HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

29 April 2009

COMBIVIR 150 mg/300 mg scored film-coated tablet
B/60 (CIP: 346 627-1)

Applicant: GLAXOSMITHKLINE

Lamivudine (150mg) and zidovudine (300mg)

ATC code: J05AR01

List I
Initial annual hospital prescription.

Date of Marketing Authorisation: Initial MA 18 March 1998 – amended 13 November 2007

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for use by hospitals in the extension of indication in children weighing 14 kg to 30 kg.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Lamivudine (150mg) and zidovudine (300mg)

1.2. Novel aspects

This is an extension of indication to paediatric patients weighing 14 kg to 30 kg.

1.3. Indication

COMBIVIR is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection" (see Posology and method of administration in the SPC).

1.4. Dosage

"Therapy should be initiated by a physician experienced in the management of HIV infection.

COMBIVIR may be administered with or without food.

Adults and adolescents weighing at least 30 kg: the recommended dose of COMBIVIR is one tablet twice daily.

Children weighing between 21 kg and 30 kg: the recommended oral dose of COMBIVIR is one-half tablet taken in the morning and one whole tablet taken in the evening.

Children weighing from 14 kg to 21 kg: the recommended oral dose of COMBIVIR is one-half tablet taken twice daily.

The dosing regimen for children weighing 14-30 kg is based primarily on pharmacokinetic modelling and supported by data from clinical studies using the individual components lamivudine and zidovudine.

A pharmacokinetic overexposure of zidovudine can occur, therefore close safety monitoring is warranted in these patients.

If gastrointestinal intolerance occurs in patients weighing 21-30 kg, an alternative dosing schedule with one-half tablet taken thrice daily can be applied in attempt to improve tolerability.

COMBIVIR tablets should not be used for children weighing less than 14 kg, since doses cannot be appropriately adjusted for the weight of the child. In these patients, lamivudine and zidovudine should be taken as separate formulations according to the prescribed dosing recommendations for these products. For these patients and for patients who are unable to swallow tablets, oral solutions of lamivudine and zidovudine are available.

For situations where discontinuation of therapy with one of the active substances of COMBIVIR, or dose reduction is necessary separate preparations of lamivudine and zidovudine are available in tablets/capsules and oral solution."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

J : Antiinfectives for systemic use
J05 : Antivirals for systemic use
J05A : Direct acting antivirals
J05AR : Antivirals for treatment of HIV infections, combinations
J05AR01 : Zidovudine and lamivudine

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

The similar medicinal products are nucleoside reverse transcriptase inhibitors indicated for use in children (aged 4 years to 12 years).

INN	Medicinal product	Pharmaceutical form	Indication
Abacavir	**ZIAGEN*** (GSK)	Tablet Oral solution	Adults and children > 3 months
Didanosine	VIDEX (BMS)	Capsule Tablet for oral susp.	Adults and children > 3 months
Emtricitabine	EMTRIVA (GILEAD)	Capsule Oral solution	Adults and children > 4 months
Lamivudine	**EPIVIR*** (GSK)	Tablet Oral solution	Adults and children > 3 months
Stavudine	ZERIT (BMS)	Capsule Oral solution	Adults, neonates, infants, children
Zidovudine	**RETROVIR*** (GSK)	Capsule, tablet Oral solution	Adults and children > 3 months

*recommended by experts (Yeni report 2008)
- in free combinations: Abacavir+lamivudine or zidovudine+abacavir or zidovudine+lamivudine
- in fixed combinations: KIVEXA and COMBIVIR

2.3. Medicines with a similar therapeutic aim

Other medicines indicated for treating children with Human Immunodeficiency Virus Type 1 (HIV-1) infection.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy/pharmacokinetics

No clinical study has been performed with scored tablets.

The clinical development of COMBIVIR in paediatrics is based on pharmacokinetic data. Pharmacokinetic models based on data from clinical studies performed with lamivudine (EPIVIR) and zidovudine (RETROVIR) administered separately made it possible to suggest harmonising the dosage regimen for the 2 active ingredients solely as a function of body weight (conversion of zidovudine doses in mg/m^2 body surface area into mg/kg).

Moreover, pharmacokinetic studies have validated the possibility of administering COMBIVIR in 2 doses per day (instead of the 3 doses/day currently indicated in children for zidovudine and 2 doses/day for lamivudine).

3.2. Adverse effects

No clinical study has been performed with the scored tablet presentation.

“Adverse reactions have been reported during therapy for HIV disease with lamivudine and zidovudine separately or in combination. For many of these events, it is unclear whether they are related to lamivudine, zidovudine, the wide range of medicinal products used in the management of HIV disease, or as a result of the underlying disease process.

As COMBIVIR contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of added toxicity following concurrent administration of the two compounds.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported after the use of nucleoside analogues.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise”.
(See the SPC for the adverse effects that may be attributable to either lamivudine or zidovudine)

3.3. Conclusion

The clinical development of COMBIVIR in paediatrics is based on pharmacokinetic data and models obtained with lamivudine and zidovudine administered separately and with the COMBIVIR scored tablet.

These data allow the validation of the COMBIVIR dosage regimen of 2 doses per day in children weighing 14-30 kg.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

HIV infection is a serious, life-threatening condition.

This product is intended to prevent and/or correct immunodeficiency caused by HIV infection.

The efficacy/adverse effects ratio is high in combination with other antiretrovirals.

Alternative medicinal products exist for children weighing 14-30 kg (in non-fixed combinations).

