HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

4 July 2007

PREZISTA 300 mg, film-coated tablets
Bottle of 120 tablets (CIP code: 378 318-4)

Applicant : JANSSEN-CILAG

darunavir

List I
Initial annual hospital prescription
Unrestricted renewal

Date of Marketing Authorisation (MA): 12/02/2007
Conditional MA

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

Health Technology Assessment Division

1 PROPERTIES OF THE MEDICINAL PRODUCT

1.1. Active substance:

Darunavir

1.2. Background

This is a new antiretroviral drug in the HIV-I protease inhibitor class.

1.3. Indication

PREZISTA, co-administered with 100 mg of ritonavir, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor (PI).
This indication is based on week-24 analyses of virological and immunological response from 2 controlled dose range finding Phase II trials and additional data from uncontrolled studies (see paragraph 5.1 of the SPC).

In deciding to initiate treatment with PREZISTA co-administered with 100 mg ritonavir careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use of PREZISTA.

1.4. Dosage

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

PREZISTA must always be given orally with low dose ritonavir as a pharmacokinetic enhancer and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must therefore be consulted prior to initiation of therapy with PREZISTA

Adults: The recommended dose of PREZISTA is 600 mg twice daily (b.i.d.) taken with ritonavir 100 mg b.i.d.and with food.. The type of food does not affect the exposure to darunavir.

Children and adolescents: the use of PREZISTA is not recommended in children and adolescents in view of the absence of data regarding safety, efficacy and pharmacokinetics for those age groups.

Elderly patients: Limited information is available for this population.

Liver failure: Darunavir is metabolised by the hepatic system.. Severe hepatic impairment could therefore increase exposure to darunavir, and a worsening of its safety profile.PREZISTA should therefore be used with caution in patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B), and should not be used in patients with severe hepatic impairment (Child-Pugh class C) (see paragraphs 4.3, 4.4 and 5.2 of the SPC).

Kidney failure: No dose adjustment is required in patients with renal impairment (see paragraphs 4.4 and 5.2 of the SPC).

In case a dose of PREZISTA and/or ritonavir was missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of PREZISTA and ritonavir with food as soon as possible. If this was noticed later than 6 hours of the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule. (see SmPC)

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

J	GENERAL ANTIINFECTIVE FOR SYSTEMIC USE
J05	ANTIVIRALS FOR SYSTEMIC USE
J05A	DIRECT-ACTING ANTIVIRALS
J05AE	PROTEASE INHIBITORS
J05A-E010	darunavir

2.2. Medicines in the same therapeutic category

2.2.1 Comparator medicines

Protease inhibitors in combination with antiretrovirals in heavily pre-treated adult patients:

- tipranavir: APTIVUS soft capsules, indicated for adults

Other protease inhibitors in combination with antiretrovirals in adult patients*:

- Indinavir: CRIXIVAN capsules,
- nelfinavir: VIRACEPT film-coated tablets and oral powder
- amprenavir: AGENERASE capsules and oral solution
- saquinavir mesylate: INVIRASE capsules
- lopinavir associated with ritonavir: KALETRA soft capsule and oral solution
- fosamprenavir: TELZIR film-coated tablets and oral solution,
- atazanavir: REYATAZ capsules or oral powder, indicated for adults

- ritonavir: NORVIR soft capsules and oral solution increases the bioavailability of most protease inhibitors, which explains why it is only used in association with these drugs.

* the indications of these protease inhibitors are not identical to those of the proprietary product PREZISTA

2.2.2 Competitor evaluation

None.

2.3. Medicines with a similar therapeutic aim

- Non-nucleoside reverse transcriptase inhibitors (NNRTI) in the course of combined treatment with antiretrovirals

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

- Nucleoside reverse transcriptase inhibitor in the course of combined treatment with antiretrovirals

- tenofovir: VIREAD tablets

- Nucleoside reverse transcriptase inhibitors (NRTI) in the course of combined treatment with antiretrovirals:

- abacavir: ZIAGEN tablets and oral solution
- didanosine: VIDEX capsules and powder for oral suspension
- emtricitabine: EMTRIVA capsules and oral solution
- stavudine: ZERIT capsules and oral solution
- zidovudine: RETROVIR capsules, and oral and injectable solution

- lamivudine: EPIVIR tablets and oral solution
- abacavir - lamivudine: KIVEXA tablets
- abacavir - lamivudine - zidovudine: TRIZIVIR tablets
- lamivudine - zidovudine: COMBIVIR tablets.

- Nucleoside and nucleotide reverse transcriptase inhibitor
emtricitabine – tenofovir: TRUVADA tablets
- Fusion inhibitor:
enfuvirtide FUZEON powder and solvent for injectable suspension (patients unresponsive to a treatment including at least one drug in 3 antiretroviral classes).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The clinical dossier comprises:

- 2 open-label* comparative phase II b trials: the POWER 1 trial (TMC114-C213) and POWER 2 trial (TMC114-C202) conducted within HIV-1 infected patients, pre-treated with at least three classes of antiretrovirals. The results of the pooled analysis of the trials have been submitted to and accepted by EMEA.

