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TRANSPARENCY COMMITTEE

Opinion
3 April 2013

PREZISTA 100 mg/ml, oral suspension

200 ml vial (CIP: 34009 267 049 5 7)

PREZISTA 75 mg, film-coated tablet

B/480 (CIP: 34009 395 951 3 9)

PREZISTA 150 mg, film-coated tablet

B/240 (CIP: 34009 395 953 68)

PREZISTA 300 mg, film-coated tablet

B/120 (CIP: 34009 378 318 4 0)

PREZISTA 600 mg, film-coated tablet

B/60 (CIP: 34009 393 140 8 2)

Applicant: JANSSEN-CILAG

INN	darunavir
ATC Code (2012)	J05AE10 (protease inhibitor class of antiretrovirals)
Reasons for the request	Inclusion for the oral suspension Extension of the indication for 75 mg, 150 mg, 300 mg and 600 mg tablets
Lists concerned	National Health Insurance (Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)
Indications concerned	<i>PREZISTA 100 mg/ml, oral suspension</i> “PREZISTA, co-administered with a 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 patients, as well as in antiretroviral therapy (ART)-experienced paediatric patients from the age of 3 years and at least 15 kg body weight.” <i>PREZISTA 75 mg, 150 mg, 300 mg and 600 mg, film-coated tablet</i> “Treatment of HIV-1 infection in ART-experienced paediatric patients from the age of 3 years and at least 15 kg (at least 40 kg for the 600 mg tablet).”

Actual Benefit	The Actual Benefit is substantial in the Marketing Authorisation indications.
Improvement in Actual Benefit	<u>PREZISTA 100 mg/ml, oral suspension</u> In view of the small number of alternative treatments, the Committee considers that the proprietary medicinal product PREZISTA oral solution, co-administered with a low dose of ritonavir and other antiretroviral preparations, constitutes an improvement in actual benefit (IAB III) in the treatment of human immunodeficiency virus (HIV-1) infection in ART-experienced children aged 3 to 6 years and weighing at least 15 kg. <u>In the management of HIV-1 infection in children from the age of 6 years, previously-treated adolescents and adults</u> The Committee considers that the proprietary medicinal product PREZISTA oral solution, co-administered with a low-dose of ritonavir and other antiretroviral agents is an addition to the range and does not therefore offer any improvement in actual benefit: IAB V (non-existent) in the treatment of human immunodeficiency virus in treatment-experienced children and adolescents from the age of 6 years and in adults. <u>PREZISTA 75 mg, 150 mg, 300 mg and 600 mg, film-coated tablet</u> In the extension of indication for the tablet forms in the previously-treated paediatric population aged from 3 to 6 years weighing between 15 and 20 kg, the Committee considers that the medicinal product PREZISTA, co-administered with a low dose of ritonavir and other antiretroviral agents, constitutes a moderate improvement in actual benefit (IAB III) in the treatment of human immunodeficiency virus (HIV-1) infection.
Therapeutic use	PREZISTA is a first- or second-line treatment in children aged from 3 to 6 years with HIV previously treated with antiretrovirals.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	PREZISTA 100 mg/ml, oral suspension: 24 October 2012 PREZISTA 75 and 150 mg, tablet: 23 Jun 2009 PREZISTA 300 mg, tablet: 12 February 2007 PREZISTA 600 mg, tablet: 29 January 2009
Prescribing and dispensing conditions/ special status	List I Medicine requiring initial annual hospital prescription. Unrestricted renewal.
ATC Classification	2012 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, PREZISTA in tablet form, co-administered with a low dose of ritonavir, has Marketing Authorisation in adults previously treated with antiretrovirals, including highly pretreated patients, and since June 2009 for the treatment of HIV-1 infection in children and adolescents, previously treated with antiretrovirals, from the age of 6 years and weighing at least 20 kg . This paediatric indication was assessed by the Transparency Committee on 2 December 2009 [substantial actual benefit and moderate improvement in actual benefit (level III) in the management].

The Marketing Authorisation in paediatric patients was extended on 24 October 2012 to children previously treated with antiretrovirals from the age of 3 years and weighing at least 15 kg for the entire PREZISTA range (except for the 400 and 800 mg tablets).

This opinion relates to a request:

- for inclusion on the lists of medicines covered by National Health Insurance and for hospital use of a new presentation of PREZISTA in the form of an oral suspension,
- for an extension of indication to the paediatric population previously treated with antiretrovirals aged from 3 to 6 years and weighing at least 15 kg for the 75, 150, 300 and 600 mg tablets.

The Applicant has at the same time requested the listing of a new PREZISTA presentation in the form of an 800 mg tablet, which is covered in a separate opinion given that it is an addition to the range specifically intended (as is the 400 mg tablet) for the treatment of adults:

- antiretroviral treatment (ART) naive or
- ART experienced with no darunavir resistance-associated mutations and who have a plasma HIV-1 RNA level of < 100,000 copies/ml and a CD4+ cell count of ≥ 100 cells $\times 10^6/l$; at the regimen of 800 mg/day with 100 mg ritonavir.

Lastly, the medicinal product PREZISTA in the form of 75, 150, 300, 400 and 600 mg tablets was approved for renewal of listing on 19/10/2012; the Committee considered that the actual benefit remained substantial.

