HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 March 2010

APTIVUS 100 mg/ml oral solution
Pack of 1 95 ml bottle (CIP: 395 883.8)

Applicant: BOEHRINGER INGELHEIM

Tipranavir

ATC code: J05AE09

List I
Medicine for initial hospital prescription. Unrestricted renewal.
Medicinal product for prescription only by certain specialists: physicians who are experienced in the treatment of HIV-1 infection.
Registered on the French "rétrocession" [dispensing of drugs to outpatients by hospital pharmacies] list (Journal Officiel, 22 September 2009).

Date of Marketing Authorisation: 23 June 2009

Centralised procedure

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Medical, Economic, and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tipranavir

1.2. Indication

“APTIVUS 100 mg/ml oral solution, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated children from 2 to 12 years of age with virus resistant to multiple protease inhibitors. APTIVUS should only be used as part of an active combination antiretroviral regimen in patients with no other therapeutic options.

This indication is based on the results of one phase II study investigating pharmacokinetics, safety and efficacy of APTIVUS oral solution in mostly treatment-experienced children aged 2 to 12 years.

In deciding to initiate treatment with APTIVUS, co-administered with low dose ritonavir, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents.
Genotypic or phenotypic testing (when available) and treatment history should guide the use of APTIVUS.
Initiation of treatment should take into account the combinations of mutations which may negatively impact the virological response to APTIVUS, co-administered with low dose ritonavir”.

1.3. Dosage

“APTIVUS must always be given with low dose ritonavir as a pharmacokinetic enhancer, and in combination with other antiretroviral medicinal products. The Summary of Product Characteristics of ritonavir must therefore be consulted prior to initiation of therapy with APTIVUS (especially as regards the contraindications, warnings and undesirable effects sections).”

APTIVUS should be prescribed by physicians who are experienced in the treatment of HIV-1 infection. APTIVUS oral solution co-administered with low dose ritonavir should be taken with food.

APTIVUS/ritonavir should not be used in treatment-naïve patients.

The recommended dose for children (age 2 to 12 years) is 375 mg/m^2 APTIVUS co-administered with 150 mg/m^2 ritonavir, twice daily. The paediatric dose should not exceed the 500 mg/200 mg dose.

APTIVUS/ritonavir dose (375 mg/m^2 APTIVUS + 150 mg/m^2 NORVIR)				
BSA range [m^2]	**Dose APTIVUS [mg]**	**Volume APTIVUS [ml]**	**Dose ritonavir [mg]**	**Volume ritonavir [ml]**
0.37-0.42	140	1.4	56	0.7
0.43-0.47	160	1.6	63	0.8
0.48-0.52	180	1.8	71	0.9
0.53-0.58	200	2	79	1
0.59-0.63	220	2.2	87	1.1
0.64-0.68	240	2.4	95	1.2
0.69-0.74	260	2.6	103	1.3
0.75-0.79	280	2.8	111	1.4
0.80-0.84	300	3	119	1.5
0.85-0.90	320	3.2	127	1.6
0.91-0.95	340	3.4	135	1.7
0.96-1.00	360	3.6	143	1.8
1.01-1.06	380	3.8	151	1.9
1.07-1.11	400	4	159	2
1.12-1.16	420	4.2	167	2.1
1.17-1.22	440	4.4	174	2.2
1.23-1.27	460	4.6	182	2.3
1.28-1.32	480	4.8	190	2.4
> 1.33	500	5	200	2.5

Doses of ritonavir lower than 150 mg/m^2 twice daily should not be used as they might alter the efficacy profile of the combination.
APTIVUS is not recommended for use in children under 2 years of age due to insufficient data on safety and efficacy.
APTIVUS is available as soft capsules for adults and adolescents from 12 years of age (please refer to the respective SPC for further details). Patients treated with APTIVUS and reaching the age of 12 years should be switched to the capsule formulation.
Switching from APTIVUS oral solution to the capsules: APTIVUS oral solution is not interchangeable with the capsules. Compared to the oral solution, tipranavir exposure is lower when administering the same dose as capsules. However, children previously treated with APTIVUS oral solution and becoming 12 years of age should be switched to capsules, particularly because of the more favourable safety profile of the capsules. It has to be noted that the switch from the oral solution to the capsule formulation of APTIVUS could be associated with decreased exposure. Therefore, it is recommended that patients switching from APTIVUS oral solution to capsules at the age of 12 years are closely monitored for the virologic response of their antiretroviral regimen.

