HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 December 2011

PREZISTA 400 mg, film-coated tablet
B/60 (CIP code: 393 138-3)

Applicant: JANSSEN-CILAG

darunavir
ATC code: J05AE10 (protease inhibitors)

List I
Initial annual hospital prescription
Unrestricted renewal.

Date of Marketing Authorisation (centralised procedure): 29 January 2009, MA amendment of 28 February 2011

Reason for request: Inclusion on the list refundable by National Health Insurance and approved for hospital use in the extension of indication for "treatment of HIV-1 infection **in antiretroviral treatment (ART) experienced adults with no darunavir resistance-associated mutations who have a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells x 10^6/l**".

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Darunavir

1.2. Indication

New wording including the extension of indication ***in bold*** (MA amendment of 28 February 2011)
"PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.

PREZISTA 400 mg tablets may be used to provide suitable dose regimens (see section 4.2 of the Summary of Product Characteristics):

- for the treatment of HIV-1 infection in antiretroviral treatment (ART) naïve adults,
- **for the treatment of HIV-1 infection in ART-experienced adults with no darunavir resistance-associated mutations who have a plasma HIV-1 RNA level of < 100 000 copies/ml and a CD4+ cell count of ≥ 100 cells x 10^6/l. On the initiation of treatment with PREZISTA in ART-experienced adults, the use of PREZISTA must be guided by a genotypic resistance test (see sections 4.2, 4.3, 4.4 and 5.1 of the SPC)"**.

1.3. Dosage

"Therapy should be initiated by a physician experienced in the management of HIV infection. Patients should be advised that, after the initiation of therapy with PREZISTA, they should not alter the dosage or discontinue therapy without instruction of their physician.

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.

Patients should be instructed to take PREZISTA with low dose ritonavir within 30 minutes after completion of a meal. The type of food does not affect the exposure to darunavir".

"Adults

ART-naïve patients

The recommended dose regimen is 800 mg once daily, administered with 100 mg of ritonavir once daily taken with food".

"ART-experienced patients

The recommended dosages are as follows:

- **In ART-experienced patients with no darunavir resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V) who have a plasma HIV-1 RNA level of < 100 000 copies/ml and a CD4+ cell count of ≥ 100 cells x 10^6/l (see section 4.1), a regimen of 800 mg once daily with ritonavir 100 mg once daily taken with food may be used.**

- **In all other ART-experienced patients or if HIV-1 genotype testing is not available, the recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. See the Summaries of Product Characteristics for PREZISTA 75 mg, 150 mg, 300 mg or 600 mg tablets.**

Paediatric population

PREZISTA is not indicated in ART-naïve children and adolescents. For the recommended dosages in ART-experienced children and adolescents see the Summaries of Product Characteristics for PREZISTA 75 mg, 150 mg, 300 mg and 600 mg tablets.

Elderly

Limited information is available in this population and therefore PREZISTA should be used with caution in this age group.

Hepatic impairment

Darunavir is metabolised by the hepatic system. No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, PREZISTA should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of darunavir exposure and a worsening of its tolerance profile. Therefore, PREZISTA must not be used in patients with severe hepatic impairment (Child-Pugh Class C).

Renal impairment

No dose adjustment is required in patients with renal impairment.

In case a dose of PREZISTA/ritonavir 800/100 mg once daily was missed within 12 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 12 hours after the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

This guidance is based on the 15 hour half-life of darunavir in the presence of ritonavir and the recommended dosing interval of approximately 24 hours".

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

J : antiinfectives for systemic use
J05 : antivirals for systemic use
J05A : direct-acting antivirals
J05AE : protease inhibitors
J05AE10 : darunavir

2.2. Medicines in the same therapeutic category

Comparator medicines

- **Protease inhibitors (PI) as part of a treatment combining antiretrovirals in adult patients.**
  - indinavir: CRIXIVAN, capsules and film-coated tablets
  - nelfinavir: VIRACEPT film-coated tablets and oral powder
  - amprenavir: AGENERASE, capsules and oral solution
  - saquinavir mesylate: INVIRASE, capsules and film-coated tablets
  - lopinavir with ritonavir: KALETRA, oral solution and film-coated tablets
  - fosamprenavir: TELZIR, film-coated tablets and oral solution
  - atazanavir: REYATAZ, capsules or oral powder, indicated in adults
  - 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
  - tipranavir: APTIVUS, soft capsules, indicated in adults

2.3. Medicines with a similar therapeutic aim

Other medicinal products indicated in the treatment of infection with Human Immunodeficiency Virus Type 1 (HIV-1).

