HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion
28 May 2014

PREZISTA 400 mg, film-coated tablet
B/60 (CIP: 34009 393 138 3 2)
PREZISTA 800 mg, film-coated tablet
B/30 (CIP: 34009 267 887 0 4)
PREZISTA 100 mg/ml, oral suspension
200 ml bottle (CIP: 34009 267 049 5 7)

Applicant: **JANSSEN-CILAG**

INN	darunavir
ATC code (year)	J05AE10 (protease inhibitor class of antiretrovirals)
Reasons for the review	**Extensions of indication**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123-2)**
Indications concerned	**PREZISTA 400 and 800 mg, film-coated tablet** **"PREZISTA 400mg or 800 mg tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection […] and paediatric patients from the age of 12 years and at least 40 kg body weight who are:** **- antiretroviral therapy (ARV) - naïve or** **- ARV-experienced, with no darunavir resistance-associated mutations and who have plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l. In deciding to initiate treatment with PREZISTA in such ARV-experienced patients, genotypic testing should guide the use of PREZISTA."** **PREZISTA 100 mg/ml, oral suspension** **The same extensions of indication are concerned.**

Actual Benefit:	**substantial in adolescents aged from 12 to 17 years and weighing at least 40 kg who are:** - **ARV-naïve;** - **ARV-experienced but with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l.**
Improvement in Actual Benefit	◗ **In the management of HIV-1 infection in ARV-naïve adolescents aged from 12 to 17 years weighing at least 40 kg** **Taking account of:** - **the very limited data on ARV-naïve adolescents weighing at least 40 kg (DIONE study), which suggest an efficacy and safety profile at 48 weeks similar to that observed in the ARV-naïve adults with, however, some uncertainty over the growth abnormalities and the long-term consequences of lipid disorders;** - **the lack of comparative data other than those versus lopinavir/ritonavir (KALETRA) in naïve adults (ARTEMIS non-inferiority study),** **PREZISTA as 400 mg and 800 mg tablets or as an oral suspension, co-administered with a low dose of ritonavir, does not provide any improvement in actual benefit (level V, non-existent) in the management of HIV-1 in ARV-naïve adolescents weighing at least 40 kg.** ◗ **In the management of HIV-1 in treatment-experienced adolescents aged from 12 to 17 years weighing at least 40 kg, but with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells × 10^6/l** **In the absence of efficacy and safety data in treatment-experienced adolescents weighing at least 40 kg but with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells × 10^6/l, and despite a simplified dosage regimen compared with other strengths of PREZISTA (600 mg, 300 mg, 150 mg, and 75 mg), the Transparency Committee considers that PREZISTA, as 400 mg and 800 mg tablets or as an oral suspension, co-administered with a low dose of ritonavir, does not provide any improvement in actual benefit (level V, non-existent) in the management of this population. These proprietary medicinal products constitute an addition to the range.**
Therapeutic use	◗ **In the management of HIV-1 in ARV-naïve adolescents aged from 12 to 17 years and weighing at least 40 kg** **The combination of PREZISTA (800 mg/day) with ritonavir (100 mg/day) represents a new therapeutic option in the protease inhibitor class.** ◗ **In the management of HIV-1 in treatment-experienced adolescents aged from 12 to 17 years weighing at least 40 kg, with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells × 10^6/l** **In this population, the proprietary medicinal products PREZISTA, as 400 mg and 800 mg tablets or as an oral suspension, constitute an addition to the range that simplifies dose adjustment and the dosage regimen compared with other strengths of PREZISTA (600 mg, 300 mg, 150 mg, and 75 mg) in two daily doses.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	PREZISTA 400 mg, tablet: 29 January 2009 PREZISTA 800 mg, tablet: 12 January 2013 PREZISTA 100 mg/ml, oral suspension: 24 October 2012 Amendment of 19 September 2013 (extensions of indication to be assessed)
Prescribing and dispensing conditions /special status	List I Medicine requiring initial annual hospital prescription. Unrestricted renewal

ATC Classification	2013 J : Antiinfectives for systemic use J05 : Antivirals for systemic use J05A : Direct acting antivirals J05AE : Protease inhibitors J05AE10 : darunavir

02 BACKGROUND

In the treatment of human immunodeficiency virus infection, the protease inhibitor PREZISTA (darunavir), as tablets of 75, 150, 300, and 600 mg or as an oral suspension, in two daily doses of 600 mg and co-administered with a low dose of ritonavir (100 mg) and in combination with other ARVs, has Marketing Authorisation for the treatment of HIV-1 infection in ARV-experienced adults, adolescents, and children aged over 3 years and weighing at least 15 kg (including highly treatment-experienced adults). In this indication, the Transparency Committee considered the AB to be substantial and the IAB moderate (level III).[1]

PREZISTA (darunavir), as tablets of 400 and 800 mg or as an oral suspension, in one daily dose of 800 mg and co-administered with a low dose of ritonavir (100 mg) and in combination with other ARVs, has Marketing Authorisation for the treatment of HIV-1 infection in adults who are:

- ARV-naïve (IAB minor or level IV) in terms of virological efficacy compared with KALETRA in the restricted population of treatment-naïve patients managed at an advanced stage of the infection, i.e. with a viral load ≥ 100,000 copies/ml,[2] or
- ARV-experienced with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l (IAB V).[3]

This opinion concerns an application for an extension of indication to paediatrics for three presentations of the proprietary medicinal product PREZISTA (oral suspension, 400 and 800 mg tablets) at a dosage of 800 mg once daily in combination with 100 mg of ritonavir, in adolescents aged from 12 to 17 years and weighing at least 40 kg who are:

- ARV-naïve (new indication)
- previously exposed to antiretroviral medicinal products but with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells × 10^6/l (modified dosage regimen to one daily dose of 800 mg instead of 600 mg twice daily, in combination with 100 mg of ritonavir).