Liver impairment
Tipranavir is metabolised by the hepatic system. Liver impairment could therefore result in an increase of tipranavir exposure and a worsening of its safety profile. Therefore, APTIVUS should be used with caution, and with increased monitoring frequency, in patients with mild hepatic impairment (Child-Pugh Class A).
APTIVUS is contraindicated in patients with moderate or severe (Child-Pugh Class B or C) hepatic impairment.

Renal impairment (see SPC)”

Warnings mentioned in the SPC of the oral solution and soft capsules pharmaceutical forms:
"APTIVUS co-administered with low dose ritonavir, has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medicinal products. Caution should be exercised when administering APTIVUS/ritonavir to patients with liver enzyme abnormalities or with a history of hepatitis".

"Fatal and non-fatal intracranial haemorrhages (ICH) have been reported in patients receiving APTIVUS, many of whom had other medical conditions or were receiving concomitant medicinal products that may have caused or contributed to these events. However, in some cases the role of APTIVUS cannot be excluded".

"APTIVUS, co-administered with low dose ritonavir, should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other medical conditions, or who are receiving medicinal products known to increase the risk of bleeding such as antiplatelet agents and anticoagulants or who are taking supplemental vitamin E. Patients taking APTIVUS oral solution should be advised not to take any supplemental vitamin E".

"Treatment with APTIVUS co-administered with low dose ritonavir and other antiretroviral agents has resulted in increased plasma total triglycerides and cholesterol. Triglyceride and cholesterol testing should be performed prior to initiating tipranavir therapy and during therapy. Treatment-related lipid elevations should be managed as clinically appropriate".

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

J:	Antiinfectives for systemic use
J05:	Antivirals for systemic use
J05A:	Direct acting antivirals
J05AE:	Protease inhibitors
J05AE09:	Tipranavir

2.2. Medicines in the same therapeutic category

Comparator medicines:
There is no other protease inhibitor specifically indicated for the treatment of highly pre-treated children infected with type 1 human immunodeficiency virus (HIV-1) in patients with no other therapeutic options.

The protease inhibitors indicated in the treatment of treatment-experienced children infected with HIV-1 are:

INN	Product name	Pharmaceutical form	Packaging	Indication in children/adolescents
*Indicated in children **previously treated with antiretrovirals,** as part of a combination therapy regimen alongside other antiretrovirals*				
Indinavir*	CRIXIVAN	Hard capsule 100 mg	Pack of 180	≥ 4 years
		Hard capsule 200 mg	Pack of 360	
		Hard capsule 400 mg	Packs of 90 and 180	
Nelfinavir	VIRACEPT	Film-coated tabl. 250 mg	Pack of 300	≥ 3 years
		Powder 50 mg/g	Bottle of 144 g	
Fosamprenavir**	TELZIR	Film-coated tabl.	Bottle of 60 tabl.	≥ 6 years
		Oral suspension	Bottle of 225 ml	
Lopinavir-ritonavir	KALETRA	Oral solution 80 mg/20 mg/ml	Bottle of 60 ml	> 2 years
		Soft capsule 133.3/33.3 mg	Pack of 180	
		Film-coated tabl. 100/25 mg	Pack of 60	> 2 yrs and < 40 kg
		Film-coated tabl. 200/50 mg	Pack of 120	≥ 40 kg
Darunavir	PREZISTA	Film-coated tabl. 75 mg	Bottle of 480 tabl.	≥ 6 yrs and ≥ 20 kg
		Film-coated tabl. 150 mg	Bottle of 240 tabl.	
		Film-coated tabl. 300 mg	Bottle of 120 tabl.	
		Film-coated tabl. 600 mg	Bottle of 60 tabl.	

* Ritonavir and indinavir are no longer recommended owing to their adverse effects.
** Fosamprenavir is a prodrug of amprenavir, for which it is substituted.

2.3. Medicines with a similar therapeutic aim

The other medicines indicated in the treatment of treatment-experienced children infected with type 1 human immunodeficiency virus (HIV-1).

3 ANALYSIS OF AVAILABLE DATA

3.1. Clinical dossier

3.1.1. Phase I/IIa study (1182.14): Description

The clinical dossier contains a non-comparative randomised phase I/IIa study evaluating the tolerability of tipranavir/ritonavir (TPV/r)[1] in children and adolescents.

Objective

The principal objective of the study was to evaluate the tolerability of tipranavir co-administered with ritonavir (TPV/r) according to two dosing regimens and in combination with optimized background therapy.