3 ANALYSIS OF AVAILABLE DATA

The PREZISTA proprietary medicinal products (PREZISTA 600 mg, PREZISTA 300 mg, PREZISTA 150 mg and PREZISTA 75 mg) are currently indicated in the treatment of HIV-1-infected, antiretroviral treatment-experienced adult patients (including those that have been highly pre-treated), in a daily dosage of 1200 mg coadministered with 200 mg of ritonavir, in two doses daily, in combination with other antiretrovirals.

The aim of this dossier is to propose a new dosage regimen with PREZISTA 400 mg coadministered with ritonavir in one daily dose (darunavir 800 mg/ritonavir 100 mg/day), making it possible to reduce the doses of darunavir/ritonavir and the number of doses in certain pre-treated adult patients.

3.1. Efficacy

The indication for PREZISTA 400 mg in the treatment of HIV-1 infection in antiretroviral treatment-experienced adults with no darunavir resistance associated mutations and a plasma HIV-1 RNA level of < 100 000 copies/ml and a CD4+ cell count of ≥ 100 cells x 10^6/l is based on the ODIN study (TMC114-C229).[1]

Objective of the study

This is an open, randomised, phase III controlled study with a duration of 48 weeks, the main aim of which was to demonstrate the non-inferiority (delta threshold = 12%) of treatment with PREZISTA coadministered with ritonavir in a single daily dose (darunavir 800 mg/ritonavir 100 mg/day) versus PREZISTA coadministered with ritonavir in two daily doses (darunavir 1200 mg/ritonavir 200 mg/day), in combination with an optimised basic treatment (OBT) comprising exclusively nucleoside reverse transcriptase inhibitors (NRTIs), in HIV-1-infected antiretroviral treatment-experienced adult patients.

Primary inclusion and non-inclusion criteria

- Inclusion criteria: adult patients (> 18 years) infected with HIV-1, with stable antiretroviral treatment for at least 12 weeks, a plasma HIV-1 RNA viral load of ≥ 1 000 copies/ml, a CD4+ cell count of > 50 x10^6 cells/ml, with no darunavir resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V).
- Non-inclusion criteria: patients pre-treated with enfuvirtide, tipranavir and darunavir.

Treatments

The eligible patients were randomised (ratio 1:1), after stratification by viral load (< 50 000 and ≥ 50 000 copies/ml), to receive the following open treatment:

- darunavir/ritonavir (800/100 mg): 2 tablets of darunavir 400 mg and 1 capsule of ritonavir 100 mg, in one daily dose,
- or darunavir/ritonavir (1200/200 mg): 1 tablet of darunavir 600 mg and 1 capsule of ritonavir 100 mg, in two daily doses.

The treatments were combined with an optimised basic treatment consisting of at least 2 NRTIs selected by the investigator according to the patient's treatment history and the resistance tests.

Primary efficacy endpoint

- Virological response defined as the proportion of patients with a viral load of < 50 copies/ml in the 48th week, calculated according to the algorithm *Time to Loss of Virologic Response* (TLOVR).

[1] *Cahn P et al. ODIN: 48-week analysis of once- versus twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients. AIDS 2011; 25 (7):* 929–939

Secondary endpoints included:

- Change in viral load from baseline;
- Immune response (change to CD4+ count compared with inclusion);
- Quality of life, assessed using the FAHI questionnaire (Functional Assessment of Human Immunodeficiency virus infection - version 4):[2] the different parameters assessed are "physical well-being", "emotional well-being", "functional and global well-being", "social well-being" and "cognitive function".
- Compliance with treatment, assessed using three parameters: the M-MASRI questionnaire (Modified Medication Adherence Self-Reported Inventory),[3,4] the plasma concentrations of darunavir and the number of tablets.