- 2 non-comparative studies (trials TMC114-C208 and TMC114-C215) in patients with HIV, pre-treated with at least three classes of antiretrovirals.
The results of the pooled data of the trials have been submitted (POWER 3 analysis).

3.1.2 POWER 1 and POWER 2 trials
3.1.3 TMC114-C208 and TMC114-C215 trials (POWER 3 analysis):
3.1.4 Analysis in sub-groups of grouped 24-week data from the POWER 1, POWER 2 and POWER 3 trials.

3.1.2 POWER 1 and POWER 2 trials

The initial objective of the two trials was to evaluate the dose-response relationship of the antiviral activity of 4 PREZISTA/ritonavir dosage regimens (400/100 mg u.i.d., 400/100mg b.i.d., 800/100mg u.i.d., and 600/100 mg b.i.d.) at 24 weeks, compared with a comparator group comprising a protease inhibitor, co-administered with ritonavir, to determine the dose to be recommended.
Following the intermediate results in patients treated with PREZISTA, the protocol was amended and the primary objective became to compare the efficacy of each dosage regimen of PREZISTA/ritonavir with that of the comparator group (open-label randomised trial).

- the patients in the treatment group received PREZISTA/ritonavir
- the patients in the comparator group received the optimised protease inhibitor(s) selected, co-administered with ritonavir.

The patients in the treatment group and the comparator group also received an optimised background regimen (OBR))**.

* apart from the dose, which was not known to the investigator
** the (associated) individually optimised background regimen (OBR)) were established before randomisation, and included at least 2 nucleoside inhibitors with or without enfuvirtide (FUZEON)

The 2 trials were conducted in 2 stages:

- a dose-finding stage, the primary objective of which was to compare the virological efficacy of each dosage regimen (4 PREZISTA dosage regimens) with that of a comparator group during a 24-week period
- a follow-up stage (scheduled for 48 weeks and extended to 144 weeks following an amendment to the protocol) during which patients who had been treated with

PREZISTA at the first stage of the trial received the recommended dose of 600 mg (determined at the end of the dose-finding stage) twice a day in combination with 100 mg of ritonavir.

Before randomisation, the following steps were taken:
- genotype analysis of the viruses of all patients, and interpretation of their sensitivity to antiretrovirals
- selection of the optimal comparative protease inhibitor (or 2 protease inhibitors) on the basis of the genotype of the virus and the case history of each patient,
- optimisation of the associated treatment (optimised background regimen (OBR))) established for each patient on the basis of genotype resistance tests and the patient's history, comprising at least 2 nucleoside inhibitors with or without enfuvirtide / FUZEON in the combined treatment.

Inclusion criteria:
Adult patients infected with HIV-1, pre-treated with at least 3 classes of antiretrovirals, who had received at least one protease inhibitor for at least 3 months, including a protease inhibitor for at least 8 weeks, and had been exposed to more than 2 nucleoside inhibitors, with:
- viral load (VL) ≥ 1,000 copies/ml (3 log10 copies/ml).
- genotype profile: patients having at least 1 primary mutation in the protease gene among 30N, 46I/L, 48V, 50V, 82A/F/T/S, 84V or 90M.

Treatments under study:
POWER 1 trial **(**N= 318):
- PREZISTA / ritonavir groups in combination with optimised primary treatment (OPT).

dose 400/100 mg once a day: N= 64
dose 800/100 mg once a day: N= 63
dose 400/100 mg twice a day: N= 63
dose 600/100 mg twice a day: N= 65
- comparator group PI/ritonavir N= 63

POWER 2 trial (N= 278):
- PREZISTA / ritonavir groups in combination with optimised primary treatment (OPT).

dose 400/100 mg once a day: N= (57*)*
dose 800/100 mg once a day: N=(56)
dose 400/100 mg twice a day: N=(55)
dose 600/100 mg twice a day: N= (57)
- comparator group PI/ritonavir: N=(53)

The scheduled duration of treatment was 24 weeks. A supplementary analysis of the results was conducted after 48 weeks on patients pre-treated with PREZISTA/ ritonavir (600 mg/100 mg twice a day). During this follow-up stage, the patients were treated with the recommended dose of PREZISTA / ritonavir only (600 mg/100 mg twice a day).

Primary endpoint:
The initial primary endpoint was a variation in VL in the 24th week compared with the baseline value. This endpoint was modified by amendment.
The primary endpoint chosen for the analysis was the percentage of patients with a VL reduction of ≥ 1 log10 in the 24th week compared with the baseline value.
Secondary endpoints, especially:
- Variation in VL compared with baseline value,
- Variation in CD4 count compared with baseline value
- Percentage of patients with a VL < 400 copies/ml
- Percentage of patients with a VL < 50 copies/ml

Baseline patient characteristics in the POWER 1 and POWER 2 trials:

