

WHO MODEL LIST OF ESSENTIAL MEDICINES
Supplementary Application

Abacavir tablets for the treatment of HIV-1 infection: scored form

27th April 2007

This application for inclusion of abacavir (300mg) scored tablets in the WHO Model List of Essential Medicines, for the treatment of HIV infection, has been prepared by GlaxoSmithKline (GSK) and is supplementary to the application for inclusion of the unscored form of abacavir (300mg) tablets which was prepared by WHO and as a result of which abacavir 300mg (unscored) appears in the WHO Model List of Essential Medicines (15th Edition Revised March 2007). This list, henceforth referred to as 'WHO EML 15', may be found at: <http://www.who.int/medicines/publications/EML15.pdf>

The original application for inclusion of unscored abacavir tablets was made by WHO to the 12th EML in 2002, and may be found at:
http://mednet3.who.int/EML/expcom/expcom12/arvs_submissions.htm

1. Summary statement of proposal for inclusion, change, or deletion

The unscored form of abacavir (300mg) tablets is currently included in the WHO Model List of Essential Medicines (WHO EML 15), for the treatment of HIV infection. Please refer to the WHO 12th EML abacavir Application for a summary of the rationale for inclusion of the unscored form of abacavir 300mg tablets.

The scored form of abacavir (300mg) tablets is now proposed for inclusion in the List of Essential Medicines, for the treatment of HIV infection in children, for the following reasons:

(1) One of the many challenges in the treatment of paediatric populations infected with HIV is access to the appropriate formulations of drugs for infants up to adolescents. Dosage regimens need to be adjusted as children grow and combinations of agents are needed for the treatment of HIV disease. Many antiretroviral agents are available as liquid formulations to facilitate dosing in children. However, as children gain weight, larger volumes of these formulations are required, exacerbating the problems of palatability, storage, transport, and cost associated with solutions. This creates an even greater problem when a carer is responsible for administering treatments to more than one child and where the child's treatments need to be carried by the carer throughout their daily activities away from the home. It is therefore much preferred to give children solid formulations as soon as they are able to take them.

(2) There have been increasing calls from a number of organizations, including WHO and UNICEF, for additional efforts by pharmaceutical manufacturers to develop, manufacture, register, and distribute new solid dosage forms for use by paediatric patients with HIV infection. The need for scored tablet products, in particular, has been noted as a high priority to facilitate treatment of children in resource-poor settings. As a result, GSK convened a meeting with representatives from WHO, UNICEF, MSF, EMEA and FDA in September 2005 to discuss additional work that GSK could do to support scored tablet products.

(3) The current WHO Guidelines for the treatment of HIV-infected children and infants (2006) recommend that abacavir tablets may be crushed, and include weight-based dosing that involves the administration of half-tablets for children of 11-24.9kg in weight. Anecdotal reports from treating physicians provide clear evidence that unscored tablets are split or crushed in order to treat young children with solid forms to avoid the use of copious volumes of the oral solution which would otherwise be required. However, cutting or crushing of unscored tablets is prone to inaccuracy and may lead to over-dosing or under-dosing of children, increasing the potential for toxicity or resistance development. The availability of scored abacavir tablets would facilitate improved accuracy of dosing in half-tablet increments according to existing and recommended dosing practices.

GSK Actions

In order to address the above requirements, GSK has recently developed and submitted for Regulatory review an application for registration of a scored form of the abacavir (300mg) tablet, with dosing proposals for children from ≥ 14 kg in weight. With the exception of a single score line which allows the tablet to be broken into two halves, this scored form is identical to the unscored form. Following EU approval, other world-wide registrations will be filed. It is anticipated that the unscored form of the tablets currently supplied globally will ultimately be replaced with the scored form, once registered.

2. Name of focal point in WHO supporting the application

Dr Siobhan Crowley, Dr Suzanne Hill
Medicines Policy and Standards

3. Name of the organisation(s) consulted and/or supporting the application

GlaxoSmithKline

4. International Nonproprietary Name (INN)

abacavir

5. Formulation proposed for inclusion

Scored tablet containing abacavir 300mg (identical to the unscored form currently included in the WHO EML 15, with the exception of a single score line to facilitate division of the tablet into two halves).

6. International availability

An application for registration of the scored form of the GSK abacavir (300mg) tablets has been submitted for review by the EMEA. Subsequent to EU approval, other world-wide registration applications will be filed.

7. Category of listing requested

Listing is requested in the antiretrovirals group, nucleoside reverse transcriptase inhibitors (abacavir).

8. Information supporting the public health relevance

8.1 Epidemiological information on disease burden

Please refer to the WHO EML 15 and the WHO 12th EML abacavir Application

8.2 Assessment of current use

The current WHO Guidelines for the treatment of HIV infection in infants and children (WHO 2006) state that the recommended NRTI backbone is composed of zidovudine or d4T or abacavir combined with lamivudine and with either nevirapine or efavirenz added. In addition to being a recommended first-line treatment for children, administration of abacavir also allows for the construction of a triple-NRTI regimen which can help facilitate management of toxicity, comorbidities and drug-drug interactions.

8.3 Target population

Paediatric patients with HIV infection who qualify for treatment with ARV therapy.

9. Treatment details

9.1 Dosage regimen

For the scored abacavir 300mg tablets, the proposed dosage is as follows:

- for children weighing 14 to 21 kg: one-half of an abacavir tablet twice daily,
- for children weighing >21kg to <30kg: one-half of an abacavir tablet taken in the morning and one whole tablet taken in the evening
- for patients weighing \geq 30 kg: the adult dose of 300mg twice daily or 600mg once daily should be taken

Modern treatment guidelines require that NRTI treatments are not used as monotherapy and abacavir has to be co-prescribed with at least two other agents (NNRTI, other NRTIs and/or protease inhibitor).

9.2 Treatment duration

Treatment duration is life-long – or until treatment has to be ceased, modified or switched because of adverse effects, contraindications or therapeutic failure.

10. Summary of comparative effectiveness

Please refer to the WHO 12th EML abacavir Application

11. Summary of comparative evidence on safety

Please refer to the WHO 12th EML abacavir Application

12. Summary of available data on comparative cost and cost-effectiveness

Please refer to the WHO EML 15 and the WHO 12th EML abacavir Application for information relating to the unscored form of abacavir (300mg). Data is not yet available for the scored form. However, it is anticipated that the scored form, once registered, will replace the unscored form globally, including not-for-profit supply.

13. Regulatory status

A Type II variation application for registration of the scored form of abacavir 300mg tablets was submitted to EMEA April 2007. The application was validated and the Type II variation procedure start date was 22nd April 2007. The variation is currently under review, the earliest CHMP opinion is expected June 07.

Subsequent to EU approval, other world-wide registration applications will be filed.

Please refer to the WHO EML 15 and the WHO 12th EML abacavir Application for the regulatory status of the unscored form of abacavir (300mg).

References:

(1) WHO Model List of Essential Medicines (15th Edition Revised March 2007):

<http://www.who.int/medicines/publications/EML15.pdf>

(2) WHO 12th EML abacavir Application (2002):

http://mednet3.who.int/EML/expcom/expcom12/arvs_submissions.htm

(3) WHO: Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access: Recommendations for a public health approach. 2006 Available at <http://www.who.int/hiv/pub/guidelines/WHOpaediatric.pdf>