The study was carried out simultaneously in children and adolescents (62 children aged 2 to < 12 years and 53 adolescents aged 12 years and over) infected with HIV-1 and mainly pre-treated with antiretrovirals for 48 weeks with the option of extending the treatment period to 100 weeks.

Treatments

The children and adolescents were randomised to two parallel groups and were treated according to one of the following dosing regimens for 4 weeks:

– Group 1: Tipranavir 290 mg/m^2 + ritonavir 115 mg/m^2, twice daily (N = 58)

– Group 2: Tipranavir 375 mg/m^2 + ritonavir 150 mg/m^2, twice daily (N = 57)

Tipranavir/ritonavir (TPV/r) was combined with optimized background therapy (preliminary test of genotypic resistance) consisting of at least two antiretroviral drugs not classified as protease inhibitors and including two nucleoside inhibitors in 63.5% of cases and three nucleoside inhibitors in 14.3%.

All patients (children and adolescents) began their treatment with the oral solution. After 4 weeks of treatment, the adolescents treated according to a regimen equivalent to the dosing regimen in adults (500/200 mg twice daily) could switch pharmaceutical form and continue their treatment with the soft capsules.

An interim analysis was carried out after 4 weeks of treatment. Depending on the observed results for tolerability, efficacy and pharmacokinetics, one of two TPV/r dosages could be selected for the continuation of the study in the two groups up to 48 weeks.

The initial duration of treatment was 48 weeks.

Randomisation was stratified according to age: [2 to < 6 years], [6 to < 12 years] and [12 to 18 years].

Primary endpoint at week 48

The primary endpoint was a tolerability endpoint (adverse effects and change in laboratory values relative to the date of randomisation).

Secondary endpoints at week 48, in particular

- Percentage of patients with a VL < 400 copies/ml
- Mean change in CD4 count relative to randomisation
- Time to treatment failure (loss or absence of virological response, stopping the study medication due to lack of efficacy or occurrence of adverse events, patients lost to follow-up, adding a new antiretroviral to the OBT without poor tolerability having been reported)
- Evaluation of compliance
- Pharmacokinetics data

[1] Salazar JC, Cahn P, Yogev R, et al. PACTG 1051/BI Study Team. Efficacy, safety and tolerability of tipranavir coadministered with ritonavir in HIV-1-infected children and adolescents. AIDS. 2008;22:1789-1798.

At week 100, an additional analysis was carried out; the results concerned the following endpoints in particular:

- Percentage of patients with a reduction in VL of at least one log step at week 48 and 100
- Percentage of patients with a VL < 400 copies/ml and < 50 copies/ml at weeks 48 and 100
- Mean change in CD4 count relative to randomisation
- Time to treatment failure between week 48 and week 100 (loss or absence of virological response, stopping the study medication due to lack of efficacy or occurrence of adverse events, patients lost to follow-up, adding a new antiretroviral to the OBT without poor tolerability having been reported)
- Incidence of adverse effects
- Pharmacokinetics data

Inclusion criteria:

- Boys and girls aged 2 to 18 years infected with HIV-1
- Viral load > 1500 copies/ml
- Laboratory values not exceeding grade 1 except for gamma-GT, cholesterol and triglycerides (grade 2).

Distribution of patients at randomisation

	TPV oral solution		TPV oral solution and soft capsule	Total
	2 to < 6 yrs	6 to < 12 yrs	12 to 18 years	
Patients randomised (FAS*)	25	37	53	115

*Full analysis set

Characteristics of the children aged 2 to < 12 years at inclusion according to treatment group

	TPV oral solution		
	2 to < 6 yrs n = 25	6 to < 12 yrs n = 37	2 to < 12 yrs n = 62
Mean age (years)	4.1 ± 1.1	9.5 ± 1.4	
Boys (%)	15	22	37 (59.7)
Girls (%)	10	15	25 (40.3)
Median CD4 count [cells/mm^3]	795 [115-2578]	398 [24-1689]	600 [24-2578]
Median viral load [HIV RNA log_{10} copies/ml]	5.0 [3.3-5.6]	4.6 [3.5-6.0]	4.8 [3.3-6.0]

Population of children aged 2 to < 12 years

Among the children infected with HIV-1, 50.7% were at stage C AIDS according to the CDC classification[2], 96.8% had been previously treated with antiretrovirals, and 37.1% had a viral load greater than 5 log_{10} copies/ml (> 100,000 copies/ml)

The median number of antiretrovirals previously used was 3 in children aged 2 to < 6 years and 8 in children aged 6 to < 12 years; 36.5% of the children had virus resistant to all protease inhibitors (60.3% to atazanavir, 42.9% to lopinavir/ritonavir). 53 out of 62 children completed the study at 48 weeks.