The IAB levels of PREZISTA granted by the Transparency Committee in each of the indications are given in an appendix to this opinion.

03 THERAPEUTIC INDICATIONS

► PREZISTA 100 mg/ml, oral suspension

“PREZISTA, co-administered with a low dose of ritonavir is indicated in combination with other antiretroviral preparations for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients, as well as in antiretroviral therapy (ART)-experienced paediatric patients from the age of 3 years and at least 15 kg.

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

► PREZISTA 75 mg, 150 mg, 300 mg and 600 mg, film-coated tablets

“PREZISTA, co-administered with a 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 75 mg, 150 mg, 300 mg or 600 mg tablets may be used to provide suitable dose regimens (see section 4.2 of the SPC):

- for the treatment of HIV-1 infection in antiretroviral treatment (ART) experienced adults, including those that have been highly pre-treated patients.
- for the treatment of HIV-1 infection in the ART-experienced paediatric patients **from the age of 3 years and at least 15 kg body weight** (40 kg for the 600 mg tablet).

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

It should be noted that, in the case of the above-mentioned tablet strengths, the previous paediatric indication was validated by the Marketing Authorisation in children from the age of 6 years and weighing at least 20 kg.

04 DOSAGE

“Therapy should be initiated by a doctor 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, dose form or discontinue therapy without first seeking their doctor's advice.

PREZISTA must always be given orally with a 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.”

► PREZISTA 100 mg/ml, oral suspension

“ART-naïve adult patients

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

ART-experienced adult patients

- The recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food.

- In ART-experienced adult patients with no darunavir resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V) and who have a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells $\times 10^6/l$, a regimen of 800 mg once daily with ritonavir 100 mg once daily taken with food may be used.
- If HIV-1 genotype testing is not available, the recommended dose regimen is PREZISTA 600 mg twice daily in combination with ritonavir 100 mg twice daily to be taken with food.

ART-experienced paediatric patients (aged from 3 to 17 years and weighing at least 15 kg).

The dose of PREZISTA and ritonavir to be used 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 for 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

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."

► PREZISTA 75 mg, 150 mg, 300 mg and 600 mg film-coated tablets

"ART-experienced adult patients

□ The recommended dose regimen is 600 mg twice daily taken with ritonavir 100 mg twice daily taken with food. PREZISTA 75 mg tablets may be used to obtain the regimen of 600 mg twice daily.

The use of 75 mg tablets to obtain the recommended dose is appropriate when there is a risk of hypersensitivity to the colouring agents used in the 300 mg and 600 mg tablets or in case of difficulty in swallowing these tablets.

□ In ART-experienced with no darunavir resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V) and who have a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells $\times 10^6/l$, a regimen of 800 mg once daily with ritonavir 100 mg once daily taken with food may be used (see Summary of Product Characteristics for PREZISTA 400 mg tablets).

ART-naïve adult patients

For the recommended dose regimen in ART-naïve patients, see the Summary of Product Characteristics for PREZISTA 400 mg tablets.

ART-experienced children and adolescents (aged 3 to 17 years and weighing at least 15 kg or at least 40 kg in the case of the 600 mg tablets¹).

Recommended dose for treatment-experienced children and adolescents (3 to 17 years of age) for PREZISTA tablets and ritonavir	
Weight (kg)	Dose (twice daily)
≥ 15 kg – < 30 kg	375 mg PREZISTA/50 mg ritonavir ^a
≥ 30 kg – < 40 kg	450 mg PREZISTA/60 mg ritonavir ^a
≥ 40 kg	600 mg PREZISTA/100 mg ritonavir

^a with ritonavir oral solution: 80 mg/ml

The recommended dose of PREZISTA with low dose ritonavir should not exceed the recommended adult dose (600/100 mg twice daily).

The exclusive use of 75 mg and 150 mg tablets or the 100 mg/ml oral suspension to achieve the recommended dose of PREZISTA could be appropriate when there is a risk of hypersensitivity to specific colouring agents.”

05 THERAPEUTIC NEED²

In the context of the treatment for HIV-1 infection in the extension of indication in children previously treated with antiretrovirals aged from 3 to 6 years and weighing between 15 and 20 kg:

The general aim of treatment in HIV-infected children is the same as in adults, i.e. the sustained reduction in the viral load to below the lowest possible detection threshold, the only guarantee of the absence of resistance-associated mutations selection and of long-term virological, immunological and clinical efficacy. The aim of antiretroviral treatment, regardless of the situation (first line, further lines, including after multiple failures), should be to achieve and maintain a viral load < 50 copies/ml and a CD4 lymphocyte cell count > 500/mm³.

The use of antiretrovirals in children is widely extrapolated from the results observed in adults.

In children, combinations including two nucleoside reverse transcriptase inhibitors (NRTIs) and 1 protease inhibitor (PI)/ritonavir are favoured (in contrast to the recommendations for adults).

The preferred choice of potentialised protease inhibitor is the fixed lopinavir/ritonavir combination (KALETRA), which has Marketing Authorisation from 2 years of age.