Disease Baseline characteristics	POWER 1 N = 318	POWER 2 N = 278
VL log_{10} (mean)	4,48	4,66
CD4/mm^3 count (median)	179	106
Duration of HIV infection (years), (mean)	11,6	13,2
Prior antiretroviral treatments, n (%)		
Number of PIs≥ 2, n (%)	307 (96,5)	271 (97,5)
Number of NNRTIs≥ 1, n (%)	302 (95,0)	270 (97,1)
Number of NRTIs≥ 4, n (%)	304 (95,6)	263 (94,6)
Fusion inhibitors: 1, n (%)	34 (10,7)	63 (22,7)
Genotype data		
Number of patients with ≥ 3 primary resistance mutations to PIs, n (%)	182 (66,2)	178 (56,0)
Number (median) of primary resistance mutations to PIs, median(interval)	3 (0 ; 6)	3 (0 ; 5)
Number (median) of mutations associated with resistance to PIs, median(interval)	8 (0 ;13)	8 (1 ; 13)
Co-infection with hepatitis B or C		
n (%) co-infected	44 (13,9)	6 (2,2)

NRTI : nucleoside reverse transcriptase inhibitor NNRTI: non-nucleoside reverse transcriptase inhibitor PI: protease inhibitor

The population included in the POWER 1 trial was at a less advanced stage of HIV 1 infection than the population included in the POWER 2 trial.

POWER 1 trial:
- 57% to 70% of patients were resistant to all the PIs on the market; 42% to 50% of them had not more than 1 active drug in their optimised combined treatment.
- 66.7% of patients were resistant to the protease inhibitor selected by the investigator in the comparator group.
- the percentage of patients resistant to all the antiretrovirals selected by the investigator in the optimised primary treatment (OPT) was 20.3% in the PREZISTA/ritonavir 600/100 mg twice a day group and 14.8% in the comparator group.

POWER 2 trial:
- 67% to 77% of patients were resistant to all the PIs on the market; 52% to 59% of them had not more than 1 active molecule in their optimised combined treatment.
- 78.8% of the patients were resistant to the protease inhibitor selected by the investigator in the comparator group.
- the percentage of patients resistant to all the antiretrovirals selected by the investigator in the optimised background regimen (OBR) was 27.3% in the PREZISTA/ritonavir 600/100 mg twice a day group and 15.4% in the comparator group.

Results (POWER 1 and POWER 2)
The data from the 2 trials were pooled and accepted by EMEA;
The comparison in " intent to treat analysis " was performed on the PREZISTA/ritonavir 600/100 mg twice a day (recommended dose) group and the comparator group.

I - Primary endpoint: treatment response at 24 weeks

Number and percentage of patients presenting a VL reduction of ≥ 1 log10 compared with baseline at 24 weeks:

Results at 24 weeks	**PREZISTA/ritonavir 600/100 mg twice a day N=131***	**Comparator (optimised selected PI(s)/ritonavir) N=124***	**Difference in treatment**
Reduction of ≥ 1 log_{10} in HIV RNA compared with baseline			
n (%) 95% CI (%)	**92 (70%)** **(62 ; 78)**	**26 (21%)** **(14 ; 28)**	**49%**** **(39 ; 60)*****

* Analysis of 24/09/05 PREZISTA group: N =65 patients (POWER 1) and 66 patients (POWER 2)
comparator group: N = 63 patients (POWER 1) and 61 patients (POWER 1)

** p<0.001

*** confidence interval of the difference observed between the responses expressed as a percentage of responder patients

II - Secondary endpoints: response to treatment after 24 weeks

- Change in VL compared with baseline value,
- Change in CD4+ cellcount compared with baseline value
- Proportion of patients with a viral load < 400 copies/ml
- proportion of patients with a viral load < 50 copies/ml

Results at24 weeks	**PREZISTA/ritonavir 600/100 mg twice a day N=131***	**Comparator (optimised selected PI(s)/ritonavir) N=124***	**Difference in treatment**
Change in VL compared with baseline value (log_{10}copies/ml) (95% CI)	- 1,89 (-2,11 ; -1,68)	- 0,48 (-0,65 ; -0,31)	-1,41 (-1,67 ; -1,14)**
Change in $CD4/mm^3$ count compared with baseline and (95% CI)	92 (73 ; -112)	17(0 ; 35)	75 (49 ; 101)**
HIV RNA < 400 copies/ml n(%) 95% CI (%)	82 (63%) (54 ; 71)	23 (19%) 12 ; 25)	44% (33 ; 55)**
HIV RNA < 50 copies/ml n(%) 95% CI (%)	59 (45%) (37 ; 54)	15 (12%) (7 ; 18)	33% (23 ; 43)**

* Analysis of 24/09/05 PREZISTA group: N =65 patients (POWER 1) and 66 patients (POWER 2)
comparator group: N = 63 patients (POWER 1) and 61 patients (POWER 1)

** confidence interval of the difference observed between the responses expressed as a percentage of responders

At 24 weeks the virological efficacy (proportion of patients with a VL reduction of ≥ 1 log10) was superior in the PREZISTA group compared tocomparator group comprising one or two selected optimised PIs with or without enfuvirtide included in the associated optimised treatment (70% vs. 21%).