[1] Transparency Committee opinion of 10 June 2009, 02 December 2009, and 03 April 2013 on PREZISTA.
[2] Transparency Committee opinion of 10 June 2009 on PREZISTA.
[3] Transparency Committee opinion of 14 December 2011 on PREZISTA.

03 THERAPEUTIC INDICATIONS

◗ PREZISTA 400 and 800 mg, film-coated tablet

"PREZISTA, co-administered with low dose of 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 or 800 mg tablets may be used to provide suitable dosing regimens for the treatment of HIV-1 infection in adult and **paediatric patients from the age of 12 years and at least 40 kg body weight who are**:

- **antiretroviral therapy (ARV) - naïve** (see section 4.2).
- **ARV-experienced with no darunavir resistance-associated mutations and who have plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l.** In deciding to initiate treatment with PREZISTA in ARV-experienced patients, genotypic resistance testing should guide the use of PREZISTA (see sections 4.2, 4.3, 4.4, and 5.1 of the SPC)."

◗ PREZISTA 100 mg/ml, oral suspension

"PREZISTA, co-administered with low dose of ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight **(see section 4.2 of the SPC).**[4]

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

The extensions of indication for the oral suspension with which this opinion is concerned are the same as those for the PREZISTA presentations as 400 or 800 mg tablets.

04 DOSAGE IN PAEDIATRIC PATIENTS

"Therapy should be initiated by a physician experienced in the management of HIV infection. After therapy with PREZISTA has been initiated, patients should be advised not to alter the dosage, dose form or discontinue therapy without discussing with their health care provider.

PREZISTA must always be given orally with low dose of 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."

[4] Prior to obtaining the extensions of indication to which this opinion relates, the previous wording restricted the indication to the "ARV-experienced" paediatric population.

◗ PREZISTA 400 mg, 800 mg film-coated tablet

"ARV-naïve paediatric patients (12 to 17 years of age and weighing at least 40 kg)

The recommended dose regimen is 800 mg once daily with ritonavir 100 mg once daily taken with food.

ARV-experienced paediatric patients (12 to 17 years of age and weighing at least 40 kg)

The recommended dose regimens are as follows:

- ***In ARV-experienced patients without DRV-RAMs (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, and L89V) and 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. PREZISTA 400 mg tablets can be used to construct the once daily 800 mg regimen.***
- *In all other ARV-experienced patients or if HIV-1 genotypic testing is not available, the recommended dose regimen is described in the Summary of Product Characteristics for PREZISTA 100mg/ml oral suspension and PREZISTA 75 mg, 150 mg, 300 mg, and 600 mg tablets.*

◗ PREZISTA 100 mg/ml, oral suspension

"ARV-naïve paediatric patients (12 to 17 years of age and weighing at least 40 kilograms)

The recommended dose regimen is PREZISTA 800 mg once daily with ritonavir 100 mg once daily taken with food.

ARV-experienced paediatric patients (3 to 17 years of age and weighing at least 15 kilograms).

The weight-based dose of PREZISTA and ritonavir in children and adolescents is provided in the table below. The recommended dose of PREZISTA with low-dose ritonavir should not exceed the recommended adult dose (600/100 mg twice daily).

Recommended dose for treatment-experienced children and adolescents with PREZISTA and ritonavir[a]	
Weight (kg)	**Dose (twice daily)**
≥ 15 kg to < 30 kg	380 mg (3.8 ml) PREZISTA/50 mg (0.6 ml) ritonavir
≥ 30 kg to < 40 kg	460 mg (4.6 ml) PREZISTA/60 mg (0.8 ml) ritonavir
≥ 40 kg	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir

[a] ritonavir oral solution: 80 mg/ml

In paediatric patients 12 to 17 years of age and weighing at least 40kg with prior exposure to antiretroviral preparations but without DRV-RAMs (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, and L89V) and who have plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l, a dose regimen of 800 mg once daily with ritonavir 100mg once daily with food may be used.

PREZISTA oral suspension can be used in patients unable to swallow PREZISTA tablets. PREZISTA is also available as 75 mg, 150 mg, 300 mg, 400 mg, and 600 mg film-coated tablets."

05 THERAPEUTIC NEED[5]

In the context of the treatment for HIV-1 infection in the extension of indication to treatment-naïve adolescents:

The general aim of treatment in HIV-infected children is the same as in adults, i.e. lasting reduction of the viral load to below the lowest possible detection threshold, the only way to guarantee no selection of resistance mutations and to ensure long-term virological, immunological, and clinical efficacy. The aim of antiretroviral treatment, regardless of the situation (first-line, further lines, including after multiple failure), should be to achieve and maintain a plasma viral load of < 50 copies/ml and a CD4 lymphocyte count > 500/mm^3.
The use of antiretrovirals in children is largely extrapolated from the results observed in adults.

