HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

12 April 2006

Aptivus 250 mg, soft capsule
Vial 120 capsules: 369 252-4

Applicant: Boehringer Ingelheim International GmbH

tipranavir

list I
Annual prescription, initially in hospital.
Prescription renewal not restricted.

Date of Marketing Authorisation: 25/10/2005
Marketing Authorisation granted under exceptional conditions in view of the lack of long-term data (48 weeks) for the 2 phase III efficacy and safety trials.

Reason for application: inclusion on the list of medicinal products reimbursed by National Insurance and approved for use by hospitals.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tipranavir

1.2. Background

The drug is a novel antiretroviral in the class of HIV-1 protease inhibitors (nonpeptidic inhibitor).

1.3 Indications

Aptivus, co-administered with low-dose ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors.

This indication is based on the results of 2 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 resistance profile of patients' HIV at baseline in section 5.1).

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.

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 SPC 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.

Adults:
The recommended dose of Aptivus is 500 mg, co-administered with 200 mg of ritonavir (low-dose ritonavir), twice daily.
Paediatrics:
Safety and efficacy of Aptivus in this population has not yet been established.
General:
Aptivus soft capsules, co-administered with low-dose ritonavir, should be taken with food (see section 5.2).

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 should not be used in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) (see sections 4.3, 4.4 and 5.2).

Limited data are currently available for the use of Aptivus, co-administered with low-dose ritonavir, in patients co-infected with hepatitis B or C.

Renal impairment: see the SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

J : GENERAL ANTI-INFECTIVES SYSTEMIC
J05 : ANTIVIRALS FOR SYSTEMIC USE
J05A : ANTIVIRALS WITH DIRECT ACTION
J05AE : PROTEASE INHIBITORS

2.2 Medicines in the same therapeutic category

2.2.1 Comparator medicines

Protease inhibitors used in combination antiretroviral therapy at adult dosage*

- indinavir: Crixivan capsules, indicated in adults and children > 4
- nelfinavir: Viracept film-coated tablets and oral powder, indicated in adults and children ≥ 3
- amprenavir: Agenerase capsules and oral solution, indicated in adults and children ≥ 4
- saquinavir: Fortovase soft capsules, indicated in adults
- saquinavir mesylate: Invirase capsules, indicated in adults and adolescents
- lopinavir in combination with ritonavir: Kaletra, indicated in adults and children > 2
- fosamprenavir: Telzir film-coated tablets and oral solution, indicated in adults
- atazanavir: Reyataz capsules or oral powder, indicated in adults

- ritonavir: Norvir (soft capsules and oral solution) increases the bioavailability of most protease inhibitors, which is why it is used only in combination with these drugs.

* the indications for these protease inhibitors are not exactly the same as those for Aptivus

2.2.2 Comparisons that have been carried out

Most used (number of treatment days): Kaletra capsules
Most economical (cost of treatment): not relevant in the context of combined treatments
Most recently added to the list: Kaletra soft capsules and oral solution

2.3 Medicines with a similar therapeutic aim

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) as part of combination antiretroviral therapy:

- nevirapine: Viramune tablets and oral solution
- efavirenz: Sustiva capsules and oral solution

- Nucleotide reverse transcriptase inhibitors (NtRTIs) as part of combination antiretroviral therapy:

- tenofovir: Viread tablets

- Nucleoside reverse transcriptase inhibitors (NRTIs) as part of combination antiretroviral therapy:

- abacavir: Ziagen tablets and oral solution
- didanosine: Videx capsules and powder for oral suspension
- emtricitabine: Emitriva capsules and oral solution
- stavudine: Zerit capsules and oral solution
- zalcitabine: Hivid tablets
- zidovudine: Retrovir capsules, oral solution and solution for injection
- lamivudine: Epivir tablets and oral solution
- abacavir - lamivudine: Kivexa tablets
- abacavir - lamivudine - zidovudine: Trizivir tablets
- lamivudine - zidovudine: Combivir tablets.

- Nucleotide and nucleoside reverse transcriptase inhibitor:

emtricitabine – tenofovir: Truvada tablets

- Fusion inhibitor:

enfuvirtide (Fuzeon for injectable suspension)

3 ANALYSIS OF AVAILABLE DATA

3.1 Efficacy

The clinical dossier includes 2 comparative trials (RESIST-1 and RESIST-2) in HIV-positive patients previously treated with 3 classes of antiretrovirals. The results of the 2 trials were submitted in pooled form.