The virological and immunological responses studied at 24 weeks on the secondary endpoints (changes in VL and CD4 count compared with baseline value, proportion of patients with VL < 400 copies/ml and <50 copies/ml) were in favour of PREZISTA.

Long-term results:
Supplementary virological efficacy data after 48 weeks for the patients treated in the PREZISTA/ritonavir (600/100 mg twice a day) groups were provided
The data for the POWER 1 and POWER 2 trials have been pooled:
- the proportion of patients with a VL reduction of ≥ 1 log10 decreased between the week 24 [70% (92/131)] and week 48 [61% (67/110)].
- the proportion of patients with a VL of < 50 copies/ml was comparable at 24 weeks [45% (59/131)] and 48 weeks [46% (50/110)].

The intermediate results at 72 weeks, provided by the manufacturer, demonstrated that the virological efficacy observed at 24 weeks was maintained in terms of the proportion of patients with a VL of < 50 copies/ml.

3.1.3 TMC114-C208 and TMC114-C215 trials (POWER 3 analysis):

Two non-comparative trials (TMC114-C208 and TMC114-C215) were conducted in HIV infected patients pre-treated with at least three classes of antiretrovirals.
These trials, which were initially designed as extension studies of the POWER 1 and POWER 2 trials, were extended to new patients. Due to the limited number of patients recruited in TMC114-C208 trial and its similarity with TMC114-C215 protocol, their results have been combined (POWER 3 analysis).
The patient inclusion criteria were identical, and the baseline characteristics were comparable to those of the POWER 1 and POWER 2 trials. The data of the 2 trials have been pooled.

A total of 460 patients were included. Only the 327 new patients included, who immediately received PREZISTA / ritonavir at the dose of 600/100 mg twice a day (combined with an optimised antiretroviral treatment), were included in the POWER 3 analysis.

Results for the following endpoints:
- primary endpoint: number and proportion of patients with a viral load reduction of ≥ 1 log10 compared to baseline value at 24 weeks
- secondary endpoints:
  - . change in VL compared with baseline value,
  - . changein CD4 count compared with baseline value
  - . Proportion of patients with VL < 400 copies/ml
  - . Proportion of patients with VL < 50 copies/ml

Results at 24 weeks	PREZISTA/ritonavir 600/100 mg twice a day n=327
Reduction of ≥ 1 log_{10} in HIV RNA compared to baseline n (%) 95% CI (%)	**217 (66%) (61 ; 71)**
change in VL compared to baseline value (log_{10}copies/ml) 95% CI (%)	- 1,73 (-1,87 ; -1,58)
change in CD4+ count compared with baseline value (x $106^{/1)}$ and 95% CI (%)	80 (69 ; 90)
HIV RNA< 400 copies/ml n(%) 95% CI (%)	193 (59%) (54 ; 64)
HIV RNA< 50 copies/ml n(%) 95% CI (%)	141 (43%) (38 ; 48)

The additional data at 48 weeks suggest that the virological response obtained at 24 weeks was maintained:

- the proportion of patients with a reduction of VL ≥ 1 log_{10} compared with the baseline value was 60.8% (197/324).
- the proportion of patients with VL < 50 copies/ml was 45.1% (146/324).

3.1.4 Sub group analysis of the pooled data from POWER 1, POWER 2 and POWER 3 trials at 24 weeks in terms of virological response in patients in the PREZISTA/ritonavir 600/100 mg twice a day groups

Subgroups of patients were set up *a posteriori*, mainly on the basis of:

. the number of mutations associated with a reduction in virological response to darunavir (V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V)

. the number of mutations associated with a reduction in virological response to protease inhibitors

. co-infection by the hepatitis B or C virus

- on the basis of the number of mutations associated with a reduction in virological response to darunavir (mutations: V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V)

pooled data from the POWER 1, POWER 2 and POWER 3 trials in the PREZISTA / ritonavir (600/100 mg, twice a day) groups: per protocol analysis

Number of mutations at baseline (associated with a reduction in virological response to darunavir)*	**proportion of patients with a reduction of ≥ 1 log_{10} N= 373**	proportion of patients with VL < 50 copies/ml N=373	change in viral load in log_{10} compared with baseline value
0-2	**78% (213/274)**	50% (138/274)	-2,1
3	**45% (26/58)**	22% (13/58)	-1,12
≥ 4	**27% (11/41)**	10% (4/41)	-0,46

* Number of mutations among the list of mutations associated with a reduction in response to PREZISTA / ritonavir (V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V

The presence at baseline of 3 or more mutations among the mutations (V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V) has been associated with a reduction in virological response to PREZISTA combined with 100 mg of ritonavir.

