

WHO MODEL LIST OF ESSENTIAL MEDICINES
Supplementary Application

Zidovudine/lamivudine fixed-dose combination tablets
for the treatment of HIV-1 infection: scored form

27th April 2007

This application has been prepared by GlaxoSmithKline (GSK) and is supplementary to the Application for zidovudine/lamivudine fixed-dose combination tablets for the treatment of HIV-1 infection which was prepared by WHO for the 15th Model List of Essential Medicines (EML), and which henceforth will be referred to as 'WHO 15th EML AZT/3TC Application'. The WHO 15th EML AZT/3TC Application may be found at:
<http://mednet3.who.int/EML/expcom/expcom15/applications/formulations/AZT3TCApplication.pdf>

The WHO Model List of Essential Medicines (15th Edition Revised March 2007) in which the unscored form of AZT/3TC 300/150mg has been included may be found at:
<http://www.who.int/medicines/publications/EML15.pdf>

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

The combination tablet of zidovudine/lamivudine (AZT/3TC) was proposed for inclusion on the WHO Model List of Essential Medicines, for the treatment of HIV infection, in a separate application which was supplied to the 15th EML by WHO (WHO 15th EML AZT/3TC Application). Please refer to the WHO 15th EML AZT/3TC Application for a summary of the rationale for inclusion of the unscored form of the AZT/3TC (300/150mg) fixed dose combination (FDC).

The scored form of the AZT/3TC (300/150mg) FDC 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 this is complicated when one considers that paediatric dosage regimens for the various antiretroviral agents are based on age, weight, or body surface area, and that combinations of these 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 AZT/3TC FDC tablets may be crushed, and include weight-based dosing that involves the administration of half-tablets for children of 14-29.9 kg in weight. Anecdotal reports from treating physicians provide clear evidence that unscored AZT/3TC tablets are split or crushed in order to treat young children with solid forms to avoid the use of copious volumes of solutions of the individual components, 3TC and ZDV, 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 AZT/3TC tablets would facilitate improved accuracy of dosing in half-tablet increments according to existing and recommended dosing practices.

(4) WHO and UNICEF have also requested a switch from paediatric dosing of AZT based on body surface area (BSA) to dose administration based on body weight (BW) as this would reduce dosing complexity for paediatric patients in resource-limited settings. Additionally, to allow appropriate administration of AZT/3TC scored tablets in paediatric patients the option to reduce frequency of AZT administration to twice daily dosing is critical.

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 AZT/3TC (300/150mg) fixed dose combination 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, all other world-wide registrations will be filed. It is anticipated that the unscored forms of both the white and the red Access to Medicines (ATM) tablets currently supplied globally will ultimately be replaced with the scored forms, 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)

zidovudine/lamivudine

5. Formulation proposed for inclusion

Scored combination tablet comprised of zidovudine 300mg and lamivudine 150mg.

6. International availability

An application for registration of the scored form of the GSK AZT/3TC (300/150mg) tablets is currently under review by the EMEA. Subsequent to EU approval, all other world-wide registration applications will be filed.

7. Category of listing requested

Listing is requested as fixed dose combination of the antiretrovirals group, including two nucleoside reverse transcriptase inhibitors (zidovudine and lamivudine).

8. Information supporting the public health relevance

8.1 Epidemiological information on disease burden

Please refer to The WHO 15th EML AZT/3TC Application and Section 1 above.

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. These WHO Guidelines also stress the urgent need for standard FDC for first line treatment of younger children.

8.3 Target population

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

9. Treatment details

9.1 Dosage regimen

For AZT/3TC (300/150mg) FDC scored tablets, the proposed dosage is as follows:

- one-half tablet twice daily for children from 14 to 21 kg body weight,
- one-half plus one whole tablet daily (either 0.5 tablet TID or 0.5 tablet AM and 1 tablet PM) for children from 21kg to 30kg body weight,
- one tablet twice daily for patients weighing ≥ 30 kg.

Modern treatment guidelines require that dual NRTI treatment is not used alone and the FDC has to be co-prescribed with a NNRTI another NRTI or with a 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 15th EML AZT/3TC Application

11. Summary of comparative evidence on safety

Please refer to the WHO 15th EML AZT/3TC Application

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

Please refer to the WHO 15th EML AZT/3TC Application for information relating to the unscored form of AZT/3TC (300/150mg). 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 and Access to Medicines supply.

13. Regulatory status

A Type II variation application for registration of the scored form of both the white and red (ATM) AZT/3TC (300/150mg) tablets was submitted to EMEA in February 2007, the application was validated and the Type II variation procedure start date was 23rd February 2007. The variation is currently under review, the earliest CHMP opinion is expected May 07. Subsequent to EU approval, all other world-wide registration applications will be filed.

Please refer to the WHO 15th EML AZT/3TC Application for the regulatory status of the unscored form of AZT/3TC (300/150mg).

References:

(1) WHO 15th EML AZT/3TC Application:

<http://mednet3.who.int/EML/expcom/expcom15/applications/formulations/AZT3TCapplication.pdf>

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

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

(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>