The trials compared the efficacy and safety of Aptivus, coadministered with low-dose ritonavir and in combination with other antiretrovirals (optimised background regimen*), with a comparator comprising a protease inhibitor coadministered with low-dose ritonavir.

Before randomisation, the following actions were taken:
- genotype analysis of all patients' viruses and assessment of their antiretrovirals sensitivity.
- selection of the optimal protease inhibitor (amprenavir, indinavir, lopinavir or saquinavir) for comparison, according to each patient's viral genotype and treatment history.
- optimisation of the associated therapy (optimised background regimen/OBR) determined for each patient on the basis of genotype resistance tests and patient history (with or without enfuvirtide/Fuzeon in the combined therapy).

At randomisation, patient subgroups were stratified on the basis of:
- the number of active antiretrovirals in the associated OBR with or without enfuvirtide
- the sensitivity or resistance to the protease inhibitor included in the comparator group

*The (associated) individually optimised background regimens (OBRs) were defined before randomisation and enabled comparable groups to be created in the 2 studies, in respect of the number of active antiretrovirals selected from among nucleoside inhibitors, non-nucleoside inhibitors and enfuvirtide (Fuzeon).

Inclusion criteria:

Adult HIV-1 infected patients previously treated with 3 antiretroviral classes including at least 2 protease inhibitors and with treatment failure including a protease inhibitor at the time of enrolment in the trial, with:
- a viral load ≥ 1000 copies/mL (3 $\log_{10}$ copies/mL).
- a genotype profile: patients with at least one of the following primary mutations in the protease gene: 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M and not more than 2 key mutations among codons 33, 82, 84 or 90.

Treatment groups:

- Aptivus groups (N=582).
Aptivus was coadministered with low-dose ritonavir (500 mg/200 mg, twice daily), in combination with an optimised background regimen (OBR).

- Comparator groups (N=577).
The comparator therapy included a protease inhibitor (individually determined) coadministered with low-dose ritonavir, combined with an OBR.
The protease inhibitor was selected before randomisation from saquinavir, amprenavir, indinavir or lopinavir/ritonavir, on the basis of each patient's viral genotype and treatment history.
The expected treatment duration was 48 weeks (the Transparency Committee assessed the interim results at 24 weeks).
After the 8th week, patients in the comparator groups with inadequate initial viral response (according to a criterion predefined by the protocol) had the opportunity to discontinue treatment and replace it with Aptivus/ritonavir in a long-term follow-up study.

Primary endpoint:
A composite endpoint defined by the percentage of patients showing a confirmed decrease in viral load ≥ 1 $\log_{10}$ compared to baseline and without evidence of treatment failure at 48 weeks.

Secondary endpoints:
Change in viral load (VL) compared to baseline,
Percentage of patients with an undetectable viral load (< 400 and < 50 copies/mL),
Assessment of immune restoration (CD4 lymphocyte count)

Patient characteristics at inclusion:
1159 patients were covered by the interim analysis of the 2 trials at 24 weeks.

- Median plasma HIV-1 RNA levels were 4.83 $\log_{10}$ copies/mL (interval: 2.34-6.52) and 4.82 $\log_{10}$ copies/mL (interval 2.01-6.76 $\log_{10}$ copies/mL) in the comparator group.
- Median CD4 counts at inclusion were 155 cells/mm^3 (interval: 1-1893 cells/mm^3) in the Aptivus group, and 158 cells/mm^3 (interval: 1-1184 cellules/mm^3) in the comparator group.

- Patients had previously been treated with 6 nucleoside inhibitors, 1 non-nucleoside inhibitor and 4 protease inhibitors (median values)
- 12% of patients had previously been treated with enfuvirtide (Fuzeon)
- 55.7% of patients had had an OBR that included at least 2 active antiretrovirals and 32.4% a single active antiretroviral. Enfuvirtide (Fuzeon) was used in combination in 27.1% of the Aptivus group and in 22.2% of the comparator group.

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

Results:

I – Primary endpoint: treatment

Response to treatment at 24 weeks (interim results compiled from the RESIST-1 et RESIST-2 trials) in previously treated patients.
Treatment response is shown in the table below for the population as a whole (with or without enfuvirtide).

