HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 March 2010

APTIVUS 250 mg, soft capsule
Bottle of 120 capsules (CIP: 369 252-4)

Applicant: BOEHRINGER INGELHEIM

Tipranavir
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.

Date of Marketing Authorisation: (centralised procedure)
25/10/2005: Marketing Authorisation granted subject to special conditions given the lack of long-term data for the two phase III efficacy and tolerance studies.
22/04/2008: Previous conditions lifted.
Latest corrections to the Marketing Authorisation taken into account: 23 June 2009

Reason for request: Re-examination following the submission of new data and the amendment of the wording of the therapeutic indication.

Medical, Economic, and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Tipranavir

1.2. Indication
- Old text:
"APTIVUS, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adults with virus resistant to multiple protease inhibitors.
This indication is based on the results of two phase III studies, performed in highly pre-treated patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors (see details of the baseline resistance profile of patients infected with HIV in section 5.1 of the Summary of Product Characteristics).

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.

- New text:
"APTIVUS, co-administered with low dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adults and adolescents 12 years of age or older 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 two phase III studies, performed in highly pre-treated adult patients (median number of 12 prior antiretroviral agents) with virus resistant to protease inhibitors and of one phase II study investigating pharmacokinetics, tolerance and efficacy of APTIVUS in mostly treatment-experienced adolescent patients aged 12 to 18 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 (see SPC)
"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".

"APTIVUS should be prescribed by physicians who are experienced in the treatment of HIV-1 infection.
APTIVUS soft capsules co-administered with low dose ritonavir should be taken with food.
APTIVUS/ritonavir should not be used in treatment-naïve patients.

Adults and adolescents from 12 years of age
The recommended dose of APTIVUS is 500 mg, co-administered with 200 mg ritonavir (low dose ritonavir), twice daily.
Doses of ritonavir lower than 200 mg twice daily should not be used as they might alter the efficacy profile of the combination.

Elderly
Clinical studies of APTIVUS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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 (cf. SPC)

Warnings mentioned in the SPC:

"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. Increased ALAT/ASAT monitoring should be considered in these patients."
"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."
"Mild to moderate rashes including urticarial rash, maculopapular rash, and photosensitivity have been reported in subjects receiving APTIVUS, co-administered with low dose ritonavir".

New warning
"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. Based on the limits of exposure available from observation in clinical trials, it is recommended not to co-administer to patients more than 1200 IU vitamin E per day."

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

2.2.1 Comparator medicines

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

. Protease inhibitors (PI) used in antiretroviral combination therapy in treatment-experienced adult patients*

- indinavir: CRIXIVAN, capsules and film-coated tablets
- nelfinavir: VIRACEPT, film-coated tablets and oral powder
- amprenavir: AGENERASE, capsules and oral solution
- saquinavir mesylate: INVIRASE, capsules and film-coated tablets
- lopinavir combined with ritonavir: KALETRA, oral solution and film-coated tablets
- fosamprenavir: TELZIR, film-coated tablets and oral suspension
- atazanavir: REYATAZ, capsules or oral powder, indicated in adults
- darunavir: PREZISTA, film-coated tablets, indicated in adults
- ritonavir: NORVIR in combination with a PI as an enhancer

*The indications of these protease inhibitors are not identical to those of the product APTIVUS.

2.2.2 Medicines with a similar therapeutic aim

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

3. SUMMARY OF THE OPINION OF THE COMMITTEE of 12 April 2006

Actual benefit:
The actual benefit of this product is substantial.

Improvement in actual clinical benefit:
Compared with a selected protease inhibitor (co-administered with ritonavir), APTIVUS (co-administered with ritonavir) showed the following characteristics in the two 24-week RESIST-1 and RESIST-2 clinical studies:

- superior virological efficacy
- a less favourable hepatic and lipid safety profile.

