HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

25 June 2008

KALETRA 100/25 mg film-coated tablets
Box of 60 (CIP: 384 420-1)

Applicant: ABBOTT France

Lopinavir/ritonavir

ATC code: J05AE06

List I
Medicinal product for initial annual hospital prescription. Unrestricted renewal.

Marketing Authorisation date: 18 March 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Lopinavir-ritonavir

1.2. Background

This is an addition to the range: a new form of the proprietary drug KALETRA as a film-coated tablet containing 100 mg of lopinavir and 25 mg of ritonavir.

1.3. Indication

KALETRA is indicated in the treatment of children aged two and over and adults with HIV-1 infection, in combination with other antiretrovirals.

Most of the clinical experience with KALETRA has been obtained from its use with patients who have never previously undergone antiretroviral treatment. Limited data is available on patients who have previously had several courses of treatment with protease inhibitors. Little data is available on rescue treatment of patients in whom KALETRA treatment has failed.

When treating patients with HIV-1 infection who have previously been treated with protease inhibitors, KALETRA should only be administered if this is considered appropriate in the light of individual viral resistance test results and patients' treatment histories.

1.4. Dosage

KALETRA must be prescribed by doctors specialising in the management of HIV infection.
KALETRA tablets must be swallowed whole without being chewed, cut or crushed.

Children aged under two: the use of this product is not recommended for children aged under two because insufficient safety and efficacy data is available (see section 5.1).

Children (aged two and over): the adult dosage of KALETRA tablets (400/100 mg, twice a day) can be applied to children weighing 40 kg or with a body surface area (BSA)* of more than 1.4 m².
In the case of children weighing less than 40 kg or with a body surface area (BSA)* between 0.5 and 1.4m² who are able to swallow tablets, see the dosage recommendation tables below.
In the case of children who are unable to swallow tablets, please see the SPC for KALETRA oral solution.
Before prescribing KALETRA 100/25 mg tablets to young children, it is essential to make sure that they are able to swallow whole tablets. The oral solution form of KALETRA must be prescribed for children unable to swallow the tablets properly.
The table below contains dosage recommendations for KALETRA 100/25 mg tablets, based on the body surface area (BSA)*.

Dosage recommendations for children	
Body surface area (m^2)	Recommended number of 100/mg tablets to be taken twice a day
$\geq$ 0.5 to < 0.9	2 tablets (= 200/50 mg)
$\geq$ 0.9 to < 1.4	3 tablets (= 300/75 mg)
$\geq$ 1.4	4 tablets (= 400/100 mg)

* The body surface area may be calculated using the following equation :
taille = height, poids = weight

$$\text{BSA } (m^2) = \sqrt{[\text{taille (cm)} \times \text{poids (kg)} / 3600]}$$

Adults and adolescents: the recommended dosage of KALETRA is two tablets (=200 mg/50mg) twice a day, to be taken with or without food.

An oral solution form is available for patients who are unable to take the tablet form.
(Refer to SPC).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

J	General anti-infectives for systemic use
J05	Antivirals for systemic use
J05A	Direct-acting antivirals
J05AE	Protease inhibitors
J05AE03	ritonavir
J05AE06	lopinavir

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

KALETRA is the only medicine that combines a protease inhibitor (lopinavir) with ritonavir.

Comparable medicines are protease inhibitors indicated for use in children:

INN	Proprietary product	Pharmaceutical form	Packaging	Age
Ritonavir* and **	NORVIR	100 mg soft capsule	Boxes of 336 and 84	Adults and children over two *(only in combination with PI)*
		Oral solution 80mg/ml	90 ml vial	
Indinavir**	CRIXIVAN	100 mg gelatin-coated capsule	Box of 180	Adults and children over four
		200 mg gelatin-coated capsule	Box of 360	
		400 mg gelatin-coated capsule	Boxes of 90 and 180	
Nelfinavir	VIRACEPT	250 mg film-coated tablet	Box of 300	Adults and children over three
		Powder 50mg/g	144 g vial	
Amprenavir	AGENERASE	50 mg soft capsule	Box of 480	Adults and children over four
		15mg/ml oral solution	240 ml vial	
Fosamprenavir* **	TELZIR	Film-coated tablet Oral suspension	Box of 60 225 ml vial	Adults and children over six

Source: report by P. YENI 2006
* used at a low dose as a booster in combination with other PIs
** ritonavir and indinavir are no longer recommended because of their adverse effects
*** fosamprenavir is a pro-drug of and substitute for amprenavir.