2 1994 CDC classification of the clinical and immunological severity of HIV infection in children; category C corresponds to severe symptoms (opportunistic infection, recurrent severe bacterial infections, encephalopathy, malignant lymphoma, cachexia). The age categories in this classification are different to those used in the study, as children aged 12 years are included in the 6 to 12 years category.

3.1.2. Pharmacokinetics

The bioequivalence of the two pharmaceutical forms (APTIVUS oral solution and soft capsules) has not been demonstrated. The bioavailability of the oral solution was superior to that of the soft capsules.
Results obtained with the oral solution cannot be extrapolated to the soft capsules. Consequently, the oral solution is not indicated in adults.
There is no need for a dose adjustment when switching from the oral solution to the soft capsules in adolescents.

3.1.3. Efficacy in children aged 2 to < 12 years

In the interim analysis 4 weeks after inclusion for each patient, the lower TPV/r dosage (TPV 290 mg/m^2 + RTV 115 mg/m^2 twice daily) was selected. However, at the date on which the switch was made, all the patients in the high-dose TPV/r group (375 mg/m^2 + 150 mg/m^2 twice daily) had already reached week 48 of treatment; these patients in the high-dose group did not make a switch, except in 4 cases.

- Results according to dose employed

Contrary to the initial analysis at 4 weeks, after 48 weeks of treatment the results for the two treatment groups (low- and high-dose) in the 115 patients were non-significant, with a satisfactory tolerance profile. As a consequence, during the follow-up phase up to 100 weeks all patients were treated with the high-dose regimen.
At 48 weeks in the study population as a whole (children and adolescents), 45.6% (26/57) of patients in the high-dose group had a viral load < 400 copies/ml versus 39.7% (23/58) in the low-dose group (NS) and 35.1% (20/57) of patients in the high-dose group had a viral load < 50 copies/ml versus 34.5% (20/58) in the low-dose group (NS).
A better virological response was observed in patients with a higher genotypic inhibitory quotient (GIQ)*.
(*geometric mean minimum residual tipranavir concentration/number of tipranavir mutations at inclusion (patients with a higher number of mutations have lower GIQ values)).

After obtaining the 48-week data, the population was divided into four quartiles according to quotient value:
- Q1 corresponds to the first quartile of patients with the lowest quotient values.
- Q4 corresponds to the last quartile of patients with the highest quotient values.

A better virological response was obtained in quartile Q4 (highest quotient values), corresponding most closely to the target population of APTIVUS (highest number of tipranavir mutations at inclusion), when treated at a higher dose.

GIQ* quartiles	< 400 copies/ml n/N	< 50 copies/ml n/N
Q1 (0.56-7.19)	2/25	1/25
Q2 (7.23-13.50)	13/25	11/25
Q3 (13.68-38.61)	15/26	13/26
Q4 (39.29-215.38)	17/25	14/25

- Results according to age group

Virological and immunological response of children aged 2 to < 12 years

Endpoint	Result at 48 weeks			Result at 100 weeks (additional analysis)		
	2 < 6 yrs n = 25*	6 < 12 yrs n = 37**	**Total n = 62**	2 < 6 yrs n = 25	6 < 12 yrs n = 37	**Total n = 62**
Patients with a viral load < 400 copies/ml n (%)	18	13	**31 (50.0)**	14	11	**25 (40.3)**
Patients with a viral load < 50 copies/ml n (%)	13	13	**26 (41.9)**	12	11	**23 (37.1)**
Median reduction in viral load relative to baseline (log_{10} copies/ml)	-2.67	-0.98	**-2.06**	-2.67	-1.24	**-**
Change in CD4+ count relative to baseline (lymphocytes/mm^3)	+323	+143	**+167**	+294	+121	**-**
Median percent gain relative to baseline (% CD4+ lymphocytes)	7	5	**5**	6	4	**-**

* low dose: n = 13; high dose: n = 12
** low dose: n = 19; high dose: n = 18

At 48 weeks, 50% (31/62) of patients had achieved a viral load < 400 copies/ml and 41.9% (26/62) of patients had achieved a viral load < 50 copies/ml.