In the class of protease inhibitors and in combination with other antiretrovirals, therapeutic alternatives to lopinavir/ritonavir (KALETRA) are mainly represented by:

- the combination of fosamprenavir (TELZIR) + ritonavir (NORVIR) from the age of 6 years, either for children starting a treatment, or for previously-treated children intolerant to lopinavir/ritonavir (KALETRA) or with virological failure, whose virus is sensitive to fosamprenavir (TELZIR) + ritonavir (genotypic resistance test). The difference in resistance profiles between lopinavir/ritonavir (KALETRA) and fosamprenavir (TELZIR) + ritonavir could favour the alternate administration of the two products in the event of virological failure.
- the combination of darunavir (PREZISTA) + ritonavir (NORVIR), before the granting of the extension of indication in children aged from 3 to 6 years and weighing between 15 and 20 kg, for

¹ For the 600 mg tablet: “ART-experienced children and adolescents (aged 3 to 17 years and weighing at least 40 kg): the recommended dose of PREZISTA with a low dose of ritonavir in children is dependent on weight and should not exceed the recommended adult dose (600/100 mg twice daily). The PREZISTA/ritonavir dose used in adults (600/100 mg twice daily) may be used in children and adolescents weighing 40 kg or more. In the paediatric population weighing less than 40 kg see also the Summary of Product Characteristics for PREZISTA 100 mg/ml oral suspension, 75 and 150 mg tablets.”

² Expert group guidelines (under the guidance of Prof. P. Yeni) concerning the medical management of individuals infected with HIV (report from July 2010)

previously treated children over the age of 6 years and weighing at least 20 kg with virological failure, whose virus is sensitive to darunavir/ritonavir (genotypic resistance test). Compared with the fixed lopinavir/ritonavir combination (KALETRA) the administration of fosamprenavir (TELZIR) or darunavir (PREZISTA) is more constraining because they have to be combined with low doses of ritonavir (NORVIR), which necessitates the administration of two medicinal products with a potential risk of misuse (risk of using fosamprenavir or darunavir as monotherapy in cases of poor tolerance to ritonavir).³

In view of the currently available treatments, the following protease inhibitors remain available, though they have a very limited place in therapeutic strategy.

- tipranavir (APTIVUS) combined with ritonavir (NORVIR) is a last line treatment in highly pretreated adolescents aged 12 years and over and with viruses which are multiresistant to protease inhibitors when there is no further therapeutic alternatives.⁴
- indinavir (CRIXIVAN) as part of a triple therapy has a very restricted place in the management of adults and children over the age of 4 years, particularly for reasons of its considerable urinary toxicity (urinary lithiasis in 10% of patients). CRIXIVAN is no longer listed among the recommended preferred options. It could be a useful alternative in cases of HIV encephalitis due to its excellent brain diffusion.⁵

³ Transparency Committee opinion of 06/02/2008 on TELZIR and of 02/12/2009 on PREZISTA

⁴ Transparency Committee opinion of 01/02/2012 on APTIVUS

⁵ Transparency Committee opinion of 18/01/2012 on CRIXIVAN

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

► Protease inhibitors (PIs) as part of a treatment combining antiretrovirals in children and adolescents

INN	Medicinal product Company	Pharmaceutical form	Packaging	Indication	Date of opinion IAB
lopinavir-ritonavir	KALETRA ABBOTT	Soft capsule, 133, 3/33, 3 mg	B/180	Adults and children > 2 years	02/07/2003 IAB II
		Film-coated tab. 200/50 mg	B/120		
		Film-coated tab. 100/25 mg	B/60		
		Oral solution 80 mg/20 mg/ml	60 ml vial		
fosamprenavir	TELZIR GSK	Film-coated tabs	Bottle of 60 tabs	Adults and children > 6 years	06/02/2008 adolescents and children > 6 years: IAB IV
		Oral suspension	225 ml vial		
tipranavir*	APTIVUS BOEHRINGER INGELHEIM	Oral solution 100 mg/ml	95 ml vial	Highly pretreated children aged 2 to 12 years	10/03/2010 IAB IV
		250 mg soft capsule		Adults and adolescents aged 12 years and over, highly pretreated	10/03/2010 adolescents aged 12 years and over, highly pretreated: IAB V
ritonavir**	NORVIR ABBOTT	100 mg soft capsule	B/336 and B/84	Adults and children > 2 years (<i>reserved in combination with PI</i>)	nd
		Oral solution 80 mg/ml	90 ml vial		
indinavir*	CRIXIVAN	100 mg hard capsule	B/180	Adults and children > 4 years	06/02/2002 Children: IAB IV
		200 mg hard capsule	B/360		
		400 mg hard capsule	B/90 and B/180		
		Oral suspension	225 ml vial		

* tipranavir and indinavir are no longer recommended on account of their adverse effects.

** used at a low dose as an enhancer in combination with other protease inhibitors

► Conclusion

In treatment-experienced children aged 3 to 6 years and weighing at least 15 kg, the clinically relevant comparator in the protease inhibitor class is KALETRA, given that:

- TELZIR only has Marketing Authorisation from the age of 6 years,
- VIRACEPT, APTIVUS and CRIXIVAN are not at the same level in the therapeutic strategy (limited role),
- NORVIR is used in combination with PIs as an enhancer.

► Protease inhibitors (PIs) as part of a treatment combining antiretrovirals in adult patients.