Consequently, in the treatment of highly pre-treated adult patients infected with strains of HIV-1 having:
- virus resistant to multiple protease inhibitors,
- a genotypic profile including at least one of the following primary mutations of the protease gene: 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M and not more than two key mutations at codons 33, 82, 84 or 90,

APTIVUS, co-administered with ritonavir in combination solely with other antiretrovirals including at least one antiretroviral to which the patient's virus is genotypically sensitive, offers a moderate (level III) improvement in actual benefit in terms of virological efficacy.

4. ANALYSIS OF AVAILABLE DATA SINCE THE PREVIOUS TRANSPARENCY COMMITTEE OPINION

Since the last examination of the dossier by the Transparency Committee (12 April 2006), two extra sections of text have been added to the original indication in the SPC:
- "It should only be used as part of an active combination antiretroviral regimen in patients with no other therapeutic options".
- "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."

The new data supplied by the company concern:
- the results compiled from the RESIST-1 and RESIST-2 pivotal studies for the efficacy and tolerance at 48, 96 and 156 weeks
- the adverse effects reported since market launch of APTIVUS
- drug interactions and the resistance profile.

The RESIST-1 and RESIST-2 pivotal studies compared APTIVUS/ritonavir (TPV/r) combined with other antiretrovirals (optimized background therapy - OBT)* with a protease inhibitor/ ritonavir (PIC/r) plus OBT in treatment-experienced HIV-positive patients.

The protocol for the two RESIST pivotal studies stated that, in the event of confirmed virological failure, the patients in the PIC/r comparator group could drop out of the RESIST programme after treatment week 8 on grounds of inadequate virological response or virological failure and be included in another study in which patients received TPV/r. This meant there was a substantial difference in duration of exposure between the two groups (TPV/r and PIC/r) at 96 weeks and 156 weeks. At 96 weeks, 382 out of 746 patients in the TPV/r group and 135 out of 737 in the PIC/r group were still being treated. The profile of the treated patients was no longer comparable in the two treatment groups.
The median duration of exposure was 672 days (96 weeks) in the TPV/r group and 173 days (about 25 weeks) in the PIC/r group.
This marked difference in the duration of exposure constitutes methodological bias and so prevents any conclusions from being drawn from the follow-up data at 96 and 156 weeks.
These data are not analysed in this Opinion and are, moreover, not included in the SPC of the product.

Only the data after 48 weeks of treatment are discussed below, along with a summary of the results observed after 24 weeks (interim analysis).

* The OBT was defined before randomization, allowing comparable groups to be obtained in the two studies with regard to the number of active antiretrovirals selected [nucleoside inhibitors, non-nucleoside inhibitors, enfuvirtide (Fuzeon)].

4.1 Efficacy

The company has supplied 48-week follow-up data for two comparative studies (RESIST-1 and RESIST-2).
APTIVUS/ritonavir in combination with other antiretrovirals (optimized background therapy - OBT)* versus a protease inhibitor/ritonavir plus OBT in HIV-positive patients pre-treated with three classes of antiretrovirals. The results of these two studies have been pooled.

Primary endpoint
Composite endpoint defined as the percentage of patients showing a confirmed decrease in viral load of at least one log step relative to baseline and without signs of treatment failure at 48 weeks (endpoint previously used in clinical studies).

Secondary endpoints, in particular
- Percentage of patients with an undetectable viral load (< 400 and < 50 copies/ml) at 48 weeks.
- Change in viral load (VL) relative to baseline after 48 weeks.
- Evaluation of immunological recovery (CD4 lymphocyte count) at 48 weeks.

Treatments
- APTIVUS group, co-administered with low-dose ritonavir (500 mg/200 mg twice daily), in combination with background therapy (OBT) optimized individually and defined for each patient on the basis of genotypic resistance tests and case history.
- Comparator group: PI boosted by ritonavir (individually defined) in combination with OBT. The protease inhibitor boosted by ritonavir was selected from saquinavir, amprenavir, indinavir or lopinavir/ritonavir.