2.3. Medicines with a similar therapeutic aim

Other antiretrovirals indicated in the treatment of patients with type 1 human immunodeficiency virus (HIV-1).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

One pharmacokinetic study has compared the bioavailability of the 100/25 mg film-coated tablet with that of the film-coated tablet that is currently on the market (200/50 mg).

Population characteristics:
Adults (n= 45)
36 men and 9 women. Average age 39

Study design: open-label, randomised, among 45 adults, conducted over three periods in a cross-over design.
Patients were assigned at random to three groups: therapeutic regimens A, B and C.

	Therapeutic regimen A	**Therapeutic regimen B**	**Therapeutic regimen C**
Dose of LPV/ritonavir	Single dose of four 100/25 mg pink tablets	Single dose of four 100/25 mg pale yellow tablets	Single dose of two 200/50 mg yellow tablets

The pharmacokinetic parameters observed for the two dosages showed that both forms (the 100/25 mg and the 200/50 mg film-coated tablets) were bioequivalent.

3.2. Adverse effects

No tolerance studies have been conducted on 100/25mg KALETRA tablets;

Reminder (other galenic forms)
The tolerance profile among children aged two and over is similar to that seen in adults.

Frequent adverse effects (≥ 1/100 to < 1/10) reported in children during clinical studies:

- Infections and infestations: viral infection
- Nervous system conditions: taste disorder
- Gastrointestinal conditions: constipation, vomiting, pancreatitis
- Hepatobiliary conditions: hepatomegaly
- Skin and subcutaneous tissue disorders: skin rash, dry skin
- General disorders and administration site conditions: fever
- Biological changes (grade 3 or 4): increase in activated partial prothrombin time, hypoglobulinaemia, low platelet count, hypernatraemia, hyperkaliaemia, hypercalcaemia, hyperbilirubinaemia, increase in SGOT/ASAT, SGPT/ALAT, increase in total cholesterol, hyperamylasaemia, hyperuricaemia, hyponatraemia, hypokaliaemia, hypocalcaemia, neutropenia.

Post-marketing experience

Some cases of hepatitis and rare cases of jaundice have been reported in patients being treated with KALETRA, with or without identifiable hepatitis risk factors.

Cases of Stevens-Johnson syndrome and polymorphic erythema have been reported.

Cases of osteonecrosis have been reported, particularly in patients with known risk factors, in an advanced stage of a disease related to HIV and/or who are on a long-term course of combination antiretroviral treatment. The frequency of these cases is not known.

3.3. Conclusion

The bioequivalence of the two forms (100 mg/25 mg and 200 mg/50 mg film-coated tablets) has been demonstrated.
The tolerance profile among children aged two and over is probably similar to that seen in adults.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

HIV infection entails a severe deterioration of quality of life and has an impact on life expectancy.

This proprietary drug aims to prevent and/or correct the immune deficiency resulting from HIV infection.

The efficacy/safety ratio for this proprietary drug, combined with other antiretrovirals, is high.

There are alternative drugs available.

Impact on public health

The public health burden due to HIV infection is significant. In the population likely to benefit from KALETRA 100/25 mg tablets, the burden is low due to the limited number of people affected in relation to the total number of patients with HIV in France.
Reduction of morbidity and mortality associated with AIDS is a public health need in the context of an established priority (national programme against HIV-AIDS 2005-2008).
The data available does not indicate that KALETRA 100/25mg tablets are likely to have an additional impact in terms of morbidity and mortality compared to current management using other available forms of KALETRA.
Consequently, KALETRA 100/25mg tablets are not expected to have an impact on public health.

The actual benefit conferred by this proprietary product is substantial in the context of treatment involving other antiretrovirals.

4.2. Improvement in actual benefit

KALETRA 100/25 mg film-coated tablets does not offer any improvement in actual benefit compared to KALETRA oral solution.

The Committee emphasises that this proprietary product, which can be taken at any time with regard to food and has no particular storage requirements, will help to simplify the practical aspects of administration.

4.3. Therapeutic use

The recommendations for the management of individuals infected with HIV (YENI report) were published in 2006, and are currently being updated for 2008.

4.3.1 Management of children and adolescents with HIV infection

From: "*Prise en charge médicale des personnes infectées par le VIH - Recommandations du groupe d'experts"* - Rapport 2006 sous la direction du Professeur Patrick YENI [Medical management of individuals infected with HIV - Expert group recommendations - 2006 report produced under the guidance of Professor Patrick YENI] (www.sante.gouv.fr).