- lopinavir combined with ritonavir: KALETRA, oral solution and film-coated tablets,
- atazanavir: REYATAZ, hard capsules or oral powder, indicated in adults
- fosamprenavir: TELZIR, film-coated tablets and oral solution,
- 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
- indinavir: CRIXIVAN, hard capsules and film-coated tablets
- amprenavir: AGENERASE, capsules and oral solution, fosamprenavir (TELZIR) is a prodrug of amprenavir, which it replaces
- saquinavir mesylate: INVIRASE, hard capsules and film-coated tablets

► Conclusion

In adults, adolescents and ART-experienced children from the age of 6 years and weighing at least 20 kg:

- The most clinically relevant comparators in the protease inhibitor class are: REYATAZ or KALETRA.⁶
- In virological failure situations, the choice of treatment depends on the patient's treatment history and on the genotypic and phenotypic profiles of the patient's viruses (where available).

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) MA population or restricted
Austria	YES (100%)	
Netherlands	YES (100%)	
Germany	YES (100%)	
Ireland	YES (100%)	
Sweden	YES (100%)	
Belgium	NO	
Italy	Under assessment	
Spain	Under assessment	
Switzerland	NO	
Scotland	MA pending	
Wales	Under assessment	

⁶ Expert group guidelines (under the guidance of Prof. P. Yeni) concerning the medical management of individuals infected with HIV (report from July 2010), page 74

08 ANALYSIS OF AVAILABLE DATA

In support of its application for inclusion, the Applicant provided a clinical dossier including :

- one ARIEL phase II pharmacokinetic study (TMC114-C228). Only the efficacy and safety data from this study enabling an assessment of the quantity of the effect of darunavir are detailed below.
- one phase I bioequivalence study.

08.1 Efficacy

8.1.1 Children aged from 3 to 6 years and weighing between 15 and 20 kg

The indication for darunavir (PREZISTA) in children aged from 3 to 6 years was obtained on the basis of a non-comparative phase II study (ARIEL study) conducted with the oral suspension in 21 children (aged 3 to 6 years and weighing from 10 to 20 kg) infected with the type 1 human immunodeficiency virus (HIV-1), receiving stable antiretroviral therapy (ART) for at least 12 weeks and having to change ART treatment due to virological failure (viral load > 1000 copies/ml).

The primary objective of this phase II study was to determine the paediatric dosage of darunavir in combination with ritonavir.⁷ The secondary objectives were to evaluate the safety and efficacy up to 48 weeks in patients previously treated with antiretroviral agents aged from 3 to 6 years and weighing from 10 to 20 kg.

It should be noted that, according to the guidelines on the clinical development of medicinal products intended for the treatment of HIV,⁸ if exposure to the drug in adults and children is similar and is assumed to have the same efficacy, only pharmacokinetic data may be used for extrapolating the efficacy data observed in adults to children. Therefore, since antiviral activity of darunavir has already been demonstrated in adults, the ARIEL study does not have as its primary objective the assessment of the antiviral activity of darunavir in children.

The inclusion criteria included:

- children aged 3 to 6 years with HIV-1 infection confirmed by standard screening methods
- weight between 10 and 20 kg
- previously treated for at least 12 weeks but needing a change of treatment (virological failure with a viral load of > 1000 copies/ml)
- fewer than three darunavir-associated resistance mutations.

Treatments

The study was carried out with PREZISTA oral suspension and ritonavir oral solution.

After dose titration, the children received variable doses of darunavir(DRV) /ritonavir according to their weight, in two daily doses.

- between 10 and 15 kg (n = 5): 25 mg/kg DRV / 3 mg/kg ritonavir bid
- between 15 and 20 kg (n = 16): 375 mg/kg DRV / 50 mg ritonavir twice daily.

The protocol called for the optimised treatment co-administered with darunavir/ritonavir to contain at least 2 antiretrovirals (a combination of NRTI and/or NNRTI). All the children received an initial NRTI based optimised treatment (19 children were treated with two NRTIs and two patients with three NRTIs).

⁷ The pharmacokinetic data for darunavir combined with ritonavir in 14 previously-treated children aged from 3 to < 6 years and weighing between 15 and 20 kg showed that the doses determined on the basis of weight involved an exposure to darunavir comparable to that observed in adults receiving PREZISTA/ritonavir 600/100 mg twice daily.

⁸ Guideline on the Clinical development of medicinal products for treatment of HIV infection (EMA/CPMP/EWP/633/02)

Primary efficacy endpoint: virological response at week 48, defined as the percentage of patients with a viral load of < 50 copies/ml.⁹

Secondary endpoints

- percentage of patients with a viral load < 400 copies/ml;
- percentage of patients with a reduction of at least 1 log₁₀ in their viral load compared with inclusion;
- change in log₁₀ of the viral load since inclusion;
- change in the CD4+ percentage since inclusion;¹⁰
- change in the CD4+ percentage compared with inclusion.

Results

The initial study protocol called for the inclusion of 24 children (between 10 and 14 children for each of the following weight intervals: 10 to 15 kg and 15 to 20 kg).

A total of 27 patients were included. However, following an EMA inspection, the data for 6 patients were excluded. The analyses therefore related to 21 children.

- 5 children weighing between 10 and 15 kg (sub-population not specified in the Marketing Authorisation),
- 16 children between 15 and 20 kg: corresponding to the sub-population specified in the Marketing Authorisation.

