HAUTE AUTORITÉ DE SANTÉ

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**TRANSPARENCY COMMITTEE**

OPINION

6 February 2008

**TELZIR 700 mg film-coated tablets B**
**Bottle containing 60 tablets – CIP code: 364 063-9**
**TELZIR 50 mg/ml oral suspension**
**Bottle containing 225 ml – CIP code: 364 064-5**

**Applicant: GLAXOSMITHKLINE**

Fosamprenavir (a protease inhibitor, a pro-drug of amprenavir)

Date of Marketing Authorisation: 12 July 2004 (centralised procedure)
Extension of indication for paediatrics: 13 September 2007

Medicinal products included on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication to include adolescents and children of 6 years and above.

Medical, Economic and Public Health Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

Fosamprenavir, calcium phosphate ester of amprenavir

## 1.2. Indication

"Telzir in combination with low dose ritonavir is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults, **adolescents and children of 6 years and above** in combination with other antiretroviral medicinal products.

In moderately antiretroviral experienced **adults**, Telzir in combination with low dose ritonavir has not been shown to be as effective as lopinavir / ritonavir.
**No comparative studies have been undertaken in children or adolescents.**

In heavily pretreated patients, the use of Telzir in combination with low dose ritonavir has not been sufficiently studied.

In protease inhibitor (PI) experienced patients, the choice of Telzir should be based on individual viral resistance testing and treatment history."

## 1.3. Dosage (in the extension of indication)

Telzir must only be given with low dose ritonavir as a pharmacokinetic enhancer of amprenavir and in combination with other antiretroviral medicinal products. It must not be administered concomitantly with other medicinal products containing amprenavir. The Summary of Product Characteristics (SPC) for ritonavir must therefore be consulted prior to initiation of therapy with Telzir.

- Children aged 6 to 11 (and weighing at least 25 kg) and adolescents (aged 12 to 17)

- Fosamprenavir oral suspension is the recommended option for the most accurate dosing in children based on body weight.
- In paediatric patients, the oral suspension should be taken with food to aid palatability and assist compliance (see SPC section 5.2).
- The dosing recommendations for fosamprenavir oral suspension in paediatric patients are based on body weight.
- Children and adolescents from 25 kg to less than 39 kg: the recommended dose is 18 mg/kg of fosamprenavir twice daily combined with ritonavir 3 mg/kg in oral solution twice daily in combination with other antiretrovirals. The maximum doses of fosamprenavir and ritonavir should not exceed the respective recommended adult doses.
- The adult dosage regimen (fosamprenavir 700 mg tablets combined with ritonavir 100 mg twice daily) may be prescribed for children and adolescents who weigh at least 39 kg and are able to swallow capsules whole. Ritonavir 100 mg capsules may be prescribed for children and adolescents taking fosamprenavir oral suspension if they weigh at least 33 kg and are able to swallow capsules whole.

No dosing recommendations can be made for children weighing less than 25 kg.

- Children less than 6 years of age:

Telzir with ritonavir is not recommended in children below 6 years due to insufficient data on pharmacokinetics, safety and antiviral response.

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2007)

J : Antiinfectives for systemic use
J05 : Antivirals for systemic use
J05A : Direct-acting antivirals
J05AE : Protease inhibitors
J05AE07 : fosamprenavir

### 2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

Table 1:The comparator medicines are protease inhibitors that have a paediatric indication.

| INN | Proprietary product | Pharmaceutical form | Packaging | Indication |
|---|---|---|---|---|
| Ritonavir* | NORVIR | 100 mg soft capsules | Pack of 336 and pack of 84 | Adults and children > 2 years *(reserved in combination with PIs)* |
| | | 80 mg/ml oral solution | 90 ml bottles | |
| Indinavir** | CRIXIVAN | 100 mg capsules | Pack of 180 | Adults and children > 4 years |
| | | 200 mg capsules | Pack of 360 | |
| | | 400 mg capsules | Pack of 90 and pack of 180 | |
| Nelfinavir | VIRACEPT | 250 mg film-coated tablets | Pack of 300 | Adults and children > 3 years |
| | | 50 mg/g powder | 144 g bottle | |
| Amprenavir*** | AGENERASE | 50 mg soft capsules | Pack of 480 | Adults and children > 4 years |
| | | 15 mg/ml oral solution | 240 ml bottle | |
| Lopinavir-ritonavir | KALETRA | 133.3/33.3 mg soft capsules | Pack of 180 | Adults and children > 2 years |
| | | 250/50 mg film-coated tablets | Pack of 120 | |
| | | 80 mg/20 mg/ml oral solution | 60 ml bottle | |

Source: P. YENI report 2006

* used at low dose as a booster, in combination with other PIs.