- Results according to the number of tipranavir mutations shown by the virus

Virological response at 48 weeks in children aged 2 to < 12 years

Number of mutations	2 < 6 yrs n = 25	6 < 12 yrs n = 38
Patients with a viral load < 400 copies/ml		
0 mutations	6/7	1/4
1 to 3 mutations	9/13	10/16
4 to 10 mutations	3/5	3/18
Patients with a viral load < 50 copies/ml		
0 mutations	4/7	1/4
1 to 3 mutations	7/13	10/16
4 to 10 mutations	2/5	3/18

- Results according to genotypic sensitivity score (GSS)3
The genotypic sensitivity score represents the sum of the effective drugs in the combination therapy (OBT):
- GSS = 0 means that the virus is resistant to combination therapies
- GSS = 0.25 to 1 means that the virus is partially resistant to combination therapies
- GSS = 1.25 to 2.25 means that combination therapies are effective

Virological response at 48 weeks according to GSS

	TPV/r oral solution	
Number of patients showing a virological response at 48 weeks according to GSS:	2 to < 6 years n = 25	6 to < 12 years n = 38
VL < 400 copies/ml		
GSS 0.00	7/10	7/17
GSS 0.25-1.00	4/6	5/14
GSS 1.25-2.25	7/9	2/7
VL < 50 copies/ml		
GSS 0.00	4/10	7/17
GSS 0.25-1.00	3/6	5/14
GSS 1.25-2.25	6/9	2/7

In the subgroup of children in whom tipranavir/r was the sole treatment considered effective (GSS = 0), 7/10 children aged 2 to < 6 years achieved a viral load < 400 copies/ml and 4/10 children aged 2 to < 6 years achieved a viral load < 50 copies/ml.

3.1.4. Adverse effects

The adverse effects are similar to those observed in adults, with the exception of vomiting, rashes and fever, which were reported more frequently in children than in adults.

By way of comparison, in the RESIST clinical studies carried out in adults, adverse effects relating to hepatotoxicity, hyperlipidaemia, bleeding and rashes were seen more frequently in the patients treated with APTIVUS/ritonavir than in the patients treated in the comparator group (protease inhibitor boosted by ritonavir in combination with optimized background therapy). The clinical significance of these observations has yet to be fully investigated.

3 “The GSS (*genotypic sensitivity score*) represents the sum of the effective drugs in a dosing regimen according to the algorithm used. The predictive value of this score for the therapeutic response has been demonstrated in many studies.” Prise en charge médicale des personnes infectées par le VIH [Medical treatment of persons infected with HIV]. 2008 Report/Recommendations of the group of experts chaired by Prof. Patrick Yeni (www.sante.gouv.fr).

The moderate or severe adverse effects most frequently reported in the analysis at 48 weeks in children aged 2 to 12 years are as follows

Total number of children aged 2 to < 12 years	**62**
Adverse effects n (%)	
Diarrhoea	4 (6.5)
Vomiting	**3 (4.8)**
Nausea	3 (4.8)
Abdominal pain[1]	3 (4.8)
Fever	**4 (6.5)**
Rash[2]	**4 (6.5)**
Gamma-glutamyltransferase elevation	4 (6.5)
ALAT elevation	2 (3.2)
Anaemia	2 (3.2)

[1] Abdominal pain (N = 1), dysphagia (N = 1) and epigastric discomfort (N = 1)
[2] Rash: drug rash, macular rash, papular rash, erythema, maculopapular rash, pruritic rash and urticaria.

Approximately 30% of children experienced at least one serious adverse event (25.2% at week 48 and 30.4% at week 100).

An evaluation of bleeding, hepatitis and rashes was carried out in children aged 2 to 12 years:

- the incidence of bleeding (nosebleed, haematomas, bleeding gums, haematochezia, hypermenorrhoea, haemorrhagic diarrhoea) increased in children aged 2 to 12 years between week 48 (6.5% of patients) and week 100 (11.3% of patients).

-the incidence of the following events: ALAT and or ASAT elevation, hyperbilirubinaemia and abnormal liver function values in children aged 2 to 12 years was 11.3% at week 48 and 14.5% at week 100.

- the reported incidence of rashes (undefined rashes, papular rashes, macular rashes, maculopapular rashes, urticaria) was 22.6% at week 48 and 27.4% at week 100.