Study population

Among the randomised patients (n = 599), 590 (294 in the darunavir/ritonavir 800 mg/100 mg x 1/day group and 296 in the darunavir/ritonavir 600 mg/100 mg x 2/day group) received at least one dose of treatment and 501 (84.9%) completed the study.

The patients included (mean age 40.5 ± 0.38; men 64%) had been infected with HIV-1 (subtype B: 64.1%) for 8.5 years (mean) and 35.4% were in stage 1 (asymptomatic) of the infection, 21.2% in stage 2 (moderate symptoms), 14.9% in stage 3 (advanced symptoms), and 28.5% in stage 4 (severe symptoms) according to the WHO classification. About 11% of patients had an HCV or HBV co-infection.

On inclusion, the mean viral load (plasma HIV-1 RNA) was 4.16 $\log_{10}$ copies/ml and the median CD4+ cell count was 228 cells x 10^6/l. Most patients had a viral load of < 100 000 copies/ml (88%) and CD4+ cell counts of ≥ 100 cells x 10^6/ml (85.3%). The median number of antiretrovirals previously used was five and the median number of protease inhibitors (PI), excluding low-dose ritonavir, previously used was one (of which 46.1% not pre-treated with PI). Most patients had no darunavir resistance-associated mutations (99%) and no primary PI resistance-associated mutations (84%).

Results at 48 weeks

At 48 weeks, the non-inferiority (delta threshold = 12%) of darunavir/ritonavir 800/100 mg once daily versus darunavir/ritonavir 600/100 mg twice daily was demonstrated in the *per-protocol* analysis in terms of virological response (plasma HIV-1 RNA < 50 copies/ml): 73.4% (190/259) versus 72.5% (200/276); difference 0.9%, 95% CI [-6.7; 8.4]. Similar results were obtained in the ITT analysis: 72.1% versus 70.9%; difference 1.2 [-6.1; 8.5]. Analysis of the data using a logistic regression model (with adjustment for the viral load on inclusion) also confirms non-inferiority in the population studied.

A subgroup analysis of the virological response endpoint (viral load < 50 copies/ml) was made on the basis of the clinical characteristics of the patients on inclusion (Table 1). It should be noted that this study was not designed to allow such an analysis to be made with adequate statistical power, because of the small populations considered. Overall, the results of this analysis show that treatment with darunavir/ritonavir 800/100 mg in one daily dose is more suitable for pre-treated patients with plasma HIV-1 RNA levels of ≤ 100,000 copies/ml and a CD4+ count of > 100 x 10^6 cells/ml, which corresponds to the population used in the MA for PREZISTA 400 mg and its use in one daily dose in pre-treated patients.

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[2] Peterman AH, et al. Psychometric validation of the revised Functional Assessment of Human Immunodeficiency Virus Infection (FAHI) quality of life instrument. Qual Life Res 1997; 6: 572–84.

[3] Walsh JC, Mandalia S, Gazzard B, et al. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. AIDS 2002; 16: 269-77

4 The M-MASRI questionnaire asked patients to give information about their compliance with treatment using a horizontal visual analogue scale to quantify the percentage of doses of treatment received during the last month. On the basis of the percentages reported by patients, two categories were identified: patients complying with treatment (who received more than 95% of the doses of treatment) and patients not complying with treatment (≤ 95%).

The limited data in patients with a viral load of > 100,000 copies/ml, CD4+ cell counts of < 100 cells x 10^6/l and patients infected with non-B HIV-1 mean that it is not possible to validate non-inferiority in these subpopulations, since the results are more in favour of the use of darunavir/ritonavir (600/100 mg) in two daily doses.

Table 1: Virological response (VL < 50 copies/ml) in the 48th week, based on the characteristics of the patients on inclusion (ITT-TLOVR).