- on the basis of the number of mutations associated with a reduction in virological response to protease inhibitors:
pooled data from the POWER 1, POWER 2 and POWER 3 trials in the PREZISTA / ritonavir (600/100 mg, twice a day) groups: per protocol analysis

Number of mutations at baseline (associated with a reduction in virological response to protease inhibitors)*	proportion of patients with a reduction of ≥1 log_{10}		proportion of patients with < 50 copies/ml	
	N	**% (n)**	**N**	**% (n)**
Total	377	67 (252)	377	42 (157)
<10	299	72 (215)	299	45 (136)
≥10	75	47 (35)	75	25 (19)

**mutations associated with resistance to protease inhibitors according to the 2004 IAS (international Aid Society) - USA PI list of mutations*

At 24 weeks:
- 47% of patients with viral strains presenting 10 or more mutations associated with protease inhibitors had a reduction in VL of ≥1 log_{10}
- 25% of patients with viral strains presenting 10 or more mutations associated with protease inhibitors had a VL of < 50 copies/ml.

- on the basis of co-infection with hepatitis B or C virus

Group/endpoint	**VL reduction of ≥ log_{10}**		**VL < 50 copies/ml**		**change in VL vs baseline, log_{10}**	
	N	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Patients not co-infected	261	179 (68,6)	261	110 (42,2)	261	- 1,75 (1,297)
Progressive HVC or HBV co-infection	3	3	3	1	3	- 2,80 (0,508)
Non-progressive HVC or HBV co-infection	46	28 (60,9)	46	21 (45,7)	46	- 1,67(1,455)

Co-infection with the hepatitis B or C virus does not seem to have affected the virological response at 24 weeks. However, the number of patients per group was limited.

3.2. Safety

During the clinical trials, the safety of darunavir was evaluated in a limited number of patients treated with drugs with potential drug-drug interactions. The safety of darunavir has not been evaluated in patients whose antiretroviral treatment included non-nucleoside reverse transcriptase inhibitors.
Consequently, the data obtained may not be wholly applicable to a more general use of darunavir.

The safety data for PREZISTA 600 mg combined with 100 mg of ritonavir, twice a day, are those issued from two phase IIb trials and two open-label trials. A total of 458 patients received treatment at the recommended dose (PREZISTA / ritonavir (600/100 mg, twice a day). 40% of them had at least one drug related adverse effect, and 1% discontinued the treatment due to adverse effects.

The most common reported adverse effects (≥ 2%), with severity of grade 2 or more, were:
- diarrhoea (2.6%)
- vomiting (2.2%)
- hypertriglyceridaemia (2.0%).

The adverse reactions of all grades most frequently reported were nausea (7.2%), diarrhoea (6.6%) and headache (3.3%). All the other adverse reactions were reported by less than 3% of patients.

grade 3 or 4 laboratory abnormalities reported by 2% or more of patients were:
- an increase in triglycerides (8.6%), pancreatic amylase (6.6%), total cholesterol (4.9%), gamma-glutamyl-transferase (GGT) (3.8%), partial thromboplastin time (3.6%), pancreatic lipase (3.5%), alanine aminotransferase (ALAT) (2.4%) and aspartate aminotransferase (ASAT) (2.2%)
- a reduction in the white blood cell count (6.4%), neutrophil count (4.7%), total absolute neutrophil count (4.2%) and lymphocyte count (3.8%).

Severe skin rashes have been reported, including one case of Stevens-Johnson syndrome (rare).

Combination antiretroviral therapy has been associated with a redistribution of the body fat (lipodystrophy) including loss of subcutaneous facial and peripheral adipose tissue, an increase in the intra-abdominal and visceral fat, mammary hypertrophy, and an accumulation of the retrocervical mass (buffalo hump) (see paragraph 4.4 of the SPC).
Treatment with a combination of antiretrovirals has also been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Cases of osteonecrosis have been reported, especially in patients with known risk factors, at an advanced stage of HIV infection, or after long-term exposure to treatment with a combination of antiretrovirals. Their frequency of onset is unknown.

In patients with HIV infection who present a severe immune deficiency when treatment with a combination of antiretrovirals begins, an inflammatory reaction to asymptomatic or residual opportunistic infections may appear.

Cases of increase in spontaneous bleeding have been reported in haemophiliac patients receiving protease inhibitors (see paragraph 4.4 of the SPC).

Patients co-infected with the hepatitis B and/or C virus
In patients who have received PREZISTA in combination with ritonavir 600/100 mg twice a day, an increase in liver transaminases was more frequent in co-infected patients than in patients not suffering from chronic viral hepatitis.

Safety and efficacy have not been established in patients with severe liver disorders. PREZISTA is contraindicated in patients with severe liver failure, and must be used with caution in patients with mild to moderate liver failure.

Its safety profile seems to be comparable with those of other protease inhibitors, observed in phase IIb trials.

3.3 Drug interactions

Darunavir (PREZISTA) and ritonavir are both inhibitors of the CYP3A4 isoform. Co-administration of darunavir and ritonavir with drugs mainly metabolised by CYP3A4 may cause an increase in the systemic exposure of these drugs, which can increase or prolong their therapeutic effect or adverse effects.

PREZISTA co-administered with 100 mg of ritonavir must not be combined with drugs whose clearance is strongly dependent on CYP3A4, and for which an increase in systemic exposure could cause serious adverse effects and/or be life-threatening (narrow therapeutic margin).