3.1.5. Drug interactions

(Excerpt from the SPC)

“The interaction profile of APTIVUS, co-administered with low dose ritonavir, is complex and requires special attention in particular in combination with other antiretroviral agents. Interaction studies have only been performed in adults.

Tipranavir is a substrate, an inducer and an inhibitor of cytochrome P450 CYP3A. When coadministered with ritonavir at the recommended dosage there is a net inhibition of P450 CYP3A. Co-administration of APTIVUS and low dose ritonavir with agents primarily metabolised by CYP3A may result in changed plasma concentrations of tipranavir or the other agents, which could alter their therapeutic and undesirable effects (see SPC)”.

3.1.6. Resistance

(Excerpt from the SPC)

“Through a series of multiple stepwise regression analyses of baseline and on-treatment genotypes from all clinical studies (carried out in adults), 16 amino acids have been associated with reduced tipranavir susceptibility and/or reduced 48-week viral load response: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V. Clinical isolates that exhibited a ≥ 10-fold decrease in tipranavir susceptibility harboured 8 or more tipranavir-associated mutations. In Phase II and III clinical trials, 276 patients with on-treatment genotypes have demonstrated that the predominant emerging mutations with

APTIVUS treatment are L33F/I/V, V82T/L and I84V. Combination of all three of these is usually required for reduced susceptibility".

3.2. Conclusion

In children aged 2 to 12 years, the pharmacokinetics, immunovirological efficacy and tolerability of tipranavir administered in combination with ritonavir and other antiretrovirals have been evaluated in a non-comparative phase I/IIa study carried out in 62 children, mostly treatment-experienced (96.8%) with a viral load > 1500 copies/ml. APTIVUS oral solution is not indicated in adults.

The population included in the study was at an advanced stage of the disease: at inclusion 50.7% of patients were at AIDS stage C according to the CDC classification and 37.1% had a viral load greater than 5 $\log_{10}$ copies/ml (> 100,000 copies/ml). The median number of antiretrovirals previously used was 3 in children aged 2 to < 6 years and 8 in children aged 6 to < 12 years; 36.5% of children had virus resistant to all protease inhibitors (60.3% to atazanavir, 42.9% to lopinavir/ritonavir).

After 48 weeks of treatment, the results for the two treatment groups (low dose and high dose) were non-significant. The high-dose TPV/r regimen (375 mg/m^2 + 150 mg/m^2 twice daily) has been approved by the EMEA, even though data are limited.

The virological efficacy in terms of the percentage of patients who achieved:
- a viral load < 400 copies/ml was 50% (31/62) at 48 weeks and 40.3% (25/62) at 100 weeks (secondary endpoint)
- a viral load < 50 copies/ml was 41.9% (26/62) at 48 weeks and 37.1% (23/62) at 100 weeks (secondary endpoint)

The adverse effects are similar to those observed in adults, with the exception of vomiting, rashes and fever, which were reported more frequently in children than in adults.

APTIVUS is co-administered with ritonavir at a higher dose than that used with other protease inhibitors. In addition, the oral solution has a high vitamin E content and, compared with the capsules, results in higher exposure to tipranavir during administration of the oral solution.
The tolerance profile of the oral solution is less favourable than that of the capsules.

In children, APTIVUS co-administered with ritonavir oral solution is not well tolerated.

APTIVUS may be a last resort option in a very limited population of children with virus resistant to multiple protease inhibitors, in particular to lopinavir/ritonavir (KALETRA) oral solution in children aged 2 to 6 years.
The oral solution has been adapted to paediatric use.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

HIV infection is a serious disease that is life-threatening.
This product is intended to prevent and/or correct immunodeficiency caused by HIV infection.

In combination with ritonavir and other antiretroviral drugs, the efficacy/adverse effects ratio is moderate.

Among protease inhibitors, there are few therapeutic alternatives in treatment-experienced children. Tipranavir is the only protease inhibitor indicated in highly pre-treated children with no other therapeutic options.

Public health benefit
The public health burden due to HIV infection is substantial. In the population corresponding to the indication (highly pre-treated children aged 2 to 12 years with virus resistant to multiple protease inhibitors, in combination therapy only and in patients with no other therapeutic options), the burden is low given the very small number of patients concerned compared with the total number of children with HIV in France.

The reduction in AIDS-related morbidity and mortality meets a public health need, particularly in patients resistant to current therapies in whom treatment has failed.
APTIVUS oral solution is a pharmaceutical form adapted to the treatment of HIV infection in children. Taking into account the scarcity of available therapeutic alternatives in children, and in view of the available efficacy data, tolerability and resistance profile of APTIVUS, it is expected that APTIVUS would have a moderate impact on reducing HIV-related morbidity and mortality in children.