	Darunavir/ritonavir 800/100 mg x1/day		**Darunavir/ritonavir 600/100 mg x2/day**		**Difference DRV/r x1/day – DRV/rx2/day**	
Clinical characteristics at inclusion	**N**	**Responders n (%)**	**N**	**Responders n (%)**	**% response**	**95% CI***
Viral load (copies/ml)						
< 100 000	255	198 (77.6)	265	194 (73.2)	4.4	[-3.0; 11,9]
≥ 100 000	39	14 (35.9)	31	16 (51.6)	-15.7	[-39.2; 7.7]
CD4+ count (x 10^6/L)						
< 100	49	28 (57.1)	38	23 (60.5)	-3.4	[-24.5; 17.8]
≥ 100	245	184 (75.1)	258	187 (72.5)	2.6	[-5.1; 10.3]
HIV-1 subtype						
B	179	126 (70.4)	199	128 (64.3)	6.1	-3.4; 15.6
Non-B	115	86 (74.8)	97	82 (84.5)	-9.8	-20.7; 1.2
Primary PI resistance mutations						
0	247	175 (70.9)	250	175 (70.0)	0.9	[-7.2; 8.9]
≥ 1	47	37 (78.7)	46	35 (76.1)	2.6	[-14.6; 19.9]
Previous number of PIs received						
0	135	111 (82.2)	137	109 (79.6)	2.7	[-6.7; 12.0]
1	74	48 (64.9)	77	49 (63.6)	1.2	[-14.2; 16.6]
≥ 2	85	53 (62.4)	82	52 (63.4)	-1.1	[-15.8; 13.7]

* The lower limit of the 95% CI for the difference between the two groups had to be > -12% to demonstrate non-inferiority.
DRV/r = darunavir/ritonavir

The results for the secondary endpoints also confirm the non-inferiority analysis in the population studied:

- Virological response: the mean variation in the viral load by comparison with on inclusion was -1.84 log10 copies/ml for the DRV/r x1 /day group and -1.80 log10 copies/ml for the DRV/r x 2/day group (difference: -0.04 [-0.24; 0.16]). The times before the first virological response and before the loss of virological response were similar in the two groups.
- The immune response (mean variation in the CD4+ cell count by comparison with on inclusion) was similar in the two treatment groups: 108 x 10^6/L versus 112 x 10^6/L (difference: -5 [-25; 16]).
- The quality of patients' life measured by the FAHI score (value on inclusion: 124.1 [71%] versus 121.2 [69%])[5] remained relatively good throughout the study, with a mean increase in the FAHI score of 2.7 versus 3.1 (difference: 0.55 [-2.97; 4.06]).
- Compliance with treatment was similar in the two groups. The virological response according to compliance with treatment confirms non-inferiority in compliant patients (Table 2).

[5] The maximum FAHI score was 176.

Whatever the method used to assess compliance, the virological response was greater in compliant patients than in patients who did not comply with treatment.

Table 2: Virological response (VL < 50 copies/ml) in the 48th week (ITT-TLOVR), as a function of treatment compliance

Parameters	Darunavir/ritonavir 800/100 mg x1/day		Darunavir/ritonavir 600/100 mg x 2/day		Difference DRV/r x1/day – DRV/rx2/day	
	N	Responders n (%)	N	Responders n (%)	% response	95% CI*
Compliance with treatment measured by the M-MASRI questionnaire method						
Compliant	166	141 (84.9)	149	127 (85.2)	-0.3	[-8.2; 7.6]
Non-compliant	97	55 (56.7)	119	74 (62.2)	-5.5	[-18.7; 7.7]
Compliance with treatment measured by the plasma darunavid concentration method						
Compliant	238	197 (82.8)	248	203 (81.9)	0.9	[-5.9; 7.7]
Non-compliant	48	15 (31.3)	35	7 (20.0)	11.3	[-8.1; 30.6]
Compliance with treatment measured by the tablet number method						
Compliant	169	139 (82.2)	160	134 (83.8)	-1.5	[-9.7; 6.7]
Non-compliant	125	73 (58.4)	136	76 (55.9)	2.5	[-9.6; 14.6]

* The lower limit of the 95% CI for the difference between the two groups had to be > -12% to demonstrate non-inferiority.
DRV/r = darunavir/ritonavir

3.2. Tolerance: 48-week data from the ODIN study

Tolerance was evaluated in 590 patients who received at least one dose of treatment. The mean duration of exposure was 44.8 weeks in the darunavir/ritonavir 800 mg/100 mg x1/day group and 43.1 weeks for the darunavir/ritonavir 600mg x2/day group.

