the expert group recommends (*see table 6*):

- Whatever the type of failure is (first-line, next 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, safety and any possible drug interactions (AIII).
- Bearing in mind the whole of the patient's treatment history 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).
- If there are no resistance mutations in treatment, evaluate and optimise compliance as a priority, with the aid of therapeutic drug monitoring (BIII).
- Combining at least two new medicinal products, with ideally one from a therapeutic class that has not been used yet (AIIa).

[1] Grading recommendations:
A: Strong evidence to support the recommendation
B: Moderate evidence to support the recommendation
C: Insufficient evidence to support the recommendation
Quality of evidence: type of data used in recommendations:
Ia, Ib: Evidence from 1 or more published randomised, controlled clinical trials
IIa, IIb: Evidence from nonrandomised clinical trials; cohort or case-control studies; meta-analyses of cohort or case-control studies
III: Recommendation based on the panel's analysis of the accumulated available evidence

a: data published in the peer-reviewed literature
b: data presented in abstract form at peer-reviewed scientific meetings

Table 8: Summary of suggested treatment strategies in cases of virological failure

Virological failure and/or resistance to	**Treatment usually recommended**
NRTI and NNRTI	2 NRTI (chosen by genotype) + PI/r (no clinical trials)
NRTI and PI/r	*Preferred:* 2 NRTI (chosen by genotype) + [ATV/r or FPV/r or LPV/r] according to genotype [111,112] 2 NRTI (chosen by genotype) + NNRTI (provided that the 2 chosen NRTIs are "fully active") *Alternative (in particular after the 2nd failure):* 2 NRTI (chosen by genotype) + [LPV/r or FPV/r]+NNRTI (requires measurement of drug levels)
NRTI, NNRTI and PI/r	Enfuvirtide + PI/r ± NRTI (depending on current and previous genotypes) *Choice of PI/r:* active, depending on result of resistance genotype: Above all, TPV/r or DRV/r if there is definite or possible resistance to other PI/r.

4.3.2. Therapeutic use of CELSENTRI

Efficacy and safety of CELSENTRI in combination with OBT were assessed at 48 weeks in comparison to a placebo in combination with OBT, as part of two phase IIb/III clinical trials (MOTIVATE-1 and MOTIVATE-2).

Given the results observed in these studies, CELSENTRI in combination with OBT may be used in adult patients in antiretroviral treatment failure who are infected with HIV-1 with only CCR5 tropism detected.

As the prevalence of CCR5-tropic HIV-1 virusdecreases during the evolution of the disease, the more immunodepressed the patient is, the more likely he/she is to have CXCR4-tropic virus. As a result of this, the precise role for CELSENTRI is not well-determined yet.

4.4. Target Population

The target population for the medicinal product CELSENTRI is the population of adult treatment-experienced patients with a viral load ≥ 1,000 copies/mL and treated in hospital, who have had:

- antiretroviral-class experience greater than or equal to 6 months with at least three of the four classes of antiretrovirals: (≥ 1 nucleoside reverse transcriptase inhibitor, ≥ 1 non-nucleoside reverse transcriptase inhibitor, ≥ 2 protease inhibitors and/or enfuvirtide).
- or documented genotypic or phenotypic resistance to three of the four antiretroviral drug classes (nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, protease inhibitors or fusion inhibitors).

According to the report by the French national health monitoring institute (InVS) about HIV/AIDS monitoring[2], the number of HIV-positive people in France at the end of 2005 can be estimated using:

- the back-calculation method, which gives 106,000 patients [67,000-175,000],
- the direct method, which gives 134,000 patients [100,000-170,000].

Among these patients, 98.4% are reported to have been infected with the HIV-1 virus.
Among these patients, approximately 80.5% were reported to be on treatment[3]
Only 21.3% of patients on treatment were reported to have a viral load of ≥ 1,000 copies/ml, and approximately 55% were resistant to at least one NRTI, one NNRTI and more than one PI[4].
Among these patients, approximately 50% had CCR5 viral tropism detected [5].

2 INVS – HIV/AIDS and sexually transmitted infections in France – 10 years of monitoring, 1996-2005
3 Treatment for adult HIV infection – Recommendations of the group of experts – 2006 report, led by Professor Patrick Yeni (www.sante.gouv.fr).
4 Costagliola *et al.* Prevalence of HIV-1 Drug Resistance in Treated Patients: a French Nationwide Study. J Acquir Immune Defic Syndr. 2007;46 :,
5 Expert opinion

On the basis of these data, the target population for CELSENTRI can be estimated at 5000 or 6000 patients, depending on the method used to estimate the HIV prevalence (back-calculation *versus* direct).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the new indication and at the posology in the Marketing Authorisation.

The Committee seeks to emphasise the following points:
- availability of only one test on the market at the time this opinion was given by the Committee, pending the availability of other viral tropism tests currently being assessed
- test that should be carried out in safety and quality considerations
- the period between testing and availability of results, as announced by Pfizer,

are essential conditions for this medicinal product to be used properly.

This product should be reassessed by the Committee as soon as the viral tropism tests that are currently being evaluated are to be made generally available.

4.5.1. Packaging: the packaging is appropriate to prescription requirements

4.5.2. Reimbursement rate: 100%