In children and adolescents, combinations including two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI)/ritonavir are favoured (in contrast to the recommendations for adults). The low genetic barrier of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in a context of frequent compliance problems at the start of treatment in children justifies this choice.

In the protease inhibitor class and in combination with other antiretroviral medicinal products, five medicinal products have Marketing Authorisation, including in adolescents:
- atazanavir (REYATAZ) + ritonavir
- the fixed combination lopinavir/ritonavir (KALETRA)
- darunavir (PREZISTA) + ritonavir
- fosamprenavir (TELZIR) + ritonavir
- tipranavir (APTIVUS) + ritonavir.

The last two protease inhibitors listed above are not mentioned among the recommended preferred options[5] and have a very limited role in the treatment strategy:
- fosamprenavir (TELZIR) + ritonavir;
- tipranavir (APTIVUS), combined with ritonavir (NORVIR) is a treatment of last resort in highly treatment-experienced adolescents aged 12 years and over and with viruses which are multiresistant to protease inhibitors when there are no other treatment alternatives.[6]

[5] Medical management of individuals infected with HIV – Recommendations of the group of experts – 2013 Report under the guidance of Prof. Morlat Available at www.sante.gouv.fr.
[6] Transparency Committee opinion of 01 February 2012 on APTIVUS.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

◗ Protease inhibitors (PIs) as part of a treatment combining antiretroviral preparations

INN	Proprietary medicinal product Company	Pharmaceutical Form	Packaging	Indication	Date of Opinion Improvement in Actual Benefit
atazanavir	**REYATAZ** BMS	REYATAZ 50 mg/1.5 g oral powder 50 mg/1.5 g	Bottle of 180 g	Adults and children > 6 years	28/05/2014 IAB V in comparison with available alternatives in children aged over 6 years and adolescents
		capsule 150 mg capsule 200 mg	B/60		
lopinavir-ritonavir	**KALETRA** ABBOTT	Film-coated tab. 200/50 mg Film-coated tab. 100/25 mg	B/120 B/60	Adults and children > 2 years	02/07/2003 IAB II
		Oral solution 80 mg/20 mg/ml	Bottle of 60 ml		

◗ Conclusion

In adolescents aged from 12 to 17 years and weighing at least 40 kg, the most relevant comparators in the protease inhibitor class are: REYATAZ or KALETRA.

07 SUMMARY OF PREVIOUS ASSESSMENTS OF PREZISTA 400 MG IN ADULTS IN THE SAME INDICATIONS

Date of TC opinion	10 June 2009
Indication assessed	"PREZISTA 400 mg, co-administered with a low dose of ritonavir, is indicated in combination with other antiretroviral medicinal products in the treatment of human immunodeficiency virus (HIV-1) infection in **ARV-naïve adults**".
Efficacy and safety data	➢ <u>Efficacy in treatment-naïve patients (ARTEMIS)</u> The clinical efficacy of darunavir (800 mg once daily) co-administered with ritonavir (100 mg once daily) was evaluated in an open-label, controlled, phase III study lasting 192 weeks (ongoing), whose primary endpoint was to demonstrate its non-inferiority (delta threshold = 12%), and possibly its superiority (secondary endpoint), with respect to lopinavir/ritonavir (800/200 mg once daily or 400/100 mg twice daily) in treatment-naïve HIV-1-infected adult patients. The mean plasma RNA HIV-1 viral load at inclusion was 4.86 $\log_{10}$ copies/ml and the median CD4+ count was 228 × 10^6 cells/l (range: 4-750 × 10^6 cells/l) in the darunavir/ritonavir group. The treatments were associated with a fixed combination of 300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine in a single daily dose (TRUVADA one tablet daily). The non-inferiority of darunavir/ritonavir compared with lopinavir/ritonavir in terms of virological response, defined by the percentage of patients with a viral load < 50 copies/ml at week 48 of treatment (primary efficacy endpoint) was demonstrated: 83.8% (285/340) in the darunavir/ritonavir group *versus* 78.3% (271/346) in the lopinavir/ritonavir group (difference = 5.5%; 95% CI [-0.4; 11.4]). In the ITT analysis, the lower limit of the confidence interval of the difference between the two treatment groups was < 0, which does not allow the conclusion to be made that darunavir/ritunavir is superior to lopinavir/ritonavir in the patient population investigated. The subgroup analysis according to the predefined stratification factors (in particular HIV-1 RNA < or ≥ 100,000 copies/ml) showed a more favourable virological response in the darunavir/ritonavir group than in the lopinavir/ritonavir group in the sub-population restricted to patients with a viral load ≥ 100,000 copies/ml. It should be pointed out, however, that about 25% of patients in the lopinavir/ritonavir group were treated with the 800/200 mg form in a