The incidence of adverse events was similar in the two treatment groups (76.2% in the darunavir/ritonavir 800/100 x 1/day group versus 77% in the darunavir/ritonavir 600/100 mg x2/day group). The frequency of adverse events considered by the investigator as being at least possibly linked to the treatments was 30.6% versus 37.8%; the most common adverse effects were gastrointestinal disorders (23.5% versus 25.7%, including diarrhoea [9.9% versus 15.2%], nausea [10.9% versus 10.5%] and vomiting [3.1% versus 5.4%]). The incidence of grade 2-4 adverse effects was similar in the two treatment groups and these were primarily gastrointestinal disorders including nausea (3.7% versus 4.4%), diarrhoea (3.7% in both groups) and vomiting (2.4% versus 3.0%).
The incidence of biochemical abnormalities was generally low and similar in the two treatment groups. The incidence of lipid disorders regarded as possibly linked to the treatments was 2.4% versus 4.7%, mainly hypertriglyceridaemia (0.7% and 1.7%), hypercholesterolaemia (0.7% and 1.0%), increased total cholesterol (0.3% and 1.0%) and hyperlipidaemia (0% and 1%).
Discontinuations of treatment on account of adverse events regarded as possibly linked to treatment with darunavir/ritonavir had a low incidence in the two groups (1.7% versus 1%), with a higher incidence of discontinuations of treatment on account of gastrointestinal adverse effects in the darunavir/ritonavir 800/100 mg x1/day group (1.4% versus 0.3%).

Overall, the tolerance profile of treatment with darunavir/ritonavir 800/100 mg in one daily dose in this study was similar to that of treatment with darunavir/ritonavir 600/100 mg x2/day in the population studied.

This study did not reveal any unknown adverse effect of darunavir.

3.3. Main "Special warnings and precautions for use" relating to the use of PREZISTA 400 mg (dosage 800 mg in one daily dose) in antiretroviral treatment experienced patients (Cf. SPC section 4.4)

- In antiretroviral treatment experienced patients, the dosage PREZISTA/ritonavir 800/100 mg once daily must not be used in patients with one or more darunavir resistance-associated mutations or a plasma HIV-1 RNA level of ≥ 100,000 copies/ml or a CD4+ cell count of < 100 cells x 10^6/l. The efficacy and tolerance of use of PREZISTA/ritonavir in a dose of 800/100 mg once daily combined with an optimised treatment (OT) in the treatment of HIV-1 infection in antiretroviral treatment-experienced adults with no darunavir resistance-associated mutations were assessed during a study lasting 48 weeks. Combinations with OTs other than ≥ 2 INTI were not studied in this population. The data available in patients infected with non-type B strains of HIV-1 are limited.
- The combination of efavirenz and PREZISTA/ritonavir 800/100 mg once daily may lead to a suboptimal Cmin of darunavir. If efavirenz is used in combination with PREZISTA/ritonavir, the dosage of 600/100 mg PREZISTA/rtv twice daily must be used.

Cf. SPC for more details of precautions relating to the use of PREZISTA in the treatment of HIV infection.

3.4. Conclusion

A randomised open study (the ODIN study) compared darunavir/ritonavir 800/100 mg once daily versus darunavir/ritonavir 600/100 mg twice daily in HIV-1-infected antiretroviral treatment experienced adult patients who, on inclusion, had no darunavir resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V) and had an HIV-1 RNA level of >1000 copies/ml.
Most of the patients included were infected with subtype B HIV-1 (64.1%), had a viral load (HIV-1 RNA) on inclusion of < 100,000 copies/ml (88%) and CD4+ cell counts of ≥ 100 x 10^6 cells/ml (85.3%).
The study treatments were combined with a basic optimised treatment with at least 2 INTIs.