Updating of baseline patient characteristics
1483 randomised patients in the pooled analysis for the two studies at 48 weeks (APTIVUS group: N = 746; comparator group: N = 737)

NB: 1159 patients at the time of the interim analysis of the two studies at 24 weeks (inclusion still ongoing at the time of the interim analysis).

- Median plasma HIV-1 RNA levels were 4.79 $\log_{10}$ copies/ml [2.34-6.52 $\log_{10}$] and 4.80 $\log_{10}$ copies/ml [2.01-6.76 $\log_{10}$] in the comparator group.
- Median CD4 counts were 158 cells/mm^3 [1-1893] in the APTIVUS (TPV/r) group and 166 cells/mm^3 [1-1184] in the comparator group.

- Patients had been previously treated with 6 nucleoside inhibitors, 1 non-nucleoside inhibitor and 4 protease inhibitors (median values).
- 67% of patients had virus that was resistant and 22% potentially resistant to the preselected comparator PI.
- 10% of patients had been previously treated with enfuvirtide (Fuzeon).
- Enfuvirtide (Fuzeon) was included in the combination in 22.7% in the APTIVUS group and in 18.3% in the comparator group.

- The patients had HIV-1 isolates with a median of 16 mutations in the protease gene and a median of 3 primary mutations in the protease gene (median value), including D30N, L33F/I, V46I/L, G48V, I50V, V82A/F/T/L, I84V and L90M.
  The majority of patients had mutations associated with resistance to nucleoside and non-nucleoside inhibitors.

Results:

* The OBT was defined before randomization, allowing comparable groups to be obtained in the two studies with regard to the number of active antiretrovirals selected [nucleoside inhibitors, non-nucleoside inhibitors, enfuvirtide (Fuzeon)].

- Primary endpoint: Response to treatment at 48 weeks (pooled results of the RESIST-1 and RESIST-2 studies) in treatment-experienced patients without signs of treatment failure (= composite endpoint).

The response to treatment is shown in the table below for the population as a whole (with or without use of enfuvirtide).

Number and percentage of patients showing a confirmed decrease in viral load of at least one log step relative to baseline and without signs of treatment failure at 24 weeks (interim analysis) and at 48 weeks for the whole population:

RESIST-1/RESIST-2 studies	**TPV/r**		**Comparator**		**p**
	n (%)	**N**	**n (%)**	**N**	
24 weeks (ITT) interim analysis	**240 (41.2)**	582	**109 (18.9)**	577	< 0.0001
48 weeks (ITT)	**255 (34.2)**	**746**	**114 (15.5)**	**737**	< 0.0001
- with enfuvirtide	**85 (50.0)**	170	**28 (20.7)**	135	< 0.0001
- without enfuvirtide	**170 (29.5)**	576	**86 (14.3)**	602	< 0.0001

The percentage of patients showing a confirmed decrease in viral load of at least one log step relative to baseline and without signs of treatment failure was:
- 41.2% (240/582 patients) in the interim analysis at 24 weeks in the TPV/r group versus 18.9% (109/577 patients) in the comparator group.
- 34.2% (255/746) at 48 weeks in the TPV/r group versus 15.5% (114/737) in the comparator group.

The virological efficacy shown by the APTIVUS group was superior to that of the comparator group with or without inclusion of enfuvirtide in the combination therapy.