	single daily dose (recommended in the USA but not in Europe), suggesting a possible contribution to the observed difference. The immune response (median increase in the CD4+ count) was similar in both treatment groups (137 versus 141 × 10^6 cells/l). ➢ Safety The safety profile of darunavir/ritonavir was comparable with that of lopinavir/ritonavir and protease inhibitors in general. The safety, and especially the digestive and lipid safety, of darunavir/ritonavir appears to be more favourable than that of lopinavir/ritonavir, although the adverse effects observed in this study were essentially of moderate to weak intensity and rarely involved suspension of treatment (1.7% versus 3.5%). This study did not show any unexpected adverse effects relative to the effects already observed in previous studies (POWER, TITAN) conducted in treatment-experienced patients (cf. SPC clinical experience). It should be noted that in most patients treated with lopinavir/ritonavir the "soft capsule" formulation was used up to week 48, before the tablets became available.
Actual Benefit:	**Substantial**
Improvement in Actual Benefit	In light of the available data in treatment-naïve patients (ARTEMIS study: TMC114-C211), PREZISTA (darunavir) co-administered with a low dose of ritonavir, presents in particular the following characteristics in comparison with KALETRA (lopinavir/ritonavir): - non-inferior immunological and virological efficacy, with a more favourable virological response in the subgroup of patients with a viral load ≥ 100,000 copies/ml, - a more favourable lipid safety profile, although without any demonstrable effect on cardiovascular risk, - lower incidence of diarrhoea. It should be noted that, in most patients treated with lopinavir/ritonavir, the "soft capsule" formulation was used up to week 48, prior to the tablets becoming available. - a simplified dosage regimen (once daily rather than twice daily), although there is one constraint – ritonavir must be taken separately and has to be stored in the refrigerator. Consequently, PREZISTA (darunavir), co-administered with a low dose of ritonavir, **provides a minor improvement in actual benefit (level IV) in terms of virological efficacy compared with KALETRA in the limited population of treatment-naïve patients managed at an advanced stage of the infection (viral load ≥ 100,000 copies/ml).**

Date of TC opinion	14 December 2011
Indications assessed	PREZISTA, co-administered with a low dose of ritonavir, is indicated in combination with other antiretroviral preparations for the treatment **of HIV-1 infection in ARV-experienced adults with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l. When initiating treatment with PREZISTA in ARV-experienced adults, genotype resistance testing should guide the use of PREZISTA (see sections 4.2, 4.3, 4.4, and 5.1 of the SPC).**
Efficacy and safety data	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 × 10^6 cells/ml (85.3%). The study treatments were combined with a basic optimised treatment with at least two NRTIs. 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 treatment-experienced patients with plasma HIV-1 RNA levels of ≤ 100,000 copies/ml and a CD4+ count of > 100 × 10^6 cells/ml, which corresponds to the population used in the Marketing Authorisation for PREZISTA 400 mg for 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 one daily dose has not been validated (limited data and in favour, rather, 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 × 10^6/l and patients infected with non-B HIV-1. The safety profile of treatment with darunavir/ritonavir 800/100 mg in one daily dose in this study was similar to that of the treatment with darunavir/ritonavir 600/100 mg twice daily.
Actual Benefit:	**Substantial**
Improvement in Actual Benefit	Despite the simplification of the dose regimen in comparison with the other dosages of PREZISTA (600 mg, 300 mg, 150 mg, and 75 mg), taking into account the efficacy and safety data, **the Transparency Committee considers that PREZISTA 400 mg does not provide any improvement in actual benefit (IAB V) in the management** of HIV-1-infected ARV-experienced adult patients who have no darunavir resistance-associated mutations, and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ count ≥ 100 × 10^6 cells/l. In this population **it constitutes an addition to the range**.

08 ANALYSIS OF AVAILABLE DATA

In support of its request for inclusion in two extensions of indication in adolescents aged from 12 to 17 years and weighing at least 40 kg, the company provided a clinical dossier including the DIONE phase II pharmacokinetics study (TMC114-C230) carried out in ARV-naïve adolescents infected with HIV-1. Only the efficacy and safety data from this study enabling the effect of darunavir to be quantified are detailed below.
In the extension of indication to experienced adolescents with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l, no study was provided.

08.1 Efficacy

8.1.1 ARV-naïve adolescents

The clinical dossier is based on the results at 48 weeks of a non-comparative phase II study (DIONE study) which permitted Marketing Authorisation to be granted in the treatment of human immunodeficiency virus (HIV-1) infection in ARV-naïve adolescents aged from 12 to 17 years and weighing at least 40 kg and having a viral load > 1000 copies/ml.

The primary endpoint of this phase II study was to evaluate the pharmacokinetics, safety of use, tolerability, and efficacy of darunavir administered as a single daily dose in combination with ritonavir (800 mg/100 mg), in antiretroviral treatment-naïve adolescents aged from 12 to 17 years and weighing at least 40 kg. The secondary endpoints were to evaluate safety and efficacy up to 48 weeks.
It should be noted that, according to the guidelines on the clinical development of medicinal products intended for the treatment of HIV,[7] if exposure to the medicinal product in children is similar to that in adults, the same pharmacokinetic data may be used for extrapolating to children the efficacy observed in adults. Therefore, inasmuch as the antiviral activity of darunavir has already been demonstrated in adults in the ARTEMIS[8] non-inferiority study versus lopinavir/ritonavir (KALETRA), the DIONE study does not have as its primary endpoint the evaluation of the antiviral activity of darunavir in children.
A summary of the available data in ARV-naïve adults from the ARTEMIS study, assessed by the Transparency Committee in its opinion dated 10.06.2009, is given in section 07 Summary of previous assessments.