The analysis of efficacy is based on the virological response (plasma HIV-1 RNA of < 50 copies/ml) at 48 weeks of treatment.
At 48 weeks, the non-inferiority (delta threshold = 12%) of darunavir/ritonavir 800/100 mg once daily versus darunavir/ritonavir 600/100 mg twice daily was demonstrated in the *per-protocol* analysis in terms of virological response: 73.4% (190/259) versus 72.5% (200/276); difference 0.9%, 95% CI [-6.7; 8.4]. Similar results were obtained in the ITT analysis: 72.1% versus 70.9%; difference 1.2 [-6.1; 8.5].

A subgroup analysis shows that treatment with darunavir/ritonavir 800/100 mg in one daily dose is more suitable for pre-treated patients with plasma HIV-1 RNA levels of ≤ 100,000 copies/ml and a CD4+ count of > 100 x 10^6 cells/ml, which corresponds to the population used in the MA for PREZISTA 400 mg and its use in one daily dose in pre-treated patients with no darunavir resistance associated mutation. On the other hand, the non-inferiority of darunavir/ritonavir 800/100 mg in 1 daily dose has not been validated (limited data and more in favour of darunavir/ritonavir 600/100 mg in two daily doses) in patients with a viral load of > 100,000 copies/ml, CD4+ cell counts of < 100 cells x 10^6/l and patients infected with non-B HIV-1.

The tolerance profile of treatment with darunavir/ritonavir 800/100 mg in one daily dose in this study was similar to that of treatment with darunavir/ritonavir 600/100 mg x2/day.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

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

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

The efficacy/adverse effects ratio is substantial in combination with other antiretrovirals in antiretroviral treatment-experienced patients who have no darunavir resistance associated mutation, a plasma HIV-1 RNA level of < 100 000 copies/ml and a CD4+ cell count of ≥ 100 cells x 10^6/l.

There are treatment alternatives for pre-treated patients.

Public health benefit

The public health burden of HIV-1 infection is significant. In the population corresponding to the extension of indication (patients infected with HIV-1, in pre-treated adults), the burden is reduced by the more limited number of patients concerned by comparison with the total population of patients with HIV in France.

The reduction of morbidity/mortality linked to AIDS is a public health need, particularly in patients whose treatment has failed and who are resistant to current treatments.

There is no information that allows the impact of PREZISTA on morbidity/mortality or quality of life to be assessed directly.

On the other hand, in view of the available data, PREZISTA 400 mg is not expected to have any impact on morbidity/mortality linked to HIV-1 infection by comparison with other existing dosages of PREZISTA.

Consequently, the medicinal product PREZISTA 400 mg is not expected to benefit public health in this extension of indication (pre-treated adults).

The actual benefit of this proprietary medicinal product is substantial in the indication in the Marketing Authorisation.

4.2. Improvement in actual benefit (IAB)

Despite the simplification of the dose regimen by comparison with the other dosages of PREZISTA (600 mg, 300 mg, 150 mg and 75 mg), in view of the efficacy and tolerance data, the Committee believes that PREZISTA 400 mg does not provide any improvement in actual benefit (IAB V) in the management of HIV-1-infected antiretroviral treatment (ART)-experienced adult patients who have no darunavir resistance-associated mutations, a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells x 10^6/l. In this population, it is an addition to the range available.

4.3. Therapeutic use

4.3.1. Management of persons infected with HIV[6]

- The objective of antiretroviral therapy is to achieve and maintain an undetectable viral load (< 50 copies/ml) and a CD4 lymphocyte count of > 500/mm^3.
- Except in emergency situations, the initiation of antiretroviral treatment must be prepared with the patient to optimise his compliance with treatment.
- The discontinuation of treatment is followed by a rebound in HIV replication and a drop in CD4 lymphocytes which increases with the CD4 lymphocyte nadir.
- The persistence of viral replication under treatment is associated with the risk of the accumulation of resistance mutations which reduces the likelihood of subsequent treatment being effective and has a negative impact on CD4 lymphocytes.
- Virological failure situations must form the subject of multidisciplinary discussions. The opinion of an experienced HIV team is vital in situations where the treatment options appear to be limited.
- With the availability of six classes of antiretrovirals, the aim of regaining maximum virological suppression is nowadays possible in most cases, including in patients with a long antiretroviral history and the presence of genotypical resistance to more than one class.
- In these situations of virological failure, the factors associated with a greater chance of the virological success of the new treatment are a moderately elevated viral load (< 30,000 copies/ml), an elevated CD4 lymphocyte count, the use of a protease inhibitor potentiated by ritonavir, and the use of a new class of ART not previously received by the patient.