► Results in the study population as a whole (n = 21):

On inclusion, the median age of the children was 4.4 years and the median weight was 14.9 kg. The children had been infected with HIV for 4 years (median).

On inclusion the children had a median viral load of 4.34 log₁₀ copies/ml, a median percentage of CD4+ of 27.7% and a median percentage CD4+ of 27.7% and a median CD4+ cell count of $927 \times 10^6/l$.

The children had previously been treated with a median of four antiretrovirals (from three to eight). Most of the children had received at least one protease inhibitor (76.2%, median was 1). All the subjects had been treated with at least two nucleoside reverse transcriptase inhibitors (NRTIs) and 61.9% had been treated with at least one non-nucleoside reverse transcriptase inhibitor (NNRTI). On inclusion, 17 of the 21 children did not have primary (genomic) PI resistance mutations and 19 children had no resistance mutations to darunavir. Fifteen children had at least three secondary PI resistance mutations.

At 24 weeks, 12 of the 21 children had a viral load < 50 copies/ml. At 48 weeks, 17 of the 21 children achieved this objective, cf. Table 2.

At week 48, 18 of the 21 children had a viral load < 400 copies/ml (85.7%). A decrease in the viral load of ≥ 1 log₁₀ was observed in 19 children. The median increase in the CD4+ cell count (immunological response) was 187×10^6 cells/l in week 48.

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

¹⁰ In children, the level of CD4+ lymphocytes is generally expressed as a percentage of the total number of lymphocytes, in view of physiological changes in the number of lymphocytes with age (report by Yéni 2008)

Table 2: Virological and immunological responses in weeks 24 and 48 (ITT analysis, TLOVR¹¹)

	Darunavir / ritonavir
	n = 21
Primary efficacy endpoint	
Viral load < 50 copies/ml, n (%)	
at 24 weeks:	12 (57.1%)
at 48 weeks:	17 (81%)
Principal secondary efficacy endpoints	
Virological response	
Viral load < 400 copies/ml, n (%)	18 (85.7%)
Decrease in the viral load $\geq 1 \log_{10}$, n (%)	19 (90.5%)
Change in $\log_{10}$ of the viral load since inclusion	
Mean (standard deviation)	-2.14 (0.257)
Median (extremes)	-2.3 [-4; 0]
Immunological response	
Mean change in the CD4 % since inclusion (standard error)	4 (1.30)
Mean change in the CD4+ cell count compared to inclusion (10^6 cells/l), n (%)	+ 187 (76.7)

► Results in the sub-group of children weighing between 15 and 20 kg specified in the Marketing Authorisation (n = 16):

The efficacy data corresponding to the population validated by the Marketing Authorisation are from a subgroup of 16 children among the 21 assessed. Thirteen children of the 16 weighing between 15 and 20 kg had a viral load < 50 copies/ml (81.3%) at 48 weeks.

► Results in the sub-group of children weighing between 10 and 15 kg (n = 5):

The available efficacy data for the paediatric population weighing less than 15 kg are very limited (very small number of patients, none weighing less than 12 kg and short assessment period of 2 weeks). For the purposes of information, four of the five children weighing between 10 and 15 kg had a viral load < 50 copies/ml (80%) at 48 weeks.

No dosage recommendations can be given. The Marketing Authorisation indication had therefore not been validated between 10 and 15 kg, given that it was restricted to children aged from 3 to 6 years and weighing from 15 to 20 kg.

8.1.2 Bioequivalence

The bioequivalence between darunavir tablets (PREZISTA) and the oral suspension was demonstrated in a phase I study conducted in healthy adults. Consequently, the extension of indication to include children aged 3 to 6 years and weighing more than 15 kg was granted for 75, 150, 300 and 600 mg darunavir tablets (PREZISTA) and the set of indications already validated for the 75, 150, 300 and 600 mg tablets have been granted for the oral suspension.

The oral suspension may be used in patients unable to swallow the tablets (cf. SmPC). There is no need for any dose titration when switching from the oral suspension to tablets.

Applicant's rationale to justify the paediatric indication for tablets in children aged from 3 to 6 years:
"Taking a medicine in the form of an oral suspension is generally preferred to tablet forms, especially as a way of avoiding tablets going down the wrong way in young children. However, and for treatment compliance reasons in some patients, it may be found preferable to opt for administration of darunavir in tablet form."

¹¹ TLOVR: time to loss of virological response

08.2 Adverse effects

There are few data available on the safety of use of darunavir in children, and especially in children aged from 3 to 6 years.

The safety-of-use profile in previously treated children from 3 to 6 years of age and weighing from 15 to 20 kg is based on clinical data of ARIEL study. Of the 21 patients with HIV-1 infection, 16 children aged from 3 to 6 years and weighing between 15 and 20 kg received darunavir/ritonavir at an optimised dose in combination with other antiretrovirals for a mean period of 36.6 weeks.

The most commonly reported adverse events (> 20%) were upper respiratory tract infections (6/21, 29%), diarrhoea (5/21, 24%), ringworm of the scalp (5/21, 24%) and cough (5/21, 24%).

Most adverse events were of grades 1-2. No grade 3 adverse events were reported. Two patients reported grade 4 adverse events, but none of these events was considered by the investigator to be treatment-related.