The inclusion criteria included:
- adolescents aged from 12 to less than 18 years and with an HIV-1 infection confirmed by standard screening methods
- weight greater or equal to 40 kg
- viral load > 1000 copies/ml
- fewer than three darunavir resistance-associated mutations.

Among the non-inclusion criteria:
- previous or ongoing treatment with ARVs (including those indicated in the treatment of hepatitis B having anti-HIV activity).

[7] Guideline on the clinical development of medicinal products for treatment of HIV infection (EMEA/CPMP/EWP/633/02).
[8] Transparency Committee opinion of 10 June 2009 on PREZISTA.

Treatments
The study was conducted with tablets of PREZISTA 400 mg and capsules of NORVIR 100 mg (ritonavir).
PREZISTA was administered in accordance with the same dosage regimen as the one validated in treatment-naïve adults: darunavir + ritonavir (800/100 mg once daily) or two tablets of darunavir 400 mg and one capsule of ritonavir 100 mg. The optimised treatment consisted of a combination of two nucleoside reverse transcriptase inhibitors (NRTIs): either zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC), at the investigator's choice. These combinations were administered in the form of a fixed-dose combination or else separately, according to availability in the country concerned. These optimised treatments conform to current guidelines.

Primary efficacy endpoint: virological response at week 24, defined as the percentage of patients with a viral load < 50 copies/ml.[9]

Secondary endpoints:
- percentage of patients with a viral load < 400 copies/ml;
- change in $\log_{10}$ of the viral load since inclusion;
- change in the CD4+ percentage since inclusion.

Results (n = 12)
Twelve adolescents were included. On inclusion, the median age was 14.4 years and the median weight was 50.5 kg. The adolescents had been screened for HIV for the previous 1.7 years (median), mainly in consequence of mother-to-child transmission (5/12).
On inclusion, the adolescents had a median viral load of 4.92 $\log_{10}$ copies/ml, a median percentage of CD4+ of 18.3% and a median CD4+ cell count of 282×10^6/l. Among the 12 adolescents, the plasma HIV-1 RNA levels were between 20,000 and 100,000 copies/ml in 5 adolescents and higher or equal to 100,000 in 5 others. None of the adolescents had any primary resistance mutation to protease inhibitors and one adolescent had a mutation associated with resistance to darunavir.
The combined ARVs were either zidovudine/lamivudine (50%) or abacavir/lamivudine (50%).

At 24 weeks, 11 of the 12 adolescents had a viral load < 50 copies/ml (primary endpoint). At 48 weeks, 10 of the 12 adolescents achieved this endpoint, cf. Table 1.
The results observed at week 48 are as follows:
Eleven of the 12 adolescents had a viral load < 400 copies/ml. The mean decrease in the viral load compared with inclusion was 2.98 $\log_{10}$. A decrease in the plasma viral load ≥ 1 $\log_{10}$ compared with that on inclusion was observed in all 12 adolescents. The mean increase in the CD4+ cell count (immunological response) was 221×10^6 cells/l.

[9] The threshold of 50 copies/ml is the non-detection threshold to be aimed for, as recommended by international guidelines.

Table 1: Virological and immunological responses in weeks 24 and 48 (ITT analysis, TLOVR[10])

	Darunavir/ritonavir at 24 weeks n = 12	Darunavir/ritonavir at 48 weeks n = 12
Primary efficacy endpoint:		
Viral load < 50 copies/ml, n (%)	11 (91.7%)	10 (83.3%)
Principal secondary efficacy endpoints		
Virological response		
Viral load < 400 copies/ml, n (%)	12 (100%)	11 (91.7%)
Mean change (standard deviation) in $\log_{10}$ of the viral load since inclusion	-3.03 (0.172)	-2.98 (0.182)
Decrease in the plasma viral load ≥ 1 $\log_{10}$ compared with inclusion	12 (100%)	12 (100%)
Immunological response		
Mean change in the CD4+ cell count compared with inclusion (10^6 cells/l), n (%)	175 (19.5)	221 (22.4)

8.1.2 ARV-experienced adolescents

Since June 2009, PREZISTA has had Marketing Authorisation for the treatment of HIV-1 infection in ARV-experienced children and adolescents from the age of 6 years and weighing under 20 kg; in October 2012, this was extended to children over 3 years and weighing over 15 kg. In this indication and in children and adolescents weighing 40 kg and over, the recommended daily dosage is 1200 mg co-administered with 200 mg ritonavir, in two daily intakes, in combination with other antiretroviral preparations (same dosage regimen as that validated in adults).

The extension of indication with which this opinion is concerned corresponds to a new dosage regimen of one daily dose (PREZISTA 800 mg co-administered with 100 mg ritonavir per day) which permits a reduction in the doses of darunavir and ritonavir and the number of intakes in certain treatment-experienced adolescents, those with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 × 10^6 cells/l.

No clinical trials were conducted in adolescents in this situation (no darunavir resistance-associated mutations, a plasma HIV-1 RNA level < 100,000 copies/ml, and a CD4+ cell count ≥ 100 cells × 10^6/l). This extension of indication was granted by extrapolation of the efficacy data available for treatment-experienced adults obtained from the ODIN non-inferiority study (TMC114-C229), which compared a dosage regimen of two daily doses (600 mg twice daily) with a simplified regimen of one daily dose (800 mg/day), in combination with ritonavir (100 mg). A summary of this study, which was assessed by the Transparency Committee in its opinion of 14.12.2011, is given in section 07 Summary of previous assessments.