** ritonavir and indinavir are no longer recommended due to their adverse effects (risk of renal colic, need for abundant hydration, even when taken in a twice a day regimen, at a low dose in combination with ritonavir, retinoid-like effects [xeroderma, ingrown nails]).

*** fosamprenavir is a pro-drug of amprenavir, which it replaces.

### 2.3. Medicines with a similar therapeutic aim

Other medicines indicated for the treatment of adolescents and children infected with Human Immunodeficiency Virus Type 1 (HIV-1).

## 3 ANALYSIS OF AVAILABLE DATA

### 3.1. Efficacy

- **Efficacy in children (6 years and above) and adolescents**

The development of fosamprenavir (TELZIR) in the extension of its indication to paediatrics is based on two non-comparative phase II studies (APV20003 and APV29005) conducted on patients (aged 2-18 years) infected with Human Immunodeficiency Virus Type 1 (HIV-1) who were Protease Inhibitor (PI) naive or experienced.

The clinical benefit in the age range covered by the Marketing Authorisation (MA) (children aged 6 years and above and adolescents up to 18) was primarily assessed in the 48-week study APV29005, which evaluated the pharmacokinetic profile, safety and antiviral activity of fosamprenavir combined with ritonavir administered twice daily in combination with nucleoside reverse transcriptase inhibitors (NRTIs).
Twenty-five patients aged 6-11 years (the majority of whom received fosamprenavir/ritonavir on a 18/3 mg/kg twice daily regimen or the adult tablet dosage regimen) and 29 patients aged 12-18 years (the majority of whom were treated with the adult dosage regimen) were included in this study. Of these patients, 27 (50%) were PI naive, including 9 who were antiretroviral naive, and 27 (50%) were PI experienced.
The median duration of prior NRTI exposure was 421 weeks in PI naive subjects and 389 weeks in PI experienced subjects. The median duration of prior PI exposure was 239 weeks. At baseline, patients had a median viral load of 4.6 log10 copies/ml (33% of them had over 100,000 copies/ml at baseline) and a median CD4+ cell percentage of 18% (of whom 39% had less than 15% CD4+ at baseline).

Table 2: Virological and immunological response at week 24 (interim analysis) in study APV29005
(in the 6-18 year age group)

| | PI naive patients | PI experienced patients |
|---|---|---|
| **Virological response** | | |
| Viral load < 400 copies/ml at week 24 | 19/27 | 15/27 |
| Viral load < 50 copies/ml at week 24 | 12/27 | 8/27 |
| **Immunological response** | | |
| Median baseline level of CD4+ cells (cells/$mm^3$) | 262 (19 to 1265) | 384 (19 to 1402) |
| Increase at week 24 | 131 (50 %) | 136 (35.4 %) |

### 3.2. Safety

The adverse reaction profile in children and adolescents is based on the clinical safety data from two studies (APV29005 and APV20003) in which 126 HIV-1 infected subjects 2 to 18 years of age received ritonavir-boosted fosamprenavir in combination with NRTI therapy. Seventy per cent of the subjects received more than 48 weeks of treatment.
The safety profile was similar to that observed in the adult population. The most commonly reported adverse events were vomiting (34%), diarrhoea (22%), cough (19%) and headache (19%).

The marketing of TELZIR is conditioned by a risk management plan to monitor safety-related aspects, in particular the potential risks of neutropenia and of misuse (the risk of using TELZIR as monotherapy in cases of poor ritonavir tolerance), and to obtain further information on long-term safety in the paediatric population.

### 3.3. Conclusion

No comparative studies have been undertaken in children or adolescents.