The response to treatment at 48 weeks is shown in the table below for the population as a whole according to the PI administered in the comparator treatment:

Number and percentage of patients showing a confirmed decrease in viral load of at least one log step relative to baseline and without signs of treatment failure at 48 weeks according to PI administered in the comparator treatment:

	TPV/r		**Comparator**[1]		**p**
	n (%)	**N**	**n (%)**	**N**	
Response to treatment					
LPV/r preselected					
Resistant	66 (28.9)	228	23 (9.5)	242	< 0.0001
Sensitive	56 (41.5)	135	37 (31.9)	116	NS
APV/r preselected					
Resistant	50 (33.3)	150	22 (14.9)	148	< 0.0001
Sensitive	18 (37.5)	48	11 (23.9)	46	NS
SQV/r preselected					
Resistant	22 (30.6)	72	5 (7.0)	71	< 0.0001
Sensitive	35 (39.8)	88	14 (15.4)	91	0.0001
IDV/r preselected					
Resistant	6 (46.2)	13	1 (5.3)	19	0.0026
Sensitive	2 (20.0)	10	0 (0.0)	4	NS

[1] Comparator protease inhibitor: Lopinavir/r (LPV/r) 400/100 mg twice daily (n = 358), indinavir/r (IDV/r) 800/100 mg twice daily (n = 23), saquinavir/ritonavir (SQV/r) 1000/100 mg twice daily or 800/200 mg twice daily (n = 162), amprenavir/ritonavir (APV/r) 600/100 mg twice daily (n = 194)
Sensitive = patients sensitive or possibly resistant

The virological efficacy of APTIVUS at 48 weeks was superior to that of the comparators in patients carrying strains resistant to the selected protease inhibitor.

In the patients carrying viral strains sensitive to protease inhibitors in the comparator arm, APTIVUS was not shown to be superior to these protease inhibitors boosted by ritonavir.
The virological response at 48 weeks to treatment with APTIVUS was better when the background therapy included an antiretroviral to which the virus was genotypically sensitive (e.g. enfuvirtide).

- Secondary endpoints (pooled results of 2 studies) at 24 weeks and 48 weeks:

Secondary endpoints	Week 24: interim analysis n = 1159		**Week 48 n = 1483**	
	TPV/r n = 582	Comparator n = 577	**TPV/r n = 746**	**Comparator n = 737**
HIV-1 RNA < 400 copies/ml [%]	34.2	14.9	**30.4**	**13.8**
HIV-1 RNA < 50 copies/ml [%]	23.9	9.4	**22.8**	**10.2**
HIV-1 RNA (median change relative to baseline in log10 copies/ml)	-0.80	-0.25	**-0.64**	**-0.22**
	Week 24: interim analysis n = 1159		Week 48 n = 1467	
	TPV/r n = 582	Comparator n = 577	TPV/r n = 740	Comparator n = 727
CD4 count (median change relative to baseline in cells/mm^3)	+34	+4	**+24**	**+4**

The results for the virological and immunological response in the secondary endpoints were better for APTIVUS at 48 weeks.

These results are of the same order as those obtained in the interim analysis at 24 weeks (without statistical tests).

4.2. Adverse effects

Summary: In the RESIST-1 and RESIST-2 clinical studies, adverse events concerning hepatotoxicity, hyperlipidaemia, bleeding and rashes were seen more often at 24 weeks in the patients treated in the APTIVUS/ritonavir group than in the patients treated in the comparator group.

Hepatotoxicity:
After 48 weeks of follow-up, the incidence of grades 3 or 4 ALAT and/or ASAT abnormalities was higher in the APTIVUS group (10%) than in the comparator arm (3.4%).

NB: In the interim analysis at 24 weeks, the incidence of grades 3 or 4 ALAT and/or ASAT abnormalities was 6.2% in the APTIVUS group and 2.5% in the comparator arm.

Hyperlipidaemia:
After 48 weeks of follow-up, the incidence of grades 3 or 4 triglyceride elevations was higher in the APTIVUS group (25.2%) than in the comparator arm (15.6%).

NB: In the interim analysis at 24 weeks, the incidence of grades 3 or 4 triglyceride elevations was 20.8% in the APTIVUS group and 11.2% in the comparator arm.