Thus, based in particular on:
- pharmacokinetic results from the DIONE study (described in section 8.1.1 of this opinion) carried out in adolescents aged from 12 to 17 years and weighing at least 40 kg, which showed that plasma exposure of 800 mg of PREZISTA in a single daily dose in ARV-naïve adolescents was similar to that obtained in adults;
- efficacy data from the ODIN study in treatment-experienced adults with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l,

[10] TLOVR: time to loss of virological response.

Marketing Authorisation was granted in adolescents aged from 12 to 17 years and weighing at least 40 kg and with the same restrictions as in adults, i.e. no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l.

08.2 Safety/Adverse effects

Few data are available on the safety of use of PREZISTA in paediatric patients.

8.2.1 Data from clinical studies

◗ In ARV-naïve adolescents

The safety-of-use profile in ARV-naïve adolescents infected with the HIV-1 virus is obtained from the clinical data from the phase II DIONE study conducted in 12 adolescents aged from 12 to 17 years and weighing at least 40 kg who received PREZISTA + ritonavir in a single daily dose of 800 mg in combination with other ARVs or a mean duration of 49.6 weeks.

The adverse events most commonly reported (> 20%) were vomiting (4/12, 33%), anaemia (3/12, 25%), and nausea (3/12, 25%).
The majority of adverse events were of grade 1-2. As regards lipid disorders, which are adverse events expected in the protease inhibitor class, grade 2 increases in total cholesterol (4/12 or 33.3%) and in LDL cholesterol (3/12 or 25%) were observed. As the long-term consequences of hyperlipidaemia or cardiovascular risk are unknown, a long-term pharmacovigilance study is proposed in order to document it (cf. section 8.2.3 Data from the RMP).
Grade 3 and 4 adverse events were reported in three patients (25%). These were blood disorders (anaemia, leukopenia, and thrombocytopenia), and gastrointestinal disorders (diarrhoea, nausea, and vomiting in one patient), hypotension, and a tooth abscess. None of these events was considered by the investigator to be PREZISTA-related.
None of the adolescents discontinued treatment due to the onset of an adverse event. Long-term data are expected.

◗ Experienced adolecents with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l

As indicated in section “08.1 Efficacy”, no clinical trials have been conducted in ARV-experienced adolescents with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l. This extension of indication has been granted by extrapolation of the efficacy data available in adults that were obtained from the ODIN study. In this study in adults, the safety profile of PREZISTA in combination with ritonavir in a single daily dose (800/100 mg) was generally similar to that observed with two daily doses (600/100 mg × twice daily).

8.2.2 SmPC data

With reference to paediatric patients, the SmPC stipulates that:
“The safety assessment in paediatric patients is based on the 48-week analysis of safety data from three Phase II trials. The following patient populations were evaluated (see section 5.1):
- 80 ARV-experienced HIV-1-infected paediatric patients aged from 6 to 17 years and weighing at least 20 kg who received PREZISTA tablets with low-dose ritonavir twice daily in combination with other antiretroviral agents.
- 21 ARV-experienced HIV-1-infected paediatric patients aged from 3 to < 6 years and weighing 10 kg to < 20 kg (16 participants from 15 kg to < 20 kg) who received PREZISTA oral suspension with low-dose ritonavir twice daily in combination with other antiretroviral agents.
- 12 ARV-naïve HIV-1-infected paediatric patients aged from 12 to 17 years and weighing at least 40 kg who received PREZISTA tablets with low-dose ritonavir once daily in combination with other antiretroviral agents.

Overall, the safety profile in these paediatric patients was similar to that observed in the adult population."

8.2.3 Data from the risk management plan

In particular, the risk management plan mentions the following identified significant risks: severe skin reactions, hepatotoxicity, hyperglycaemia, metabolic disorders, pancreatitis, redistribution of body fat (lipodystrophy), immune reconstitution syndrome, development of drug resistance, overdose, medication errors, and drug interactions.

Lipid disorders and growth anomalies have been identified as potential risks associated with the use of PREZISTA in ARV-naïve adolescents and have therefore been added when updating the RMP.
In this regard, the CHMP has requested additional data concerning the long-term lipid profile of PREZISTA, which will be obtainable from the ongoing PASS study entitled "Pharmacovigilance study on the safety and use of ARVs in HIV-infected children and adolescents in Europe".
In addition, the company will need to conduct a study to evaluate the growth anomalies in the paediatric population treated with PREZISTA in comparison with the data from other ARVs (including from the EPPICC cohort). The results are expected in August 2015.

08.3 Summary and discussion

Available data in HIV-infected adolescents are limited.