In the age range covered by the MA (adolescents and children aged 6 years and above) and at the dosage adjusted for paediatric use, the immuno-virological efficacy of fosamprenavir administered in combination with low-dose ritonavir and in combination with NRTIs was analysed in a non-comparative phase II study (APV29005) conducted on patients 2-18 years of age infected with HIV-1.

Virological response (viral load < 400 copies/ml at week 24) was 19/27 in protease inhibitor naive patients and 15/27 in protease inhibitor experienced patients. The median increase in the level of CD4+ cells was 50% (median baseline value of 262 cells/$mm^3$) in the PI naive patients and 35.4% (median baseline value of 384 cells/$mm^3$) in the PI experienced patients.

Overall, the immunovirological response observed in the paediatric population appears to be lower than that observed in adults and seems to be of the same order of magnitude[1] as that described for the fixed combination of lopinavir + ritonavir.

The safety profile was similar to that observed in the adult population.

These data are currently limited, however, and no conclusions can be drawn with any certainty regarding the efficacy and safety of this product in the paediatric population, particularly in comparison with lopinavir/ritonavir.

[1] EMEA. Scientific discussion. Procedure No. **EMEA/H/C/000534/II/0018. London, 9 July 2007.**

## 4 TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

HIV infection is a serious and life-threatening disease.

These medicinal products aim to prevent and/or correct the immune deficiency caused by HIV infection.

These proprietary products are for use in first and second-line treatment.

In combination with low-dose ritonavir and other antiretroviral agents, the efficacy/safety ratio is high.

There are alternative medicinal products available. For children, the only available ritonavir-boosted PI is the fixed combination lopinavir/ritonavir (KALETRA), which is indicated for children aged 2 years and above.

Public health benefit

HIV-1 infection is a significant public health burden. In the population corresponding to the extension of indication (adolescents and children of 6 years and above), the burden is low due to the limited number of patients affected compared to the total population of HIV patients in France.

Reducing AIDS-related morbidity and mortality is a public health need, particularly in children and adolescents, for whom the number of treatment options, including PIs, is limited.

In light of the available data, fosamprenavir (TELZIR) in combination with ritonavir is not expected to reduce morbidity and mortality compared with the lopinavir-ritonavir combination in the HIV-1 infected children and adolescent population, particularly since part of this population (children aged 2-6 years) is not covered by TELZIR.

There is no guarantee that experimental data can be transposed into real life, given the limited documentation on efficacy and safety in the paediatric population, as well as the potential risk of using fosamprenavir as monotherapy in cases of poor ritonavir tolerance.

In conclusion, fosamprenavir (TELZIR) is not expected to have any public health benefit in this extension of indication.

The actual benefit provided by this medicinal product is substantial when given in combination with other antiretrovirals.

### 4.2. Improvement in actual benefit

In view of:

- the limited number of alternative protease inhibitor treatments in paediatrics
- the fact that the immunovirological efficacy and safety profiles for the fosamprenavir/ritonavir combination appear to be comparable to those of the fixed lopinavir/ritonavir combination (KALETRA)
- the different resistance profiles of fosamprenavir/ritonavir and lopinavir/ritonavir, which may favour the alternate use of these two products in the event of virological failure

The Transparency Committee considers that TELZIR, in combination with low-dose ritonavir, provides a minor Improvement in Actual Benefit (IAB level IV) in the management of HIV-1 infected adolescents and children of 6 years and above.

## 4.3. Therapeutic use

### 4.3.1. Management of HIV infected children and adolescents

The recommendations of the group of experts (under Professor P. Yeni) on the medical management of HIV infected persons have been updated (July 2006 report)[2].
The following paragraphs on the management of HIV infected children and adolescents are found in the appendix:

- key points regarding antiretroviral treatment
- choice of initial antiretroviral treatment.

### *4.3.2.* Therapeutic use of fosamprenavir (TELZIR)

Fosamprenavir should be administered with low dose ritonavir and in combination with other antiretroviral medicinal products.
In light of the data presented, the fosamprenavir/ritonavir combination may be an alternative to lopinavir/ritonavir (KALETRA) both for children beginning treatment and for previously treated children who are intolerant to lopinavir/ritonavir or who exhibit virological failure, where the virus is sensitive to fosamprenavir/ritonavir (determined by genotypic resistance testing). The different resistance profiles of lopinavir/ritonavir and fosamprenavir/ritonavir may favour the alternate use of the two products in the event of virological failure.
Compared with the fixed combination of lopinavir/ritonavir, administration of fosamprenavir is more restrictive since it must be combined with low-dose ritonavir, which requires the administration of 2 medicinal products with the potential risk of misuse (the risk of using fosamprenavir as monotherapy in cases of poor ritonavir tolerance).