Public health benefit

> The public health burden of HIV infection is heavy. The burden corresponding to the population targeted by the COMBIVIR extension of indication (children weighing 14-30 kg) is minor due to the limited number of patients concerned.
>
> The reduction in morbidity and mortality linked to HIV infection and the availability of paediatric forms of antivirals represent a public health need (cf. the 2008 Yeni report).
>
> COMBIVIR – a fixed combination of two medicines - each of which is already available in a paediatric form – could theoretically improve treatment compliance. However, this still needs to be demonstrated.
>
> Based on the available data, COMBIVIR is not expected to have any additional impact on reducing morbidity and mortality.
>
> In conclusion, COMBIVIR is not expected to provide a public health benefit in this extension of indication.

The actual benefit of this medicinal product is substantial in children weighing 14-30 kg when used in combination with other antiretrovirals.

4.2. Improvement in actual benefit (IAB)

COMBIVIR scored tablets indicated in children weighing 14-30 kg does not provide an improvement in actual benefit compared with the combination of the 2 medicinal products administrered simultaneously in oral solution form.

However, the Committee stresses that this fixed combination should help simplify the methods of administration and facilitate compliance with treatment in children weighing 14-30 kg who are able to swallow tablets. Suitable and recommended treatment options are indeed limited in this age group.

4.3. Therapeutic use

4.3.1. Management of children and adolescents infected with HIV

- Medical management of persons infected with HIV - 2008 Report - Recommendations of the group of experts (chaired by Professor P. Yeni)[1]
See appendix.
- Medical management of persons infected with HIV - Addendum of 13 April and 20 April 2009: Antiretroviral treatment.

4.3.2. The therapeutic use of COMBIVIR in children weighing 14-30 kg

In children weighing 14-30 kg who are able to swallow tablets, COMBIVIR (a fixed combination of 2 nucleoside inhibitors) used with other antiretrovirals may be a therapeutic alternative to separately administering the 2 nucleoside inhibitors in oral solution.

4.4. Target population

The target population for the extension of indication comprises children who weigh 14 kg to 30 kg and are infected with Human Immunodeficiency Virus Type 1 (HIV-1).

The number of HIV- infected children living in France is estimated to be about 1 500[1], and each year 10 to 20 new cases are diagnosed.

In practice, the number of paediatric patients likely to receive COMBIVIR will be lower since the target population for the extension of indication is limited to children of approximately 4-12 years of age. According to the expert, the target population can be estimated at 300 to 400 children.

4.5. Recommendations of the Transparency Committee

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

4.5.1. Packaging: appropriate for the prescription.

4.5.2. Reimbursement rate: 100%

[1] Prise en charge médicale des personnes infectées par le VIH - Recommandations du groupe d'experts (French experts group's recommendations for medical management of HIV infection: highlights and recommendations) - 2008 report supervised by Professeur Patrick Yeni - (www.sante.gouv.fr)

Appendix

Prise en charge médicale des enfants et adolescents infectés par le VIH - Recommandations du groupe d'experts (French experts group's recommendations for medical management of children and adolescents infected with HIV: highlights and recommendations) - 2008 report supervised by Prof. Patrick Yeni - (www.sante.gouv.fr)

Strengths and Choice of initial treatment and management of treatment failure

Strengths

• In 2008, the estimated number of children living with HIV in France was still about 1 500. Many adolescents reaching adulthood today are in good clinical and psychological condition.
• Each year in France, 10 to 20 neonates are diagnosed with HIV infection. However, most newly diagnosed children were born in countries where infection is widespread.
• Approximately one hundred adolescents are infected each year through sexual contact.
• Most of what is known about treating children is still extrapolated from experience with adult treatment.
• In children, infection with HIV continues to be a psychological "handicap" given the extent of social stigma involved. Individual psychotherapy, discussion groups and recreational activities with other seropositive children help reduce the mental suffering of infected children and their family.
• Children are progressively informed of their diagnosis in a manner appropriate to their age and their individual situation.

The group of experts recommends:

• offering antiretroviral treatment to all children under 12 months of age to prevent the development of a severe, early, progressive form accompanied by encephalopathy (AI) (abstention from treatment in this age group is possible under strict conditions)
• commencing treatment in older children only once they reach a CD4 threshold of 25% (for children aged 1-3 years) or 20% (for children > 3 years of age) (AIIa) provided they have few or no symptoms
• initially favouring triple therapy combining two NRTIs (abacavir + lamivudine or zidovudine + abacavir or zidovudine + lamivudine) and one PI/r (AIIa)
• determining the blood levels of certain antiretrovirals, particularly for substances used off-label (BIIa) and in patients for whom the virus shows PI resistance mutations (AIIa)
• not interrupting treatment, except in the event of poor tolerability or manifest noncompliance, or at the patient's request, unless allowed by a specific research protocol (BIIa)
• managing infected children at a specialised centre (AIII)
• lobbying the pharmaceutical industry to pursue research on pharmaceutical formulations suited to the needs of children (AIII)
• discussing sexuality issues with infected adolescents at an early age (AIII)
• promoting HIV/AIDS prevention in young people, particularly in schools, and raising awareness of the existence of free anonymous screening (AIII).

Choice of initial treatment

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

• *Alternative option*: combining two NRTIs and one NNRTI, provided that compliance can be rigorously ensured from the start of treatment (BIIa). If neonates have a high viral load, a combination of three NRTIs and one NNRTI (nevirapine) is then recommended.

Management of treatment failure (see 2008 Report/Recommendations of the group of experts chaired by Prof. Patrick Yeni).