In adolescents aged from 12 to 17 years and weighing at least 40 kg, the immunological and virological efficacy of darunavir (PREZISTA), administered at the same low dose as that which has been validated in adults (800mg daily), in combination with low doses of ritonavir and other antiretroviral preparations, was evaluated in a non-comparative phase II pharmacokinetic study (DIONE study) conducted in 12 ARV-naïve adolescents infected with HIV-1 (viral load > 1000 copies/ml).
At 24 weeks, 11 of the 12 adolescents achieved a viral load < 50 copies/ml (primary endpoint). At 48 weeks, 10 of the 12 adolescents achieved this objective.
Although data on PREZISTA in adolescents are limited (very small study population with 5 out of 12 adolescents having a high viral load, i.e. > 100,000 copies/ml), the immunological and virological response observed at 48 weeks in this ARV-naïve paediatric population aged from 12 to 17 years and weighing at least 40 kg appears overall to be of the same order as that observed in adult patients who are also ARV-naïve.[11] No data beyond 48 weeks are available.

The new dosage regimen for PREZISTA in a single daily dose (800 mg co-administered with 100 mg ritonavir) permits a reduction in the doses of darunavir and ritonavir and the number of intakes in certain treatment-experienced adolescents with no darunavir resistance-associated mutation and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100×10^6 cells/l. This dosage regimen was granted by extrapolation of the efficacy data available for treatment-experienced adults obtained from the ODIN non-inferiority study (TMC114-C229), which compared a dosage regimen of two daily doses (600 mg twice daily) with a simplified regimen of one daily dose (800 mg/day), in combination with ritonavir (100 mg).

Generally speaking, the safety-of-use profile in the paediatric population at 48 weeks was similar to that observed in adults. However, long-term data on the consequences of lipid disorders and growth anomalies are expected.

Lastly, there is no availability of comparative data versus another protease inhibitor (REYATAZ).

[11] EPAR on PREZISTA of 25.07.2012, page 20/33.

08.4 Planned studies

As part of a pharmacovigilance plan, three long-term follow-up studies in children are proposed:
- a follow-up study in children aged from 3 to 6 years;
- a follow-up study relating to growth;
- a follow-up study of long-term safety in children aged 3 to 17 years previously included in a clinical trial.

Please refer to section 8.2.3 Data from the risk management plan.

In addition, an application for an extension of indication to ARV-naïve children aged from 3 to 12 years and previously treated without PREZISTA-associated mutations is expected.

09 THERAPEUTIC USE

Darunavir (PREZISTA) should be co-administered with low doses of ritonavir and in combination with other antiretroviral preparations. Its use should be guided by genotypic resistance testing.

◗ In the management of HIV-1 infection in ARV-naïve adolescents aged from 12 to 17 years and weighing at least 40 kg

In the latest 2013 guidelines on the medical management of persons with HIV infection,[5] two preferred options in the protease inhibitor class are recommended for the initial treatment as part of tritherapy with two NRTIs after the age of 6 years: lopinavir/ritonavir (KALETRA) or atazanavir (REYATAZ) + ritonavir.

PREZISTA + ritonavir and fosamprenavir (TELZIR) + ritonavir are cited as other possible choices of protease inhibitors. Indeed, at the time of publication of the report by the group of experts, the extension of indication for PREZISTA to treatment-naïve adolescents had not yet been validated by the Marketing Authorisation.[12]

In light of the available data in adolescents aged from 12 to 17 years and weighing at least 40 kg, the combination of PREZISTA (800 mg/day) with ritonavir (100 mg/day) represents a new treatment option in the protease inhibitor class.

◗ In the management of HIV-1 in treatment-experienced adolescents aged from 12 to 17 years weighing at least 40 kg with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l

PREZISTA proprietary medicinal products in a daily dosage of 1200 mg of darunavir co-administered with 200 mg of ritonavir, in two daily doses, in combination with other antiretrovirals, are treatment options in the protease inhibitor class for HIV-1-infected patients aged over 3 years and weighing at least 15 kg in whom prior treatment with antiretrovirals has failed (including highly treatment-experienced adults).

The use of PREZISTA in a single daily dose (800 mg of darunavir co-administered with 100 mg of ritonavir) in combination with other ARVs, is restricted to ARV-experienced adult patients who have 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 × 10^6/l. The use of this simplified dosage regimen is now extended to include treatment-experienced adolescents weighing at least 40 kg, with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l.

In this population, the proprietary medicinal products PREZISTA, as 400 mg and 800 mg tablets or as an oral suspension, constitute an addition to the range that simplifies dosage adjustment and the dosage regimen compared with other strengths of PREZISTA (600 mg, 300 mg, 150 mg, and 75 mg) in two daily doses.

[12] It is mentioned on page 343 of the report that “Darunavir and tipranavir are still reserved for use in the event of failure of the first-line treatment.” and on page 344 “darunavir/r (forthcoming Marketing Authorisation in treatment-naïve children aged ≥ 12 years)”.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual Benefit

◗ HIV infection leads to severe deterioration in the quality of life and is also life-threatening.
◗ This proprietary medicinal product is designed to prevent and/or correct the immune deficiency brought on by the HIV infection.
◗ In combination with low doses of ritonavir and other antiretroviral preparations, the efficacy/adverse effects ratio is high.
◗ There are treatment alternatives belonging to the class of protease inhibitors.

◗ Public health benefit:

The public health burden of HIV-1 infection is substantial. In the population corresponding to the extensions of indication (ARV-naïve or experienced adolescents aged from 12 to 17 years and weighing at least 40 kg but with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells × 10^6/l), the burden is small owing to the small number of adolescents concerned in relation to the total population of HIV patients in France.

