EMEA PUBLIC STATEMENT ON EARLY VIROLOGIC NON-RESPONSE
IN PATIENTS WITH HIV INFECTION TREATED WITH
TENOFOVIR IN COMBINATION WITH LAMIVUDINE AND ABACAVIR

The European Medicines Evaluation Agency (EMEA) and its scientific committee (CPMP) have been made aware of reports of a high rate of early virologic non-response observed in a GlaxoSmithKline (GSK)-sponsored clinical study (ESS30009) of therapy-naive adults receiving once-daily three-drug combination therapy with tenofovir (Viread\textsuperscript{1}, TDF), lamivudine (Epivir\textsuperscript{2}, 3TC), and abacavir (Ziagen\textsuperscript{3}, ABC). The precise nature of any interaction leading to non-response in this study is not known.

For details of this study and of a pilot study by Farthing \textit{et al.}, see Annex 1.

The CPMP, in its meeting held from 22 to 24 July 2003, has considered the results of the above mentioned studies and has requested the Marketing Authorisation Holders to further explore the nature of these interactions through \textit{in vivo} / \textit{in vitro} studies.

The final interim study (ESS30009) report, as well as the study reports of the other relevant ongoing studies, has also been requested.

As soon as available, the results will be assessed by the competent authorities and the public will be updated accordingly.

\textsuperscript{1} On 05 February 2002, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Viread, which contains tenofovir disoproxil fumarate. The Marketing Authorisation Holder responsible for this medicinal product is Gilead Sciences International Ltd. Viread is approved for once-daily administration.

\textsuperscript{2} On 08 August 1996, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Epivir, which contains lamivudine. The Marketing Authorisation Holder responsible for this medicinal product is GlaxoSmithKline. Epivir is approved for both once and twice-daily administration.

\textsuperscript{3} On 08 July 1999, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Ziagen, which contains abacavir. The Marketing Authorisation Holder responsible for this medicinal product is GlaxoSmithKline. Abacavir is approved for twice daily administration.
As a precautionary measure, until the nature of these interactions is further explored, the EMEA wishes to point out the following information:

Information for physicians:

• **When considering a new treatment regimen for naïve or pre-treated patients:**

  Abacavir and lamivudine in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naïve or pre-treated patients and particularly, as a once-daily regimen.

• **Patients well controlled on a tenofovir, lamivudine and abacavir regimen:**

  Any patient currently controlled on therapy with this combination should be frequently monitored with a sensitive viral load test (limit of quantification <50 copies/ml), and considered for modification of therapy at the first sign of viral load increase.

Information for patients:

If you are currently receiving, or if you are about to receive, an antiretroviral treatment including abacavir (Ziagen) and lamivudine (Epivir) in combination with tenofovir (Viread), you should inform your doctor immediately.

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ANNEX 1

Study ESS30009 is a randomized, open-label, multi-center study of the safety and efficacy of efavirenz (EFV 600mg daily, Sustiva, Bristol-Myers Squibb Co.) versus tenofovir (300mg daily) when administered in combination with an investigational abacavir/lamivudine (600mg /300mg daily) fixed-dose combination tablet as a once-daily regimen in antiretroviral-naïve HIV-1 infected adults. Shortly after initiation of this study, reports of poor efficacy in patients receiving TDF+3TC+ABC have been received. An interim analysis was conducted to assess virologic non-response, defined as either:
- failure to achieve a 2 log decrease from baseline by treatment week 8,
- or a 1 log increase above nadir on any subsequent treatment visit.

Results are shown in the following table:

<table>
<thead>
<tr>
<th>Number (%) of Patients Meeting the Definition of Virologic Non-Response</th>
<th>TDF + 3TC + ABC</th>
<th>EFV + 3TC + ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA data for subjects on therapy for ≥ 8 weeks</td>
<td>50 / 102 (49%)</td>
<td>5 / 92 (5%)</td>
</tr>
<tr>
<td>HIV-1 RNA data for subjects on therapy for ≥ 12 weeks</td>
<td>30 / 63 (48%)</td>
<td>3 / 62 (5%)</td>
</tr>
</tbody>
</table>

The precise nature of any interaction leading to non-response in this study is not known.

Preliminary genotypes of viral isolates from 14 patients with non-response taking the TDF+3TC+ABC regimen have shown all 14 isolates had the M184V mutation in HIV reverse transcriptase. In addition, 8 of the 14 (57%) isolates also had the K65R mutation.

On review of these results, the TDF+3TC+ABC arm has been terminated in this study.

In addition to study ESS30009, a pilot study by Farthing et al. (2nd annual meeting of the International AIDS Society, July, 2003, Paris, France) provided data in 20 patients receiving TDF+3TC+ABC once daily for initial therapy. As in ESS30009, a high rate of virologic non-response was documented.