Bleeding:
A higher risk of bleeding was observed in the APTIVUS group than in the comparator group, with a relative risk at 24 weeks of 1.98 (95% CI = 1.03; 3.80). At 48 weeks the relative risk had decreased to 1.27 (95% CI [0.76; 2.12]). There was no sign of haemorrhagic events and no difference in coagulation parameters between the treatment groups.

"Fatal and non-fatal intracranial haemorrhage (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."
A letter addressed to healthcare professionals on 28 July 2006 stated that 14 cases of intracranial haemorrhage (ICH), including 8 fatalities, had been reported to Boehringer Ingelheim among 6840 patients infected with HIV-1 receiving APTIVUS during clinical studies.
(http://www.afssaps.fr/Infos-de-securite/Lettres-aux-professionnels-de-sante/Information-concernant-le-risque-de-survenue-d-hemo...)

Rash:
After 48 weeks of follow-up, the incidence of rashes in the APTIVUS/ritonavir group (16.3%) and in the comparator group (12.5%) was comparable. There have been no reported cases of Stevens-Johnson syndrome or toxic epidermal necrolysis during the clinical development of APTIVUS.

NB: In the interim analysis at 24 weeks, the incidence of cutaneous adverse events was 11.4% in the APTIVUS group, compared with 9.8% in the comparator group.

The other adverse events reported with tipranavir/ritonavir in more than 5% of patients are shown below at 24 weeks (as reference) and 48 weeks

Grades 1 to 4 adverse events	TPV/r Week 24 N = 582 interim analysis	TPV/r **Week 48** N = 749*	Comparator **Week 48** N = 737
	n (%)	n (%)	n (%)
Patients having at least one grades 1 to 4 adverse event	**-**	**680 (90.8)**	**604 (82.0)**
Diarrhoea	137 (23.6)	219 (29.2)	165 (22.4)
Nausea	88 (15.2)	151 (20.2)	113 (15.3)
Vomiting	45 (7.7)	92 12.3)	66 (9.0)
Abdominal pain	34 (5.8)	70 (9.3)	46 (6.2)
Fever	58 (9.3)	104 (13.9)	66 (9.0)
Fatigue	53 (9.1)	90 (12.0)	77 (10.4)
Cough	34 (5.9)	72 (9.6)	40 (5.4)
Headache	50 (8.6)	106 (14.2)	65 (8.8)
Grades 1 to 4 adverse effects	**-**	**366 (48.9)**	**225 (30.5)**
Serious adverse events	**-**	**156 (20.8)**	**116 (15.7)**
Serious adverse effects	**-**	**23 (3.1%)**	**5 (0.7)**

* three patients not randomised, but treated with TPV/r

531 out of 746 patients (71.2%) were treated for 48 weeks in the TPR/r group and 291 out of 737 (39.5%) in the comparator group.

- 215 out of 746 patients (28.8%) in the TPR/r group stopped treatment prematurely, this being due to adverse events in 8.7% and a change of treatment in 12.5%.
- 446 out of 737 patients (60.5%) in the comparator group stopped treatment prematurely.

Median exposure to treatment was 384 days in the TPV/r arm and 173 days in the PIC/r arm.

NB: In the interim analysis at 24 weeks, 16.7% of patients in the APTIVUS group had withdrawn from the study before or at week 24, compared with 57.3% in the comparator group.

During the study there had been 31 deaths by week 48: 18 in the APTIVUS group and 13 in the comparator group.

Patients co-infected with hepatitis B or C: There are currently only limited data on the use of APTIVUS co-administered with low-dose ritonavir in patients co-infected with hepatitis B or C. APTIVUS must be used with caution in patients co-infected with hepatitis B or C. APTIVUS must only be used in this patient population if the expected benefit outweighs the potential risk and if clinical monitoring and monitoring of laboratory values is stepped up.

Antiretroviral combination therapies, such as treatments containing a protease inhibitor, are associated in some patients with a redistribution of body fat mass, including a loss of peripheral subcutaneous adipose tissue, an increase in intra-abdominal fat mass, mammary hypertrophy and dorsocervical accumulation of fat mass (buffalo neck).
Protease inhibitors are also associated with metabolic disturbances such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia.