Number and percentage of patients showing a confirmed decrease in viral load ≥ 1 $\log_{10}$ compared to baseline and without evidence of treatment failure at 24 weeks:

RESIST-1 and RESIST-2 trials	**Aptivus**		**Comparator***		**p**
	n (%)	**N**	**n (%)**	**N**	
Total population					
ITT	**240 (41.2)**	582	**109 (18.9)**	577	< 0.0001
PP	166 (44.7)	371	81 (22.5)	360	< 0.0001
-with enfuvirtide	92 (58.2)	158	33 (25.8)	128	< 0.0001
-without enfuvirtide	148 (34.9)	424	76 (16.9)	449	< 0.0001

ITT: Intent to treat population
PP: Per-protocol (r= ritonavir)

* Comparator protease inhibitor: lopinavir/r 400/100 mg twice daily (n=290), indinavir/r 800/100 mg twice daily (n=20), saquinavir/ritonavir 1000/100 mg twice daily or 800/200 mg twice daily (n=118), amprenavir/ritonavir 600/100 mg twice daily (n=149)

Results at 24 weeks in terms of viral response for the primary endpoint were in favour of Aptivus in the total population: virological efficacy in the Aptivus group was statistically superior to that of the comparator group (a selected protease inhibitor) whether or not enfuvirtide was included in the associated treatment.

Results at 24 weeks in terms of viral response for the primary endpoint were:

- according to the combined antiretroviral therapy

Virological efficacy in the Aptivus group was better when the combined background regimen included at least one antiretroviral to which the virus genotype was sensitive.

- according to the selected protease inhibitor in the comparator group:

In the subgroups defined according to the selected protease inhibitor in the comparator group (patients carrying viral strains sensitive or resistant to the selected protease inhibitor):

. virological efficacy of Aptivus was statistically superior to that of the comparators (total population: patients carrying strains sensitive or resistant to the selected protease inhibitor)

. virological efficacy of Aptivus was statistically superior to that of the comparators in patients carrying strains resistant to the selected protease inhibitor.

. virological efficacy of Aptivus was not statistically superior to that of the comparators in patients carrying strains sensitive to the selected protease inhibitor.

II – Secondary endpoints

At 24 weeks, results in terms of viral and immunological response for the secondary criteria were in favour of Aptivus: virological and immunological efficacy in the Aptivus group were statistically superior to the comparators, including the selected optimised protease inhibitor, in the total population on the following criteria:

- percentage of patients with HIV-1 RNA < 400 copies/mL was 34.2% vs. 14.9% respectively ($p< 0.0001$)
- percentage of patients with HIV-1 RNA < 50 copies/mL was 23.9% vs. 9.4% ($p< 0.0001$).
- median change in HIV-1 RNA between baseline and latest value at week 24 was -0.80 $\log_{10}$ copies/mL in patients taking Aptivus/ritonavir vs. -0.25 $\log_{10}$ copies/mL ($p< 0.0001$).
- median change in CD4+ count between baseline and latest value at week 24 was +34 cells/mm^3 vs. +4 cells/mm^3 ($p< 0.0001$).

Analyses were carried out to assess virological efficacy according to the number of primary protease inhibitor-resistance associated mutations present at inclusion (any change in protease codons 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 or 90).
Response rates decreased if there were 5 or more primary protease inhibitor-resistance associated mutations.

3.2 Undesirable effects

Undesirable effects most commonly reported with tipranavir/ritonavir were gastrointestinal disorders (46.9% of patients) such as diarrhoea (23.6%), nausea (15.2%), vomiting (7.7%), and abdominal pain (5.8%).
Other undesirable effects reported in more than 5% of patients were upper respiratory tract infection (16.5%), fever (9.3%), asthenia (9.1%), headache (8.6%), pulmonary infection (7.9%), herpes virus infection (7.8%), Candida infection (7.4%), cough (5.9%) and rash (5.3%).

Hepatotoxicity, hyperlipidaemia, bleeding and rash were reported more often in the Aptivus groups than in the comparator groups (see SPC).

Hepatotoxicity: Elevated transaminases were more common with Aptivus than with the comparators.
After 24 weeks of follow-up, the frequency of grade 3 or 4 ALAT and/or ASAT abnormalities was higher in the Aptivus group (6.2%) than in the comparator group (2.5%).