No new issues came to light in this study as regards the known safety profile of darunavir combined with ritonavir.

Overall, the safety-of-use profile in the paediatric population was similar to that observed in adults.

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

08.3 Summary & discussion

In the sub-population specified by the Marketing Authorisation (children aged from 3 to 6 years and weighing between 15 and 20 kg) and at the dosage adjusted for paediatric use, the immunological and virological efficacy of darunavir (PREZISTA), administered in combination with a low dose of ritonavir and in combination with other antiretrovirals, was assessed in a non-comparative phase II study (ARIEL study), conducted in 21 children infected with HIV-1 (including 16 children aged from 3 to 6 years and weighing between 15 and 20 kg), receiving stable ART therapy for at least 12 weeks and needing to have a change of treatment owing to virological failure (viral load > 1000 copies/ml).

On inclusion, in the total study population, the median viral load was 4.34 log₁₀ copies/ml, the median CD4+ percentage was 27.7% and the median CD4+ cell count was 927 × 10⁶/l. Of the 21 children, 17 (81%) did not have any primary PI resistance mutations, 19 (90.5%) had no resistance mutations to darunavir and 15 (71.4%) had at least three acquired PI mutations.

In the total study population (n = 21), the percentage of children who have reached a viral load of < 50 copies/ml was 57.1% at week 24 and 81% at week 48 (primary efficacy endpoint). The mean increase in the CD4+ cell count (immunological response) in week 48 was 187 × 10⁶ cells/l.

In the sub-population specified in the Marketing Authorisation (n = 16 children aged from 3 to 6 years and weighing between 15 and 20 kg), the percentage of children who obtained a viral load < 50 copies/ml at week 48 was 81.3%.

The available efficacy data in the paediatric population weighing less than 15 kg are even more limited and no dosage guidelines can be given. The Marketing Authorisation indication had not therefore been validated between 10 and 15 kg, and was restricted to children aged 3 to 6 years weighing from 15 to 20 kg.

In general, the immunological and virological response observed at week 48 in the paediatric population aged from 3 to 6 years and weighing between 15 and 20 kg appears to be of the same order as that described in children over the age of 6 years and in highly pretreated adults.¹²

¹² EPAR on PREZISTA of 19 July 2012, pages 22/39, 27/39

Although experience with PREZISTA in previously-treated children aged from 3 to 6 years is limited, the safety profile in the paediatric population was similar to that observed in adults.

No comparative studies in children have ever been conducted and no data are available beyond 48 weeks.

Moreover, since bioequivalence between darunavir tablets (PREZISTA) and the oral suspension has already been demonstrated, the extension of indication to include children aged from 3 to 6 years and weighing more than 15 kg was granted for 75, 150, 300 and 600 mg darunavir tablets (PREZISTA) and the set of indications already validated for the 75, 150, 300 and 600 mg tablets have been granted for the oral suspension.

08.4 Programme of studies

Request for an extension of indication in antiretroviral therapy-naïve children and adolescents aged from 12 to 17 years.

09 THERAPEUTIC USE

Darunavir (PREZISTA) as an oral suspension should be co-administered with a low dose of ritonavir and in combination with other antiretroviral agents.

In children aged from 3 to 6 years and weighing between 15 and 20 kg, the darunavir/ritonavir combination constitutes a therapeutic option in the protease inhibitor class, as an alternative to the fixed lopinavir/ritonavir combination (KALETRA) for treatment-experienced children in virological failure whose virus is sensitive to darunavir/ritonavir (genotypic resistance test).

Compared with the fixed lopinavir/ritonavir combination (KALETRA), the administration of darunavir is more constraining because it has to be combined with a low dose of ritonavir, which necessitates the administration of two medicinal products with a potential risk of misuse (use of unenhanced PI in cases of poor tolerance to ritonavir).

The use of PREZISTA is not recommended in children below the age of 3 years or weighing less than 15 kg. No dosage guidelines can be offered for these children.

In the other populations mentioned in the Marketing Authorisation, PREZISTA retains its place in the therapeutic strategy in the protease inhibitor class for HIV-1 infected patients, both treatment-naïve and following failure of a previous antiretroviral treatment (including highly pretreated patients).

Overall, the availability of a new pharmaceutical form, represented by an oral suspension of darunavir, offers the possibility of wider use in children from the age of 3 years weighing over 15 kg and constitutes a useful addition to the range for patients unable to swallow tablets.

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

010.1 Actual benefit

10.1.1 Oral suspension

● The condition targeted by this proprietary medicinal product entails a 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 agents, the efficacy/adverse effects ratio is favourable.

● There are treatment alternatives belonging to the class of protease inhibitors. In treatment-experienced children aged from 3 to 6 years and weighing 15 to 20 kg, the alternatives are few.

● Public health benefit:

The public health burden of HIV-1 infection is substantial. In the population corresponding to the extension of indication (ART-experienced children from the age of 3 years and weighing between 15 and 20 kg), the burden is small on account of the limited number of patients concerned in comparison with the total population of patients with HIV in France.

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

PREZISTA oral solution presents a pharmaceutical form that is suited to the treatment of HIV infection in children. Given the small number of treatment alternatives available for children, in view of the available safety data and the resistance pattern, it is expected that PREZISTA will have a moderate impact on the morbidity and mortality associated with HIV in children infected with HIV-1 and previously treated with antiretroviral agents.