CPK elevations, myalgia, myositis and, in rare cases, rhabdomyolysis have been reported with protease inhibitors, particularly when given in combination with nucleoside reverse transcriptase inhibitors.

In HIV patients with severe immunodeficiency at the time of institution of antiretroviral combination therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections can occur (cf. SPC).

Cases of osteonecrosis have been reported, particularly in patients with known risk factors, at an advanced stage of HIV-related disease, or on combination antiretroviral therapy for a long time. Its frequency of occurrence is unknown.

4.3. Drug interactions

The drug interactions profile has been updated in the SPC to include in particular the risk of interactions with: atazanavir, certain anticonvulsants (carbamazepine, phenobarbital and phenytoin), buprenorphine, naloxone, omeprazole, digoxin, trazodone and bupropion. Midazolam and metoprolol are contraindicated with tipranavir (cf. SPC).

4.4. Resistance

Excerpt from the SPC: updating of data on resistance to tipranavir at 48 weeks
"Analyses of tipranavir resistance in treatment experienced patients
APTIVUS/ritonavir response rates in the RESIST studies were assessed by baseline tipranavir genotype and phenotype. Relationships between baseline phenotypic susceptibility to tipranavir, primary PI mutations, protease mutations at codons 33, 82, 84 and 90, tipranavir resistance-associated mutations, and response to APTIVUS/ritonavir therapy were assessed.

Of note, patients in the RESIST studies had a specific mutational pattern at baseline of at least one primary protease gene mutation among codons 30N, 46I, 46L, 48V, 50V, 82A, 82F, 82L, 82T, 84V or 90M, and no more than two mutations on codons 33, 82, 84 or 90.
The following observations were made:

- Primary PI mutations:
Response rates were higher in APTIVUS/ritonavir patients than comparator PI boosted with ritonavir in new enfuvirtide patients, or patients without new enfuvirtide.

- Mutations at protease codons 33, 82, 84 and 90:
A reduced virological response was observed in patients with viral strains harbouring two or more mutations at HIV protease codons 33, 82, 84 or 90, and not receiving new enfuvirtide.

- Tipranavir resistance-associated mutations:

Sustained decreases in HIV-1 viral load up to week 48 were observed in patients who received APTIVUS/ritonavir and new enfuvirtide.

Mean decrease in viral load from baseline to week 48, according to tipranavir baseline mutation score and enfuvirtide use in RESIST patients.

	With enfuvirtide	Without enfuvirtide*
TPV mutation score **	TPV/r	TPV/r
0.1	-2.3	-1.6
2	-2.1	-1.1
3	-2.4	-0.9
4	-1.7	-0.8
≥ 5	-1.9	-0.6
All patients	-2.0	-1.0

* Includes patients who did not receive ENF and those who were previously treated with and continued ENF.
** Mutations in HIV protease at positions L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, 58E, H69K, T74P, V82L/T, N83D or I84V
ENF Enfuvirtide; TPV/r Tipranavir/ritonavir

4.5. Conclusion

Additional 48-week data from the RESIST 1 and RESIST 2 pivotal studies, available for adult patients only, have been provided by the company.

Just as at the interim analysis after 24 weeks,
- APTIVUS (co-administered with ritonavir) was more effective than the comparator treatment as regards virological response at 48 weeks when given in combination with other antiretrovirals in highly pre-treated adults with virus resistant to multiple protease inhibitors versus a selected protease inhibitor (co-administered with ritonavir).
The virological efficacy was superior to that of the comparator in patients carrying strains resistant to the selected protease inhibitor. It was non-superior to that of the comparator group only in those patients carrying viral strains sensitive to the preselected protease inhibitor.
- the observed results as regards virological and immunological response in the secondary endpoints were superior in the APTIVUS group to those observed in the comparator group at 48 weeks.

