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12 July 2005

Dear Ms Miller

RE: SOUTHAMPTON HEALTH TECHNOLOGY ASSESSMENT CENTRE (SHTAC) ASSESSMENT REPORT ON ADEFOVIR DIPIVOXIL AND PEGINTERFERON ALPHA-2A FOR THE TREATMENT OF CHRONIC HEPATITIS B (CHB)

Gilead Sciences welcomes the opportunity to comment on this report and its technical content and consider this to be a thorough and accurate review of this complex and technically difficult disease area. We believe the results of the SHTAC report are in line with our own submission, and both reports support adefovir dipivoxil as a first-line treatment for CHB, as well as an agent that can be effectively used in sequential strategies following treatment failure or viral resistance.

We warmly support the conclusions of this report in its finding that, "adefovir dipivoxil is both clinically-effective and cost-effective in the treatment of CHB in relation to current standard treatments and supportive care" (SHTAC Assessment Report; Pg 17). Clinical effectiveness has already been established via a comprehensive clinical evaluation programme, with long-term follow up for safety, efficacy and viral resistance out to three years[1-3] that will continue for at least two more years.

Furthermore, we note that "adefovir dipivoxil may be particularly suitable for long-term treatment, particularly in advanced disease states due to relatively low rates of resistance" (SHTAC Assessment Report; pg 17), and with reference to the modelled costs for adefovir dipivoxil, "these increased costs are associated with substantial health gains" (SHTAC Assessment Report; pg 136).

We would also like to point out that there has been even more data published on adefovir dipivoxil in the interim period since our submission was completed and in some cases after the assessment report was published. This new evidence beyond 144 weeks of therapy shows that adefovir dipivoxil provides a durable, sustained and efficacious treatment for both HBeAg-positive and HBeAg-negative disease[1,3,4]. We would be delighted to provide this to both SHTAC and NICE for evaluation.

We know that the development of lamivudine resistance increases the risk of disease progression, morbidity and mortality[5,6], as well as conferring cross-resistance to other nucleosides, such as entecavir, clevudine, emtricitabine and famciclovir[7-9]. The use of a nucleotide analogue, such as adefovir, as first-line treatment limits development of resistance and avoids cross-resistance with currently licensed agents, including lamivudine[4,9-12]. This approach is critical as it provides patients with long-term effectiveness and additional therapeutic options if necessary. Indeed, in the future, it is probable that combinations of agents, from different classes, will be required to enable durable treatment of CHB with low resistance and no cross-resistance similar to the current management of HIV.

We also have some comments on specific areas of the SHTAC assessment report, which we have outlined in the remainder of this letter, beginning with comments on the HTA group's economic evaluation:

1. The HTA group assumed that patients receiving lamivudine experienced a reduced risk of cirrhosis during the first year of treatment that was not applied to patients receiving adefovir (Tables 34 and 35; pg 127-8); this meant that 2% of lamivudine-treated patients were assumed to develop cirrhosis during the first year of therapy, compared with 5% of those receiving no treatment or adefovir, implying that the risk of cirrhosis is 2.5-times higher with adefovir than lamivudine.

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It has been shown that adefovir is effective at reducing the necroinflammation and fibrosis after 48, 96 and 144 weeks of treatment[1,13,14]. This translated into 'no incident' cases of advanced fibrosis or cirrhosis among HBeAg-negative patients treated with adefovir during 48 and 96 weeks[14,15].

Furthermore, it has been shown that adefovir improves underlying cirrhosis and advanced fibrosis: 34% of patients with advanced fibrosis or cirrhosis at baseline reverted to mild or no fibrosis after 48 weeks treatment.

We would very much welcome the opportunity for SHTAC to re-evaluate their model, assuming that the risk of progressing from active CHB to compensated cirrhosis is 0% or 2% per year for patients receiving adefovir.

2. It was not apparent from the report which resistance rates were used in the HTA model for adefovir or lamivudine; since this is an important driver of cost-effectiveness, it would be extremely informative to see what values were used within the analysis.

3. The scenarios considered within the HTA model assume that all patients would receive pegylated or conventional interferon-alfa first-line. In reality, this does not reflect current clinical practice and would not be appropriate, given the licensed indications of interferon-alfa, in particular with regard to decompensated disease. Due to the contraindications and the determinants of viral response, first-line therapy with interferon-alfa is not appropriate for a significant proportion of patients. Interviews with UK hepatologists suggest that around 5-10% receive interferon-alfa in UK clinical practice. The HTA model would therefore reflect best clinical practice more closely if patients unlikely to tolerate and/or respond to interferon-alfa progressed directly to oral anti-viral medications.

4. The cost of therapy used within the economic analysis assumes that patients receiving lamivudine or adefovir will be seen by a consultant or hepatology nurse a total of 11 times during the first year of treatment. This level of contact is substantially higher than was suggested by expert interviews conducted as part of the Gilead submission and may not be typical of all centres treating CHB.

We also broadly agree with the data presented within the comprehensive systematic review of the literature, but would like to take this opportunity to clarify a small number of points:

1. Section 4.1.2.5 of the report discusses HBsAg loss/seroconversion, but gives little or no data on adefovir. Evidence presented at the 2004 EASL conference demonstrates that 1.9% (9/469) of patients receiving adefovir in clinical trials have undergone HBsAg seroconversion, including 1.6% (2/125) of HBeAg-negative patients[16]. In addition, outcomes over three years of follow-up within study GS-438 have now been published in the New England Journal of Medicine[1]. Alongside other key outcomes, this paper reports that two patients within this trial underwent HBsAg seroconversion while receiving adefovir.

2. A range of thresholds of HBV DNA levels are used within the literature and within this report, which suggests that there may be a need for expanded discussion on what level of viral load constitutes an appropriate goal for treatment.

3. It is stated on page 47 of the report that only study GS-438 presented the proportion of patients with compensated cirrhosis or bridging fibrosis at baseline; although the proportion of patients with cirrhosis was not reported in the primary publication of these studies, 6% of patients within study GS-437 and 9% of those within study GS-461 had cirrhosis.

4. Within the discussion of current research needs (page 159), it is stated that patients with renal problems were excluded from the RCTs included within this systematic review. Although patients with renal impairment were generally excluded from the primary RCTs evaluating adefovir, study GS-473 suggested that the pharmacokinetics of adefovir within patients with mild renal impairment were similar to those in healthy patients, while adefovir can be safely given every 48-72 hours in patients with reduced creatinine clearance. An additional study involving patients with impaired renal function (GS-526) is likely to be completed in late 2006.

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5. The critique of the Gilead model was fair and useful; however, we would like to comment on the HTA group's statement that the Gilead submission "contains no estimate of any additional costs arising from the assessment and monitoring of patients during treatment the early stages of treatment," (page 118). Although the cost of treatment and monitoring was assumed to be constant over time, patients receiving lamivudine or adefovir were assumed to have additional outpatient and GP consultations and undergo renal function tests, liver function tests and assessment of virological parameters more frequently than treated patients with the same disease severity.

Once again, we are grateful for the opportunity to comment on the SHTAC assessment report, and welcome such a comprehensive and thorough evaluation, which supports the clinical and cost effectiveness of adefovir dipivoxil for the treatment of chronic hepatitis B, demonstrating that it improves the quality of life and reduces morbidity and mortality among patients living with this important viral liver disease.

We hope that NICE will reflect this in the ACD, and provide positive guidance for those managing the treatment of this important public health problem in England and Wales.

Yours sincerely

[redacted]

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