In conclusion, APTIVUS is expected to have a low public health benefit in its indication in children aged 2 to 12 years.

The actual benefit of this product is substantial.

4.2. Improvement in actual benefit (IAB)

The APTIVUS pharmaceutical form is a presentation well adapted to paediatric use.
It represents a benefit primarily in children aged 2 to 6 years, allowing the treatment of very young children resistant to KALETRA, the only other protease inhibitor available in the form of an oral solution for children under 6 years.
This product co-administered with ritonavir is not well tolerated in highly pre-treated children aged 2 to 12 years with virus resistant to multiple protease inhibitors.
However, considering its moderate immunovirological efficacy and specific resistance profile tipranavir oral solution may be indicated in combination with other antiretroviral drugs in a population with no other therapeutic options.
Consequently, APTIVUS oral solution co-administered with ritonavir offers a minor improvement in actual benefit (level IV) in terms of efficacy in the management of highly pre-treated children aged 2 to 12 years with virus resistant to multiple protease inhibitors and with no other therapeutic options.

4.3. Therapeutic use

4.3.1 Treatment of children infected with HIV

According to: Prise en charge médicale des personnes infectées par le VIH [Medical treatment of persons infected with HIV]. 2008 Report/Recommendations of the group of experts chaired by Prof. Patrick Yeni (www.sante.gouv.fr).
The following sections concerning the treatment of children and adolescents infected with HIV are given in the appendix:

- Strengths of antiretroviral therapy
- Choice of initial antiretroviral therapy
- Management of treatment failure

4.3.2. Therapeutic use of the medicinal product APTIVUS in highly pre-treated patients with virus resistant to multiple protease inhibitors and with no other therapeutic options
APTIVUS co-administered with ritonavir and used in combination with other antiretrovirals represents a therapeutic option primarily in highly pre-treated children aged 2 to 6 years with virus resistant to multiple protease inhibitors and with no other therapeutic options.

4.4. Target population

The number of children living in France infected with HIV is estimated at about 1500 and each year some 10 to 20 neonates are diagnosed[4].

There are no available epidemiological data that allow us to calculate the number of highly pre-treated children in virological failure likely to be given APTIVUS.

By extrapolation from a study on the development to adolescence of children monitored in the French Perinatal Cohort[5], 81% of children infected with HIV will have been pre-treated and the percentage of treatment-experienced children with a viral load > 1000 copies/ml can be estimated at 35% (i.e. approx. 425 patients).

In practice, the number of children likely to be given APTIVUS oral solution will be very small, as its use is restricted to highly pre-treated patients aged 2 to < 12 years with virus resistant to multiple protease inhibitors and with no other therapeutic options.

According to expert opinion, fewer than 200 multiply treated children will be likely to benefit from treatment with APTIVUS, of which 50 will be aged 2 to 6 years.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and at the dosages in the Marketing Authorisation.
The Transparency Committee requests that the pharmaceutical company applies for inclusion on the list of medicines reimbursed by National Insurance.

4.5.1. Packaging: appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 100%

[4] Ministry of Health. Report 2008. Prise en charge médicale des personnes infectées par le VIH [Medical treatment of persons infected with HIV]. Chair: Prof. Patrick Yeni. Epidemiology. Available at: http://www.sante-jeunesse-sports.gouv.fr/IMG//pdf/03_Epidemiologie.pdf (retrieved 29/12/2009).
[5] Dollfus C. Devenir à l'adolescence des patients VIH après transmission mère-enfant [Development to adolescence of HIV patients after mother-child transmission]. Available at http://www.infectiologie.com/site/medias/JNI/JNI06/CP/cp2-Dollfus.pdf (retrieved on 13/10/09).

Appendices

Appendix 1: Medical treatment of persons infected with HIV.

Treatment of children and adolescents infected with HIV
According to: Prise en charge médicale des personnes infectées par le VIH [Medical treatment of persons infected with HIV]. 2008 Report/Recommendations of the group of experts chaired by Prof. Patrick Yeni (www.sante.gouv.fr).