The incidence of grades 1 to 4 adverse events at 48 weeks, in particular gastrointestinal events, fever, fatigue, cough, and headache, and that of hepatotoxicity, hyperlipidaemia, and bleeding were higher in the APTIVUS group than in the comparator group.
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 is used in combination with a higher dose of ritonavir than that used with other protease inhibitors.

APTIVUS must only be used in patients co-infected with hepatitis B or C if the expected benefit outweighs the potential risk and if clinical monitoring and monitoring of laboratory values is stepped up.

The drug interactions profile of APTIVUS co-administered with ritonavir is complex and merits close attention, particularly when given alongside other antiretroviral therapies.

5. DRUG USAGE DATA

Sales data for APTIVUS obtained from the GERS panel (cumulative annual as of October 2009) are as follows:
- 2026 bottles of 120 (in the community),
- 301,440 capsules (in hospitals).
This product has not been prescribed enough for obtaining qualitative information on the prescription indication (IMS/EPPM).

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Actual benefit

The condition treated with this medicinal product causes a severe deterioration in quality of life and 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.

Tipranavir is the only protease inhibitor indicated in highly pre-treated adults 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 adults 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 HIV patients 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.

On the basis of the available efficacy and tolerance data, the impact of APTIVUS on the reduction of HIV-related morbidity and mortality will be at best low.

In conclusion, APTIVUS is not expected to benefit public health in its indication in adults.

The actual benefit of this medicinal product is substantial.

6.2. Improvement in actual benefit (IAB)

APTIVUS soft capsules in combination with other antiretrovirals is indicated as last-line treatment in highly pre-treated adults, taking into consideration the following characteristics confirmed by 48-week follow-up data:
- a moderate immunovirological response with a specific resistance profile
- poor clinical and biochemical tolerability
- a complex drug interactions profile, particularly with other antiretrovirals, making its management especially tricky.

Consequently, the Committee considers that the medicinal product APTIVUS, co-administered with ritonavir and other antiretroviral drugs, does not offer any improvement in actual benefit (level V) in the current therapeutic management of highly pre-treated adult patients with virus resistant to multiple protease inhibitors.

6.3. Therapeutic use

6.3.1. Management of HIV patients with virological failure[1]

Strengths

• The introduction of an antiretroviral treatment must be preceded by a multidisciplinary study to optimise compliance with treatment (AIII).
• The objective of antiretroviral treatment is to attain and maintain an undetectable viral load (< 50 copies/ml) and a CD4 lymphocyte count > 500/mm^3 (A).
• Stopping antiretroviral treatment is of no benefit (AIIa).
• The persistence of viral replication during treatment exposes patients to a risk of accumulation of resistance mutations, which reduces the likely efficacy of subsequent treatment (AIIb) and adversely affects the CD4 lymphocyte count (AIIa).
• Cases of virological failure must be the subject of multidisciplinary discussions (AIII). The advice of an experienced team is indispensable in cases where the therapeutic options appear limited (AIII).

The group of experts recommends[2]:

In cases of virological failure:
– regardless of the failure situation (first line, last line, including after multiple failure), to continue to strive to attain and maintain a plasma viral load of less than 50 copies/ml (AIII);
– to analyse the failure, evaluating the clinical situation, the CD4 count and viral load, compliance, tolerability and possible drug interactions (AIII);
– to take account of the patient's treatment history in order to optimise the choice of new antiretroviral treatment and to carry out genotypic testing during treatment (AIIa). The results of any previous tests (AIII) and, where available, of pharmacological assays are likewise to be taken into account (BIII);
– to use a combination of at least two new drugs, ideally including one belonging to a therapeutic category not yet used (AIIa);
– if at least one drug is still effective and the CD4 count is less than 200/mm^3, to attempt to optimise treatment with the drugs currently used or used previously, possibly by increasing the PI dosage and making use of pharmacological assays (AIII);
– to not interrupt treatment, even briefly (AIa).