Several interaction studies have been conducted with doses of darunavir lower than the recommended dose. The effects on co-administered drugs may consequently be underestimated, and clinical safety monitoring may be required.

Combining PREZISTA (co-administered with ritonavir) with lopinavir/ritonavir (KALETRA) or saquinavir (INVIRASE) is not recommended. The efficacy and safety of PREZISTA (co-administered with ritonavir) have not been established in combination with the following protease inhibitors: fosamprenavir, nelfinavir and tipranavir).

The drug interaction profile of PREZISTA co-administered with ritonavir seems to be comparable with those of other protease inhibitors.
Supplementary data should be supplied by the manufacturer.

3.4 Resistance

The *in vitro* selection of viruses resistant to darunavir from wild type HIV-1 virus was lenghty (up to 2 years). The selected viruses were unable to grow in the presence in the presence of darunavir concentrations exceeding 220 nM. The viruses selected under these conditions showed reduced sensitivity to darunavir harboured 3 to 6 aminoacid substitutions in the protease gene.

Identification of determinants of decreased susceptibility to darunavir in those viruses is under investigation. The *in vitro* selection of HIV-1 viruses resistant to darunavir (EC_{50} values multiplied by a factor of 53 to 641), from 9 HIV-1 strains presenting multiple mutations associated with resistance to protease inhibitors demonstrated that a minimum of 8 mutations to darunavir selected *in vitro* were necessary for HIV-1 protease to make the virus resistant to darunavir (resistance index or fold change [FC] > 10).
In the POWER 1, POWER 2 and POWER 3 trials, in patients with no virological response, the most frequent darunavir resistance mutations were:
- L33F, 147V and L89V in 10 to 20% of cases
- V32I and 154L in over 20% of cases.

Cross-resistance:
Analysis of 3309 clinical isolates taken from patients infected with HIV and presenting reduced susceptibility to at least one of the protease inhibitors on the market (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir) demonstrated that:

- 90% of these viral strains remain sensitive to darunavir, their susceptibility being reduced by less than 10 times compared with the susceptibility of a wild virus strain
- the effective concentration (EC_{50}) of darunavir measured for these 3309 strains was less than 10nM in 78% of cases, vs. 0% to 32% of cases for the other protease inhibitors
- moreover, the virus strains presenting up to 3 primary mutations and/or 8 protease inhibitors resistance associated mutations remained susceptible to darunavir.

These results show that virus strains resistant to most protease inhibitors remain susceptibility to darunavir.

3 .5 Conclusion

In the pooled analysis of the 2 open-label clinical trials POWER1 and POWER 2, PREZISTA (co-administered with ritonavir) was more effective in terms of virological response at 24 weeks than a selected protease inhibitor (co-administered with ritonavir) in combination with other antiretrovirals in highly pre-treated adults with at least 1 primary mutation in the protease gene among the mutations: 30N, 46I/L, 48V, 50V, 82A/F/T/S, 84V or 90M (70% vs. 21 % of patients presenting a VL reduction of ≥ 1 log10 compared with baseline)

The results observed at 24 weeks for the secondary virological and immunological endpoints (increase in CD4 count) were in favour of PREZISTA (co-administered with ritonavir), especially as regards to the proportion of patients with a VL of < 50 copies/ml (45% vs. 12 % with a selected protease inhibitor).

Supplementary virological efficacy data suggested that the virological response obtained at 24 weeks is maintained at 48 weeks.

However, the Committee wishes to emphasise that these trials are open to criticism in methodological terms:

- phase IIb dose-finding studies whose protocol was amended during the trial to efficacy evaluation studies (modification of objective and primary endpoint) and whose results were secondarily pooled
- inclusion of a relatively small number of patients (131 patients in the PREZISTA group, only representing about a quarter of the patients initially recruited to the 2 trials)

According to the pooled analysis of the 24-week results of the 2 non-comparative trials:
- 66% (217/327) of patients had a reduction in VL $\geq$ 1 $\log_{10}$ compared with the baseline value
- 43% (141/327) of patients had a VL of < 50 copies/ml.

The presence at baseline of 3 or more mutations in the protease gene among the mutations (V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, 184V or L89V) was associated with a reduction in virological response in the patients treated with PREZISTA.

Tests on the 3309 clinical isolates taken from patients infected with HIV and presenting reduced susceptibility to at least one of the protease inhibitors on the market (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir) demonstrated that the virus strains resistant to most protease inhibitors remained susceptibility to darunavir.

The safety profile seems to be comparable to those of the other protease inhibitors in the context of the phase IIb clinical trials and two non-comparative open-label trials. The most frequent adverse reactions reported were nausea, diarrhoea, headache and hypertriglyceridaemia.

The drug interaction profile of PREZISTA, co-administered with ritonavir, seems to be comparable with those of the other protease inhibitors.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

The disorder which this proprietary product is designed to treat involves a serious deterioration in the quality of life, and can be life-threatening.
This product is designed to prevent and/or correct the immune deficiency caused by HIV infection.
The efficacy/adverse effects ratio of this proprietary product, administered in combination with other antiretrovirals in highly pre-treated adult patients infected with HIV-1, with protease inhibitors multi-resistant viruses to, is high.