Due to the current lack of data, the impact on quality of life is unquantifiable. No impact on the organisation of healthcare is expected.

The transferability of the data to current practice is debatable, especially given the small number of children included in the phase II study and their diverse profile.

In conclusion, public health benefit is not expected from darunavir (PREZISTA) oral solution in this indication.

● This is a first- or second-option treatment.

The actual benefit of these proprietary medicinal products is substantial.

Taking account of these points, the Committee considers that the actual benefit of PREZISTA, co-administered with a low dose of ritonavir and in combination with other antiretroviral agents, is substantial in the Marketing Authorisation indications.

10.1.2 Tablets of 75, 150, 300 and 600 mg in the extension of indication for children aged from 3 to 6 years and weighing between 15 and 20 kg

● The condition targeted by this proprietary medicinal product entails a severe deterioration in the quality of life and is also life-threatening.

- These proprietary medicinal products seek to prevent and/or correct immune deficiency brought on by HIV infection.
- In combination with low doses of ritonavir and other antiretroviral agents, the efficacy/adverse effects ratio is favourable.
- In treatment-experienced children aged from 3 to 6 years and weighing between 15 and 20 kg, the treatment alternatives belonging to the class of protease inhibitors are few.

● Public health benefit:

The public health burden of HIV-1 infection is substantial. In the population corresponding to the extension of indication (ART-experienced children from the age of 3 years and weighing between 15 and 20 kg), the burden is small on account of the limited number of patients concerned in comparison with the total population of patients with HIV in France.

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

PREZISTA tablets are not expected to have any additional impact compared with existing alternatives on the morbidity and mortality of treated children. Due to the current lack of data, the impact on quality of life is unquantifiable. No impact on the organisation of healthcare is expected.

In conclusion, public health benefit is not expected from darunavir (PREZISTA) tablet in this indication.

- This is a second-option treatment.

The actual benefit of these medicinal products is substantial.

Taking into these points, the Committee considers that the actual benefit of PREZISTA, co-administered with a low dose of ritonavir and in combination with other antiretroviral agents, is substantial in the treatment of HIV-1 infection in previously treated children aged from 3 to 6 years and weighing at least 15 kg.

010.2 Improvement in actual benefit (IAB)

- Oral solution:
- ✓ In the management of HIV-1 infection in previously-treated children aged from 3 to 6 years weighing at least 15 kg

In view of:

- the immunological and virological response, comparable to that described in the adult population,
- the favourable safety profile;
- the limited number of treatment alternatives among the protease inhibitors in paediatric medicine,
- The Committee considers that the medicinal product PREZISTA oral solution, co-administered with a low dose of ritonavir and other antiretroviral agents, does constitute a moderate improvement in actual benefit (IAB III) in the treatment of human immunodeficiency virus (HIV-1) infection in ART-experienced children aged from 3 to 6 years and weighing at least 15 kg.

- ✓ In the management of HIV-1 infection in children over the age of 6 years, pretreated adolescents and adults.

There are many treatment alternatives, including the tablet form of PREZISTA.

The Committee considers that the PREZISTA oral solution, co-administered with a low dose of ritonavir and other antiretroviral agents, is an addition to the range and does not therefore offer any improvement in actual benefit: IAB V (non-existent) in the treatment of human immunodeficiency virus (HIV-1) in children and previously treated adolescents over the age of 6 years and in adults.

- Tablets of 75, 150, 300 and 600 mg:

In the extension of indication for the tablet forms in the previously-treated paediatric population aged from 3 to 6 years weighing between 15 and 20 kg, the Committee considers that the medicinal product PREZISTA, co-administered with a low dose of ritonavir and other antiretroviral agents, constitutes an improvement in actual benefit (IAB III) in the treatment of human immunodeficiency virus (HIV-1) infection.

010.3 Target population

“Thanks to the preventive treatment of mother-to-child transmission during pregnancy, no more than 10 to 15 HIV-infected newborns are diagnosed in France each year. It is estimated that there are 1500 HIV-infected children living in France.¹³ In the Transparency Committee’s opinion on APTIVUS 100 mg/ml oral solution, the estimated number of previously-treated children in a situation of virological failure in France (viral load > 1000 copies/ml) was 425.¹⁴ Moreover, according to INSEE data,¹⁵ children aged from 3 to 6 years accounted for around one-third (30%) of the children in the general population (≤ 12 years) on 1 January 2012.

*By extrapolation, the population which might benefit from treatment with PREZISTA oral suspension is thus estimated in France to be **about 130 patients.**”*

¹³ Medical treatment of persons infected with HIV. 2010 report under the directorship of Professor Patrick Yeni – page 186

¹⁴ Transparency Committee: Opinion of 10 March 2010 relating to APTIVUS 100 mg/ml oral solution

¹⁵ Institut National de la Statistique et des Etudes Economiques (French national institute of statistics and economic studies). Age pyramid as at 1 January 2012. www.insee.fr (consulted on 30 July 2012)

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use of PREZISTA, oral suspension, in the indications and at the dosages in the Marketing Authorisation and of PREZISTA 75, 150, 300 and 600 mg tablets in the extension of indication for children aged from 3 to 6 years and weighing between 15 and 20 kg at the dosage in the Marketing Authorisation.