Strengths (*)
• In 2008, the number of children infected with HIV living in France was estimated at about 1500. Many adolescents nowadays reach adulthood in an often-good clinical and psychological state.
• Each year in France, 10 to 20 neonates are diagnosed with HIV infection. Most children newly diagnosed are, however, born abroad in countries where infection is widespread.
• About a hundred adolescents are infected each year sexually.
• Most of our understanding of the treatment of children is extrapolated from experience of the treatment of adults.
• In children, HIV infection remains a psychological handicap because of the considerable social stigma. Individual psychotherapy sessions, discussion groups, and shared leisure activities with other seropositive children help reduce mental suffering and distress to their families.
• Children are informed of their diagnosis on a step-by-step basis appropriate to age and to the individual situation of each child.

The group of experts recommends:
– to offer antiretroviral treatment to all children under 12 months, to prevent the development of a severe early form accompanied by encephalopathy (AI). Abstention from treatment in this age group remains possible, subject to strict conditions;
– to commence treatment in older children only once they reach a CD4 threshold of 25% (1-3 years) or 20% (> 3 years) (AIIa), provided they have few or no symptoms;
– to initially favour triple therapy combining two NRTIs (abacavir + lamivudine or zidovudine + abacavir or zidovudine + lamivudine) and one PI/r (AIIa);
– to determine blood levels of certain antiretrovirals, particularly in the case of substances used off-label (BIIa) and patients in whom the virus shows PI resistance mutations (AIIa);
– to not interrupt treatment, except in the event of poor tolerability, manifest noncompliance, or at the patient's request, unless allowed by a specific research protocol (BIIa);
– to manage infected children at a specialised centre (AIII);
– to lobby the pharmaceutical industry to pursue research into pharmaceutical formulations suited to the needs of children (AIII);
– to discuss sexuality issues at an early age in infected adolescents (AIII);
– to promote HIV/AIDS prevention in young people, particularly in schools, and to raise awareness of the existence of anonymous, free screening (AIII).

***** 1 Grading of the recommendations:

A: Data available justifying a high-level recommendation
B: Data available justifying an intermediate-level recommendation
C: Data available insufficient to justify a recommendation

2 Level of evidence: Nature of data on which recommendations are based:
I a, b: At least one randomised clinical study; meta-analyses of randomised studies
II a, b: Non-randomised clinical studies, case-control cohorts or studies, meta-analyses of case-control cohorts or studies
III: Expert analyses based on other available data
a: data published in a scientific journal with a peer-review board
b: data presented at a scientific conference with a selection board and available in abstract form

Choice of initial treatment (summary)

• Treatment of choice: In all age groups, regardless of initial immunovirological parameters: combination of two NRTIs (abacavir + lamivudine or zidovudine + abacavir or zidovudine + lamivudine) and one PI/r (lopinavir/r at any age or fosamprenavir/r in children over 6 years) (AIIa). The abacavir + lamivudine combination is the preferred option if the child is able to ingest the co-formulation (AIa). Because of a risk of hypersensitivity to abacavir, systematic testing for the HLAB57*01 group is advisable prior to prescription. Lamivudine is to be avoided if there is a high risk of poor compliance with treatment.

• Alternative option: Combination of two NRTIs and one NNRTI, provided good compliance can be rigorously ensured from the start of treatment (BIIa). In neonates with a high viral load, a combination of three NRTIs and one NNRTI (nevirapine) is however recommended.

Management of treatment failure

As has been shown by many observational studies, a significant proportion of children are clinically asymptomatic, with no immunodeficiency, despite being in a state of "virological failure" characterised by persistent viral replication and often the presence of resistance mutations to antiretroviral drugs.

There are no data that allow us to recommend a different approach in children to that laid down for adults as regards the criteria for virological failure, the role of the resistance genotype, and the selection of second-line combinations (or beyond).

As in adults, viral replication, even low, can lead to the emergence of resistance mutations. Conversely, premature changes of treatment can swiftly lead to a situation of multidrug resistance and the exhaustion of available therapeutic options.

Before considering a change of treatment, it is essential to ensure good compliance with treatment, to carry out antiretroviral assays, and to have knowledge of the patient's treatment history and previous genotypic resistance tests, following the example recommended for adults in this situation.

The use of substances that do not have paediatric marketing authorisation is often essential here. Even after several lines of treatment and prolonged virological failure, the objective remains the achievement of an undetectable viral load through the interpretation of genotypic resistance tests and the optimised use of new substances, again including ones that are unlicensed where necessary.

The causes of failure and the means of remedying it – above all the problem of poor compliance – must be scrupulously evaluated before instituting a new line of treatment.