Public health benefit :

> The public health burden represented by HIV-1 infection is high. In the population corresponding to the indication (patients infected with HIV-1, in highly pre-treated adults who have failed to respond to more than one treatment including a protease inhibitor, the burden is moderate due to the smaller number of patients concerned compared with the total population of HIV infected patients in France.
>
> Reducing the morbidity and mortality associated with AIDS corresponds to a public health need, especially in patients failing to treatment and resistant to current treatments, in view of the number of available treatments.
>
> There is no evidence allowing the impact of PREZISTA on the morbidity/mortality or quality of life criteria to be directly estimated. However, based on available data, PREZISTA is expected to make an impact on the reduction of morbidity/mortality associated with HIV-1 infection. This impact would at best be low on the population scale.
>
> Consequently, in view of available data, PREZISTA is expected to benefit public health. However, this benefit is slight.

There is an alternative to this product in the protease inhibitor class for highly pre-treated patients who have failed to respond to more than one treatment with a protease inhibitor.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

In combination with other antiretrovirals, compared with a selected protease inhibitor (co-administered with ritonavir), PREZISTA (co-administered with ritonavir) presented the following characteristics in two phase II b clinical trials after 24 weeks' treatment, the results of which were pooled:

- superior virological efficacy
- comparable safety.

Supplementary virological efficacy data suggest that the virological response is maintained at 48 weeks and 72 weeks.

Pending the results of a phase III clinical trial currently being finalised, the Committee considers that PREZISTA, co-administered with ritonavir, in combination with other antiretrovirals, provides a moderate improvement in actual clinical benefit (Level III) in terms of virological efficacy in the treatment of highly pre-treated adult patients infected with strains of HIV-1, who have:

- viruses multi-resistant to protease inhibitors,
- a genotype including at least 1 primary mutation in the protease gene among the mutations 30N, 46I/L, 48V, 50V, 82A/F/T/S, 84V or 90M.

4.3. Therapeutic use

4.3.1 - Management of persons infected with HIV (major/multiple therapeutic failure)

Medical management of persons infected with HIV.

According to "Medical management of persons infected with HIV - Guidelines of Expert Group led by Professor Patrick YENI - 2006 Report" - (www.sante.gouv.fr)

STRENGTHS (*)

• The initiation of antiretroviral treatment must be prepared by a multidisciplinary team to optimise compliance with the treatment (AIII).

• The objective of the antiretroviral treatment is to achieve and maintain an undetectable VL (< 50 copies/ml) and a lymphocyte CD4 count exceeding 500/mm^3 (A).

• There is no benefit in discontinuing an antiretroviral treatment. In patients who respond to treatment, treatment interruptions are followed by a rebound of HIV replication and a reduction in the CD4 lymphocyte count; the lower the CD4 lymphocyte count nadir, the more rapid the reduction (AIIa).

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*

[1] Grading of guidelines:

A: Available data justifying a high-level guideline
B: Available data justifying an intermediate-level guideline
C: Available data insufficient to justify a guideline

[2] Evidence levels: type of data used in the guidelines:

I a, b: At least one randomised clinical trial; meta-analyses of randomised trials
II a, b: Non-randomised clinical trials; cohorts or case-control studies; meta-analyses of cohorts or case-control studies
III : Analyses by experts on the basis of other available data

a: data published in a peer-reviewed scientific journal
b: data presented at a scientific conference with a selection committee, available in abstract form.

• The persistence of viral replication (VL > 500 copies/ml) during treatment exposes the patient to the risk of accumulation of resistance mutations, which reduces the chances of efficacy of further treatment (AIIb) and has an adverse impact on the CD4 lymphocytes (AIIa).
• Situations of virological failure must should be subject of multidisciplinary discussions (AIII). The opinion of an experienced HIV team is essential in situations where there are few therapeutic options (AIII).

The Expert Group's recommendations in situations of virological failure (see table summarising the treatment strategies proposed for non reponders) are:

- whatever the failure situation (first-line, further lines, including after multiple failures), to aim at achieving and maintaining a plasma VL of less than 50 copies/ml (AIII);
- to analyse the virological failure, by evaluating the clinical situation, the CD4 lymphocyte count and the plasma viral load, compliance, safety and possible drug interactions (AIII);
- to take into account the whole patient history and perform a genotype test during treatment (AIIa) in order to optimise the choice of the new antiretroviral treatment. The results of any prior tests (AIII), and pharmacological assays if available, will also be taken into account (BIII);
- in the absence of resistance mutations during treatment, to evaluate and optimise compliance as a priority, using pharmacological assays (BIII);
- to combine at least two new active drugs, one of which should ideally belong to a therapeutic class which has not yet been used (AIIa).