1 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).
2 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
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

6.3.2. Therapeutic use of the medicinal product APTIVUS

APTIVUS can be used, depending on the genotypic profile of the patient's virus, as a protease inhibitor in highly pre-treated adults with multiple treatment failure with virus resistant to multiple other protease inhibitors, in patients with no other therapeutic options.

APTIVUS must be used in combination with other antiretrovirals including at least one antiretroviral to which the patient's virus is genotypically sensitive.

6.4. Target population

The number of seropositive persons living in France in 2007 was estimated at 140,000[3]. It is estimated that approximately 30% of these individuals are unaware they are seropositive and consequently cannot be treated[4]. From this, the number of diagnosed seropositive persons in 2007 can be estimated at 98,000. It is, however, probable that a proportion of these 98,000 seropositive persons do not meet the criteria for the institution of treatment with antiretrovirals.

Conversely, it can be assumed that a certain number of persons infected with HIV will have reached a stage of the disease that justifies antiretroviral therapy, but due to being unaware of their seropositivity are unable to benefit from treatment.

Moreover, at the end of 2007 86,485 persons were claiming under the general health insurance scheme for chronic illness due to HIV infection[5]. Taking account of the fact that, at the end of 2007, approximately 88% of people living in France were covered by general health insurance, the number of persons being treated for HIV infection at the end of 2007 can be estimated at 98,000, i.e. a figure entirely comparable to the one estimated above, which confirms the soundness of the estimates.

Among seropositive persons treated in 2006, 82.8% were receiving treatment with antiretrovirals, 11.3% were not receiving antiretrovirals and 5.9% had been treated previously, but had stopped. The number of patients treated in 2007 can therefore be estimated at 81,000.

The objective of antiretroviral therapy must be to attain and maintain a plasma viral load of less than 50 copes/ml. The current treatment strategy recommends swift therapeutic intervention in cases of virological failure where the viral load is greater than 500 copies/ml. In cases of "moderate" failure (confirmed viral load of between 50 and 500 copies/ml), it is recommended to modify or step up treatment.

In 2007, 12% of patients receiving polytherapy for more than 6 months had a viral load greater than 500 copies/ml and 23% a viral load greater than 50 copies/ml (Yéni report, 2008). Applying these proportions to the 81,000 patients infected with HIV-1 and treated with antiretrovirals, the number of patients with a viral load > 500 copies/ml is estimated at 9700 and the number with a viral load of between 50 and 500 copies/ml at 8900.

The indication for tipranavir being limited to patients with no other therapeutic alternatives, this population is overestimated.

3 UNAIDS. Report on the global HIV/AIDS epidemic 2008. Geneva: UNAIDS, 2008. Available at http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp (retrieved 05/02/2009).

4 Hamers FF, Phillips AN. Diagnosed and undiagnosed HIV-infected populations in Europe. HIV Med. 2008;9 Suppl 2:6-12.

5 Païta M, Weill A. Les personnes en affection de longue durée au 31 décembre 2007 [Persons with chronic illness as of 31 December 2007]. Points de repère 2008; 20: 1-8. Available at: http://www.ameli.fr/fileadmin/user_upload/documents/Points_de_repere_n__20.pdf (retrieved 14/05/2009).

As a guide, in 2008 out of the 34,016 infected patients treated on the basis of INSERM[6], 239 patients were treated with tipranavir. Extrapolating this result to the 81,000 patients infected with HIV-1 and treated with antiretrovirals, it is estimated that 567 patients have been treated with APTIVUS.

6 INSERM, Retour d'Informations Clinico-Épidémiologiques [Clinical Epidemiological Information Return] No. 16, October 2009. Available at: http://www.ccde.fr/_fold/fl-1256658847-705.pdf (retrieved 09/03/2010)