Reducing AIDS-related morbidity and mortality is a public health need, especially in children and adolescents, for whom the treatment options remain limited.

PREZISTA tablets and oral suspension are not expected to have any additional impact compared to existing alternatives on the morbidity and mortality of treated adolescents. No impact is expected on quality of life or on the organisation of healthcare.

The transferability of the data to current practice is debatable, especially given the small number of adolescents included in the phase II study and owing to the fact that the efficacy data are extrapolated to adolescents from those obtained in adults.

In conclusion, it is not expected that PREZISTA will have any impact on public health in the extensions of indication to either ARV-naïve or experienced adolescents aged from 12 to 17 years and weighing at least 40 kg, but with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells × 10^6/l.

◗ This is a first- or second-line treatment.

Consequently, the Transparency Committee considers that the actual benefit of PREZISTA, co-administered with a low dose of ritonavir in combination with other antiretroviral medicinal products is substantial in the treatment of HIV-1 infection in ARV-naïve or experienced adolescents aged from 12 to 17 years and weighing at least 40 kg but with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells × 10^6/l.

010.2 Improvement in actual benefit (IAB)

◗ In the management of HIV-1 in ARV-naïve adolescents aged from 12 to 17 years and weighing at least 40 kg

Taking into account:
- the very limited data in ARV-naïve adolescents weighing at least 40 kg (DIONE study), which suggest an efficacy and safety profile at 48 weeks similar to that observed in the adult ARV-naïve population with, however, some uncertainty over the growth anomalies and the long-term consequences of lipid disorders;
- the lack of comparative data other than those versus lopinavir/ritonavir (KALETRA) in naïve adults (ARTEMIS non-inferiority study),

PREZISTA as 400 mg and 800 mg tablets or as an oral suspension, co-administered with a low dose of ritonavir, does not provide any improvement in actual benefit (level V, non-existent) in the management of HIV-1 in ARV-naïve adolescents weighing at least 40 kg.

◗ In the management of HIV-1 in treatment-experienced adolescents aged from 12 to 17 years weighing at least 40 kg with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells × 10^6/l

In the absence of efficacy and safety data in treatment-experienced adolescents weighing at least 40 kg with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells × 10^6/l, and despite a simplified dosage regimen compared with other strengths of PREZISTA (600 mg, 300 mg, 150 mg, and 75 mg), the Transparency Committee considers that PREZISTA, as 400 mg and 800 mg tablets or as an oral suspension, co-administered with a low dose of ritonavir, does not provide any improvement in actual benefit (level V, non-existent) in the management of this population. These proprietary medicinal products constitute an addition to the range.

010.3 Target population

In ARV-naïve adolescents

The target population of PREZISTA in this extension of indication is represented by adolescents aged between 12 and 17 years and weighing at least 40 kg infected with the human immunodeficiency virus and not previously treated with ARVs.

According to the report on the management of persons infected with HIV,[5] the number of new infections in the paediatric population is very small, with fewer than 10 to 15 newborns infected with HIV-1 being born in France each year. There are around 1500 HIV-infected children living in France. The great majority of new diagnoses of infection are in immigrant children coming from highly endemic areas.
Each year in France, a hundred or so adolescents are infected by sexual transmission.

In conclusion, the target population of PREZISTA in ARV-naïve HIV-infected adolescents aged between 12 and 17 years and weighing at least 40 kg may be estimated at fewer than 100 patients.

In ARV-experienced adolescents with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l

The target population of PREZISTA in this extension of indication is represented by ARV-experienced adolescents aged between 12 and 17 years and weighing at least 40 kg infected with the human immunodeficiency virus and with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l.

In the absence of epidemiological data, the target population of ARV-experienced children and adolescents, but whose treatment had failed, likely to receive PREZISTA, had been estimated in the Transparency Committee's opinion of 02.12.2009 by extrapolation from the study on the outcome at adolescence for children followed up in the French perinatal survey.[13] Based on the following data:

- the number of HIV-infected children living in France was estimated at around 1500, and 10 to 20 new cases are diagnosed each year.[14,5]
- 81% of HIV-infected children would be treatment-experienced and the percentage of treatment-experienced children with a viral load > 1000 copies/ml could be estimated at 35% (or about 425 patients).

However, it was stressed that, in practice, the number of children and adolescents likely to receive PREZISTA will be smaller because its use is limited to treatment-experienced patients aged over 6 years and weighing at least 20 kg, and whose virus is susceptible to darunavir/ritonavir.

As in adults, the target population of PREZISTA, with a simplified dosage regimen of 800 mg in a single daily dose, is included in the target population of treatment-experienced children and adolescents, and it is even smaller as it is limited to adolescents aged from 12 to 17 years and weighing at least 40 kg with no darunavir resistance-associated mutations and a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l.

[13] DOLLFUS C. Devenir à l'adolescence des patients VIH après transmission mère-enfant. Communication available at http://www.infectiologie.com/site/medias/JNI/JNI06/CP/cp2-Dollfus.pdf (consulted on 13/10/09).
[14] Yéni Report 2008.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion of PREZISTA, 400 mg and 800 mg tablets and oral suspension, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the extensions of indication in adolescents aged from 12 to 17 years and weighing at least 40 kg and at the dosage in the Marketing Authorisation.

◗ Proposed reimbursement rate: 100%

◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.