## 4.4. Target population

The target population is adolescents and children of 6 years and above infected with HIV-1.

The number of HIV infected children living in France was estimated to be roughly 1,500 in 2005, and 10 to 20 new cases are diagnosed each year[3].

In practice, the number of patients likely to receive TELZIR in the paediatric population will be lower, since its use is limited to adolescents and children of 6 years and above.

## 4.5. Transparency Committee recommendations

The Transparency Committee recommends the 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 for the new indications and at the dosages in the Marketing Authorisation.

4.5.1. Packaging: appropriate for the prescription requirements.

4.5.2. Reimbursement rate: 100 %

[2] "*Prise en charge médicale des personnes infectées par le VIH - Recommandations du groupe d'experts - Rapport 2006 sous la direction du Professeur Patrick YENI*" ("Management of HIV infected persons – Recommendations of the Group of Experts – 2006 Report under the direction of Professor Patrick Yeni") - (www.sante.gouv.fr)

## APPENDIX:

Medical management of HIV infected persons.

**Management of HIV infected children and adolescents**

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*" ("Management of HIV infected persons – Recommendations of the Group of Experts – 2006 Report under the direction of Professor Patrick Yeni") (www.sante.gouv.fr).

***Key points***

• In 2005, the number of HIV infected children living in France was estimated at roughly 1,500.
• In France, 10 to 20 neonates are diagnosed with HIV infection every year.
• A hundred or so adolescents are infected each year through sexual activity.
• The basis of our knowledge about treating paediatric patients is still extrapolated from experience in treating adults.
• In children, HIV infection remains a psychological handicap because of the significant social stigma. Individual psychotherapy, discussion groups and communal leisure activities mitigate the mental distress of HIV positive children and their families.
• The diagnosis should be disclosed to the child gradually, according to the child's age and individual circumstances.

***The group of experts recommends:***

*- initiating treatment at a CD4 threshold of 15%, even in the absence of any clinical symptoms (AIIa). For some experts, the threshold could be raised to 20% for children 1-3 years of age (BIII)*
*- proposing initial triple therapy combining two NRTIs (abacavir + lamivudine or zidovudine + abacavir or zidovudine + lamivudine) and one PI/r (AIIa)*
*- measuring the blood levels of certain antivirals, particularly for substances used off-label and for nelfinavir (BIIa), and in patients in whom the virus shows mutations for PI resistance (AIIa)*
*- not discontinuing treatment, except in cases of intolerance, clear non-compliance or patient choice, other than under a specific research protocol (BIIa)*
*- caring for infected children at a specialist centre (AIII). Since the idea of "accredited reference centres" does not exist in France, in contrast to other European countries, the concept ought to be debated*
*- urging the pharmaceutical industry to carry out research on pharmaceutical formulations suited to paediatric needs (AIII)*
*- discussing matters of sexuality with infected adolescents at an early age (AIII)*
*- reinforcing measures to prevent HIV/AIDS among young people, particularly in schools, and raising awareness of the anonymous, free screening programme (AIII).*

***Which initial treatment to choose?***

*• Preferred option: for all ages, regardless of the initial immunovirological parameters - combine two NRTIs (abacavir + lamivudine or zidovudine + abacavir or zidovudine + lamivudine) and one PI/r (AIIa).*
*If the various pharmaceutical forms of lopinavir/r cannot be taken, nelfinavir may be proposed instead.*
*Abacavir + lamivudine is the best combination if the child is able to swallow the combined formulation and/or if nelfinavir has been chosen (AIa). The risk of severe abacavir allergy should be taken into account and discussed in advance with the child and his/her family.*
*• Alternative option: combine two NRTIs and one NNRTI, provided that strict compliance can be guaranteed from the outset of treatment (BIIa).*