► **Proposed reimbursement rate: 100%**

► **Packaging**

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

APPENDIX:
Reminder of the IAB levels for PREZISTA granted by the Transparency Committee in chronological order, by presentation

PREZISTA presentation	Indication	Date of TC opinion (IAB)	IAB rationale
300 mg	highly pre-treated adults having failed with more than one treatment including a protease inhibitor	4 July 2007 IAB III	In combination with other antiretrovirals, in comparison with a selected protease inhibitor (co-administered with ritonavir), PREZISTA (co-administered with ritonavir) presented the following characteristics during the course of two 24-week, phase IIb clinical studies and whose results were grouped together: - greater virological efficacy - comparable tolerance Additional virological efficacy data suggested that virological response was maintained up to 48 and 72 weeks, respectively. While awaiting the results of a phase III study in course of being finalised, the Committee considers that PREZISTA, co-administered with ritonavir, in combination with other antiretrovirals, offers a moderate improvement in actual benefit (level III) in terms of virological efficacy in the management of adult patients infected with strains of HIV-1, highly pretreated having: - viruses multiresistant to protease inhibitors, - a genotypic profile including at least one primary mutation in the protease genes among the mutations: 30N, 46I/L, 48V, 50V, 82A/F/T/S, 84V or 90M.
400 mg	ART-naïve adults	10 Jun 2009 IAB IV	In light of the available data in the naïve patients (ARTEMIS study: TMC114-C211), PREZISTA (darunavir) co-administered with a low dose of ritonavir, presents in particular the following characteristics in comparison to KALETRA (lopinavir/ritonavir): - non-inferior immunological and virological efficacy, with a more favourable response in the subgroup of patients with a viral load $\geq$ 100,000 copies/ml. - a more favourable lipid tolerance profile, although without any demonstrated effect on cardiovascular risk, - lower incidence of diarrhoea. It should be noted that, in most patients treated with lopinavir/ritonavir, the “soft capsules” formulation was used up to week 48, before the tablets became 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, affords 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 $\geq 100,000$ copies/ml).
300 mg	moderately pretreated adults	10 Jun 2009 IAB IV	In light of the available data (TITAN study), PREZISTA (darunavir) co-administered with a low dose of ritonavir, presents in particular the following characteristics in comparison to KALETRA (lopinavir/ritonavir): - superior virological efficacy, though the effect quantity was modest, - similar immunological efficacy, - comparable lipid tolerance and digestive profile. Consequently, PREZISTA (darunavir), co-administered with a low dose of ritonavir, affords a minor improvement in actual benefit (level IV) in terms of virological efficacy compared to KALETRA in the population of moderately pretreated patients.
600 mg	In previously treated adults, including highly pretreated patients.	10 Jun 2009 IAB V	The Marketing Authorisation for PREZISTA 600 mg was obtained on the basis of a bioequivalence study versus PREZISTA 300 mg. PREZISTA 600 is an addition to the range which does not offer any improvement in actual benefit compared with PREZISTA 300 mg (IAB V). <i>The Committee emphasises that this proprietary medicinal product will help simplify administration procedures.</i>
300 mg, 600 mg, 75 mg and 150 mg	ART-experienced children and adolescents from the age of 6 years and weighing at least 20 kg	2 December 2009 IAB III	- <u>In the management of HIV-1 infection in previously-treated children/adolescents</u> In view of: - the immunological and virological response, comparable to that described in the highly pretreated population, - the favourable safety profile; - the limited number of treatment alternatives among the protease inhibitors in paediatric medicine, The Committee considers that the medicinal product PREZISTA (75 mg, 150 mg, 300 mg and 600 mg) co-administered with a low dose of ritonavir and other antiretroviral agents, offers a moderate improvement in actual benefit (IAB III) in the treatment of human immunodeficiency virus (HIV-1) infection in ART-experienced children and adolescents from the age of 6 years and weighing at least 20 kg.

75 mg and 150 mg	previously-treated adults, in addition to PREZISTA 300 and 600 mg The use of PREZISTA 75 and 150 mg is recommended only when the PREZISTA 300 mg or 600 mg tablets available are considered unsuitable owing to difficulties in swallowing these tablets or hypersensitivity to the colourants they contain	IAB V	- <u>In the management of HIV-1 in previously treated adults, including highly pretreated patients</u> Proprietary medicinal products PREZISTA 75 mg and 150 mg offer no improvement in actual benefit (IAB V). They constitute additions to the range, justified for the treatment of human immunodeficiency virus (HIV-1) infection in adults previously treated with antiretrovirals (ART), including highly pretreated patients in cases of difficulty swallowing the 300 mg or 600 mg tablets or in cases of hypersensitivity to some of the colourants contained in the 300 mg and 600 mg tablets.
400 mg	ART-experienced adults with no darunavir resistance-associated mutations who have a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count $\geq 100 \text{ cells} \times 10^6/\text{l}$	14 December 2011 IAB V	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 safety data, the Committee considers that PREZISTA 400 mg does not offer 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+ count $\geq 100 \times 10^6 \text{ cells/l}$. In this population it constitutes an addition to the range.