Hyperlipidaemia: Grade 3 or 4 elevations of triglycerides occured more frequently in the Aptivus group (20.8%) than in the comparator group (11.2%).

17.7% of patients prematurely discontinued in the Aptivus group (17% because of undesirable effects and 3.8% because of virological failure) compared with 60.1% in the comparator group (8.5% because of undesirable effects and 39.5% because of virological failure).

Patients co-infected with hepatitis B or C: Limited data are currently available for 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 should be used in this patient population only if the potential benefit outweighs the potential risk, and with increased clinical and laboratory monitoring.

Combination antiretroviral therapy including regimens containing a protease inhibitor, is associated with redistribution of body fat in some patients, including loss of peripheral subcutaneous fat, increased intra-abdominal fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).
Protease inhibitors are also associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and hyperglycaemia.

Increased CPK , myalgia, myositis and, rarely, rhabdomyolysis, have been reported with protease inhibitors, particularly in combination with nucleoside reverse transcriptase inhibitors.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may occur (see SPC).

3.3 Drug interactions

The drug interaction profile for Aptivus coadministered with low-dose ritonavir is complex and requires special attention, in particular in combination with other antiretroviral agents (notably protease inhibitors).

Coadministration of Aptivus and low-dose ritonavir with agents metabolised mainly by CYP3A may change plasma concentrations of tipranavir or other agents, which can alter both their therapeutic effects and their undesirable effects. Coadministration of Aptivus and low-dose ritonavir together with active substances whose clearance is highly dependant on CYP3A is contraindicated (see SPC).

3.4 Resistance

Clinical isolates whose sensitivity to tipranavir dropped by a factor of ≥ 10 showed 8 or more mutations associated with tipranavir.
Genotypes found in the clinical trials (Phase II and Phase III), in 276 patients under treatment with Aptivus, indicated that the main emergent mutations were L33F/I/V, V82T/L and I84V. The combination of these three mutations generally results in reducing sensitivity.

3.5 Conclusion

In the 2 clinical trials RESIST-1 et RESIST-2, compared to a selected protease inhibitor (coadministered with ritonavir), Aptivus (coadministered with ritonavir) was more effective in the total population in terms of viral and immunological response at 24 weeks when combined with other antiretrovirals in highly treatment-experienced adults with viruses resistant to multiple protease inhibitors.
However, virological efficacy in the Aptivus group was not statistically superior to that of the comparator group in only those patients carrying viral strains sensitive to the preselected protease inhibitor.

Virological efficacy in the Aptivus group was better when the combination antiretroviral therapy included at least one antiretroviral to which the virus genotype was sensitive (such as enfuvirtide).

Virological efficacy was lower when there were 5 or more primary protease inhibitor-resistance associated mutations.

Hyperlipidaemia and hepatic cytolysis were more common in patients in the Aptivus groups than in the comparator groups.

Aptivus should be used in patients coinfected with hepatitis B or C only if the anticipated benefit outweighs the potential risk, and with increased clinical and laboratory monitoring.

The interaction profile of Aptivus, coadministered with low-dose ritonavir, is complex and requires particular attention, especially when given in combination with other antiretrovirals.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The condition concerned by this drug severely impairs quality of life and is life-threatening.

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

The efficacy/safety ratio for this drug in combination with other antiretroviral therapies in highly treatment-experienced adult HIV-1 infected patients with viruses resistant to multiple protease inhibitors is high.

Public health benefit

HIV infection is a substantial burden on public health.

In the population concerned by this indication (highly treatment-experienced HIV-1 infected patients with viruses resistant to multiple protease inhibitors), the burden is moderate because there are fewer patients involved compared to the total population of HIV patients in France.

Reducing AIDS-related morbidity and mortality is a public health requirement, especially in patients for whom treatment has failed and who are resistant to current treatments, and given the limits of available therapies.

There is no available evidence on which to base a direct estimate of the impact of Aptivus on the criteria of morbidity and mortality. However, on the basis of available data, Aptivus is expected to have at best a minor impact on HIV-related morbidity and mortality. No impact is anticipated on quality of life.

In view of the available data it is therefore expected that Aptivus will benefit public health. This benefit is minor.