Key points*

- In 2005, it was estimated that there were approximately 1,500 children infected with HIV living in France.
- 10 to 20 neonates are diagnosed as being infected with HIV each year in France.
- Around a hundred adolescents are infected each year by the sexual route.
- Most of the information regarding the treatment of children is still extrapolated from experience of treating adults.
- In children, HIV infection remains a psychological "handicap" because of the significant social stigma associated with the condition. Individual psychotherapies, discussion groups and shared leisure activities for groups of HIV-positive children relieve their mental suffering and that of their families.
- The diagnosis should be disclosed to a child in accordance with the principle of progressive information taking his or her age and personal circumstances into account.

The expert group recommends:

- starting treatment at a CD4 threshold of 15 in 100, even if no clinical symptoms are present (AIIa). Some experts are of the opinion that this threshold can be increased to 20 in 100 for children aged one to three (BIII);
- offering tritherapy as an initial treatment, comprising a combination of two RTNIs (abacavir + lamivudine or zidovudine + abacavir or zidovudine + lamivudine) and one PI/r (AIIa);
- measuring blood levels of some antivirals, particularly in the case of chemicals used on an off-label basis and nelfinavir (BIIa), and in patients whose virus is undergoing PI resistance mutations (AIIa);
- not interrupting treatment except in the case of intolerance, clear non-compliance, or in response to the patient's wishes, where no specific research protocol is involved (BIIa);
- managing infected children in a specialised centre (AIII). Unlike other European countries, France does not have a system of "accredited reference centres". This possibility should be explored;
- encouraging the pharmaceutical industry to continue research into galenic formulations suited to the needs of children (AIII);
- addressing issues related to sexuality with infected adolescents at an early stage (AIII);
- reinforcing HIV/AIDS prevention campaigns addressed at young people, especially in the context of school and college, and drawing attention to the availability of free, anonymous screening (AIII).

What initial treatment should be given?

• First preference: for all ages and irrespective of the patient's initial immunovirological parameters: combination of two RTNIs (abacavir + lamivudine or zidovudine + abacavir or zidovudine + lamivudine) and one PI/r (AIIa).
Nelfinavir may be offered to patients unable to ingest the various galenic forms of lopinavir/ritonavir.
The combination of abacavir + lamivudine is the preferred choice if the child is able to ingest the co-formulation and/or if nelfinavir has been selected (AIa). The risk of serious allergy to abacavir must be taken into account and discussed with the child and his or her family.
• Alternative choice: combination of two RTNIs and one RTNNI, provided that good compliance is definitely assured from the start of treatment (BIIa).

* Grading of the recommendations:

A: Data available justifies a strong recommendation
B: Data available justifies a moderate recommendation
C: Data available is insufficient to justify a recommendation
Levels of evidence: type of data used in the recommendations:
I a, b: At least one randomised clinical trial; meta-analysis of randomised trials
II a, b: Non-randomised clinical trials; cohort or case studies; meta-analysis of cohort or case studies
III: Expert analyses based on other data available

a: data published in a scientific journal with a review committee
b: data submitted to a scientific conference with a selection committee and available in the form of an abstract.

4.3.2 Management of adults infected with HIV

As this new dosage will probably only be prescribed for adults under exceptional circumstances, its therapeutic use in adults will not be described below: See: Prise en charge médicale des personnes infectées par le VIH - Recommandations du groupe d'experts - Rapport 2006 sous la direction du Professeur Patrick YENI [Medical management of individuals infected with HIV - Expert group recommendations - 2006 report produced under the guidance of Professor Patrick YENI] - (www.sante.gouv.fr)

4.4. Target population

In children

The target population comprises children aged two or over with type 1 human immunodeficiency virus (HIV-1) infection.

The number of HIV-infected children living in France was estimated at around 1,500 in 2005, and 10 to 20 new cases are diagnosed each year1.

In practice, the number of children likely to be suitable for KALETRA in the paediatric population will be smaller, as its use is limited to young children weighing under 40 kg or with a body surface area between 0.5 and 1.4m2 who are able to swallow tablets.

In adults

KALETRA 100mg/25mg tablets should only be prescribed for adults under exceptional circumstances, i.e. to patients who are likely to benefit from a dose adjustment requiring the use of a tablet containing specifically 100mg/25mg of the active substances.

[1] Prise en charge médicale des personnes infectées par le VIH - Recommandations du groupe d'experts - Rapport 2006 sous la direction du Professeur Patrick YENI [Medical management of individuals infected with HIV - Expert group recommendations - 2006 report produced under the guidance of Professor Patrick YENI] (www.sante.gouv.fr)

No epidemiological data allowing the estimation of the size of the target population is available.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and dosages of the Marketing Authorisation.

4.5.1. Packaging: appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 100%