The expert group recommends, in situations of virological failure:

- attempting to achieve and maintain a plasma viral load of < 50 copies/ml;
- putting together a treatment regimen including, wherever possible, three active medications, based on the treatment history, successive genotypes and possibly measurements of the plasma concentrations of the antivirals;
- when just one medication remains active:
  - o if the CD4 lymphocyte count is > 200/mm^3, and until new substances are available, not changing the treatment and monitoring the level of CD4 lymphocytes and the occurrence of clinical manifestations,
  - o if the CD4 lymphocyte count is < 200/mm^3, with a risk of clinical progression, trying to optimise the treatment by recycling the substances already used and combining them, and maintaining the prophylaxis of opportunistic infections.

4.3.2. Therapeutic use of the medicinal product PREZISTA

The PREZISTA proprietary medicinal products (600 mg, 300 mg, 150 mg and 75 mg), in a daily dosage of 1200 mg of darunavir coadministered with 200 mg of ritonavir, in two daily doses in combination with other antiretrovirals, are treatment options in the protease inhibitor class for adult patients infected with HIV-1 in whom previous treatment with antiretrovirals has failed (including highly pre-treated patients).

The use of PREZISTA 400 mg in a daily dose (800 mg of darunavir coadministered with 100 mg of ritonavir) in combination with other ARTs, is restricted to antiretroviral-treatment experienced adult patients who have no darunavir resistance associated mutations a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells x 10^6/l (cf. SPC, special warnings and precautions for use).

[6] Yéni P. 2010 Report. Prise en charge médicale des personnes infectées par le VIH. Recommendations de groupe d'experts. [Medical management of persons infected with HIV.] Recommendations of the group of experts. Available at www.sante.gouv.fr.

4.4. Target population

According to the Yéni report of 2010, the number of persons infected with HIV can be estimated at 152,000 in 2008. The number of patients being treated has been increasing by 4% a year since 2006, taking the number of patients with the chronic condition HIV in the general scheme to 93,911 on 31 December 2009, which covers about 88% of the population. Extrapolating the data from the general scheme to the whole of the population in France, the number of persons classed as having the chronic condition HIV infection can be estimated at 110,000 persons in 2010.

Since the percentage of patients treated among the patients followed up was 88% in 2010,[7] it can be estimated that 96,800 persons are receiving antiretroviral treatment.

The aim of an antiretroviral treatment must be to achieve and maintain a plasma viral load of less than 50 copies/ml. The current treatment strategy recommends rapid therapeutic intervention in the event of virological failure when the viral load is greater than 200 copies/ml, and whatever the level of CD4 lymphocytes. In a situation where the viral load is between 50 and 200 copies/ml, it is recommended that these patients should be monitored closely in order to discuss, in this situation, a change in treatment or its intensification with a substance that preferably has a high genetic barrier.
In 2010, 14% of the patients treated for at least 6 months with multiple therapy had a viral load of ≥ 50 copies/ml (5.7% ≥ 500 copies/ml and 0.9% ≥ 100,000 copies/ml). Applying this percentage to the population of patients infected with HIV-1 and treated with antiretrovirals, the number of patients whose viral load remains detectable after six months of antiretroviral treatment is estimated to be 13,000.

The total target population for the proprietary medicinal products PREZISTA (all presentations together) in pre-treated patients could be estimated as at most about 13,000 patients.
The target population for PREZISTA 400 mg is represented, in all pre-treated patients, by a population limited to patients with no darunavir resistance-associated mutations who have a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells x 10^6/l.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the extension of indication and at the dosages in the Marketing Authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions

4.5.2. Reimbursement rate: 100%

[7] FHDH - ANRS CO4. Retour d'informations Clinico-Épidémiologiques [Return of clinico-epidemiological information.] June 2011. http://www.ccde.fr