Summary of the treatment strategies proposed in the event of virological failure

Virological failure and/or resistance to:	**Treatments usually recommended:**
NRTI and NNRTI	2 NRTIs (chosen by genotype) + PI/r (no clinical trials)
NRTI and PI/r	Preferential choices 2 NRTIs (chosen by genotype) + [ATV/r or FPV/r or LPV/r], according to genotype [111,112] 2 NRTIs(chosen by genotype) + NNRTI (provided that the 2 NRTIs chosen are "fully active") *Alternative (especially after the 2nd failure)* 2 NRTIs (chosen by genotype) + [LPV/r or FPV/r]+ NNRTI (pharmacological testing needed)
NRTI and NNRTI and PI/r	Enfuvirtide + PI/r ± NRTI (according to current, prior and historical genotypes) *Choice of PI/r:* active according to the result of the resistance genotype: Especially TPV/r or DRV/r in the event of certain or possible resistance to other PI/r's.

4.3.2 Role of the proprietary product PREZISTA in the treatment strategy

Depending on the patient's case history and the genotype and phenotype profile of the patient's viruses (if available), PREZISTA can be used as a protease inhibitor in highly pre-treated adults who failed more than one regimen containing a protease inhibitor (PI).

4.4. Target population

The target population of the proprietary product PREZISTA corresponds to the population of highly pre-treated adult patients who have failed to respond to more than one treatment including a protease inhibitor, and whose case history and analysis of the mutation profiles associated with the various antiretrovirals have been evaluated.

According to the report by the Institut de Veille Sanitaire (French Health Surveillance Institute) relating to HIV / AIDS monitoring[1] between 1996 and 2005:

- the number of seropositive persons in France at the end of 2005 was estimated at between 100,000 and 170,000
- 98.4% of the persons who were seropositive in 2005 were infected by the HIV-1 virus.

There are no epidemiological data relating to the population of highly pre-treated adult patients who have failed to respond to more than one treatment including a protease inhibitor An analysis has been supplied by the manufacturer to estimate this population. It is an epidemiological population analysis based on treatments and virological failures (final report of March 2007 by J. Fichou and D. Costagliola - INSERM Transfert and INSERM UMR S 720) (unpublished analysis).

The data analysed (including the 1st week of 2005) are extracted from the French Hospital Database on HIV (FHDH) collected with the DMI 2 software. This database includes 44,819 patients over 15 years old, infected with HIV-1. 83.7% of them, namely 37,520 patients, have been treated with antiretrovirals.

In particular, a subgroup of patients treated with antiretrovirals was selected. This subgroup corresponds to patients failing current treatment and failing at least one treatment including a protease inhibitor.

Virological failure was defined in the analysis of the database as one of the following events:

- a patient whose VL still exceeds 500 copies/ml 6 months after treatment in tiation ("primary" failure)
- a patient with a VL of < 500 copies/ml before treatment, and rebound with 2 values > 1000 copies/ml ("secondary failure")

The following 3 populations were identified in the subgroup as defined:

- 756 patients with a documented failure to a treatment including a protease inhibitor, with an average of 2.3 previously used protease inhibitors . It should be noted that 25% of the patients in this population have been treated with only one treatment including a protease inhibitor, and therefore should not be included in the target population.

[1] INVS - Campaign against HIV/AIDS and Sexually Transmitted Diseases in France - 10 years' monitoring 1996- 2005

- 345 patients with 2 documented failures to a treatment including a protease inhibitor, with an average of 3.3 protease inhibitors previously used.

- 979 patients with 3 or more documented failures to a treatment including a protease inhibitor, with an average of 5.1 protease inhibitors previously used.

Consequently, 1,890 patients (i.e. 5% of the treated patients according to the analysis of this database) are liable to benefit from a treatment corresponding to the indication of PREZISTA.

If it is assumed that the observed percentage (5%) in the FHDH database of managed and treated patients can be extrapolated to all patients infected with HIV-1 and treated, the population of patients treated as in- and out-patients who fail to respond to the current treatment, and have previously failed 2 or more treatments including a protease inhibitor, can be estimated at between 4,100 and 7,000 patients.

Consequently, the target population of the proprietary product PREZISTA can be estimated at between 4,100 and 7,000 persons.

The definition of virological failure in this analysis does not correspond exactly to that recently defined in the 2006 Report entitled “Medical management of persons infected with HIV - Guidelines of Expert Group led by Professor Patrick YENI”; in fact, virological failure is currently defined as from a threshold plasma VL of 50 copies/ml (as opposed to 500 copies/ml in the analysis).

Moreover, virological failure corresponding to non-response to the treatment defined as a reduction in plasma VL of under 1 $\log_{10}$ copies/ml, 1 month after the commencement of treatment, is not taken into account in this analysis. Consequently, the definition of virological failure in this analysis may tend to underestimate all situations of virological failure corresponding to the indication of PREZISTA, which could lead to an underestimated target population. However, this underestimation cannot be evaluated in the absence of other data.

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 indications and at the dosage given in the marketing authorisation.

The Committee wishes to receive new available data within 18 months so that the virological efficacy and clinical and biological safety of the product can be better established in comparative terms.

4.5.1. Packaging: the packaging is appropriate to prescription requirements

4.5.2. Reimbursement rate: 100%.