In this specific situation there are no alternative drugs to this one in highly treatment-experienced adults with viruses resistant to multiple protease inhibitors.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

Compared with a selected protease inhibitor (coadministered with ritonavir), Aptivus (coadministered with ritonavir) showed the following characteristics in the 2 clinical trials RESIST-1 and RESIST-2 at 24 weeks:

- improved virological efficacy
- worse hepatic and lipid safety profile

In the management of highly treatment-experienced adult patients infected with strains of HIV-1, with:

- viruses resistant to multiple protease inhibitors
- genotype profile including at least 1 of the following primary mutations in the protease gene: 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M, and not more than 2 key mutations in codons 33, 82, 84 or 90,

Aptivus coadministered with ritonavir and used only in combination with other antiretrovirals, including at least one antiretroviral to which the patient's virus genotype is sensitive, therefore offers a moderate improvement in actual benefit (level III) in terms of virological efficacy.

4.3. Therapeutic use

4.3.1 – Management of HIV-infected patients (major/multiple treatment failure)

Based on the report *Prise en charge des personnes infectées par le HIV - Recommandations du groupe d'experts - Rapport 2004* [Therapeutic management of HIV-infected patients – Recommendations of an expert group – 2004 report] produced under the supervision of Jean-François Delfraissy and published in French - June 2004 - Médecine-Sciences Flammarion (www.sante.gouv.fr).

The usual situation is:

- high viral load, over 30 000 copies/mL;
- multiple treatment regimens (> 5 lines of treatment; all therapeutic categories used)
- multiple viral resistance defined by resistance to several drugs in each therapeutic category.

The immunological situation may range from moderate immune deficiency with CD4 lymphocyte count above 200/mm^3, to severe deficiency with CD4 count below 200/mm^3, or very severe with CD4 count below 100/mm^3.
The priorities are:
- to maintain or re-establish CD4 lymphocyte count of 200/mm^3 or above, or at least 100/mm^3 or above;
- to reduce viral load by at least 1 $\log_{10}$;
- to prevent opportunistic infection and clinical progression of HIV disease.

Treatment options are still under debate.
In this situation of multiple treatment failure together with multiple virological resistance, there is no simple solution and no guarantee of a significant virological result.
Several studies have shown that in a situation of multiple resistance, virological response is better if several active drugs are combined, either drugs from new therapeutic categories (e.g. enfuvirtide), new protease inhibitors (tipranavir), or drugs from a previously used category which had retained their antiretroviral activity.
All new drugs and those being developed show greatest antiretroviral potency when they can be combined with drugs to which the virus is still sensitive.

The best guarantee of avoiding treatment failure is substantial involvement by both medical staff, who must understand the different mechanisms of treatment escape, and of patients, who must always bear in mind the aims of treatment and the importance of compliance.
In severe treatment failure, it is essential to avoid compromising a new drug by using it as quasi-monotherapy. The proposed new combination should combine at least two new active drugs.

4.3.2 Place of Aptivus in the treatment strategy

Depending on the patient's virus genotype profile, Aptivus may be used as a protease inhibitor in highly treatment-experienced adults with multiple treatment failure, with viruses resistant to many other protease inhibitors.
Aptivus should be combined with other antiretrovirals including at least one antiretroviral to which the patient's virus genotype is sensitive.

4.4. Target population

The target population for Aptivus is highly treatment-experienced adult patients with viruses resistant to multiple protease inhibitors, and whose treatment history and mutations profile associated with the various antiretrovirals have been assessed.

The estimated prevalence of HIV infection in 2003 was 97 000 people [CI: 61 000–176 000] (BEH [Weekly Epidemiological Record] no. 11:2005).

According to the French Hospital Database on HIV infection, produced using DMI2 software in the first half of 2004 (D. Costagliola - M. Mary-Krause INSERM U 720), around 80% of patients attending hospital were treated.

Assuming that the DMI2 database percentage for patients attending and patients treated can be extrapolated to all HIV-infected patients, the estimated population of patients treated both inside and outside hospital would be 48 000–140 800 people.

According to expert opinion, 5% of patients treated are likely to benefit from treatment with Aptivus, i.e. 2400–7000 people.

The estimated target population for Aptivus is 2400–7000 people.

4.5. Transparency Committee recommendations

The committee recommends approval of inclusion on the list of medicinal products reimbursed by National Insurance and approved for use by hospitals and various public services in all the therapeutic indications and dosages specified in the Marketing Authorisation.

Packaging

The packaging is appropriate for the conditions under which it is prescribed.

Reimbursement rate 100%