**Comments on Health Technology Appraisal: Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B**

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The major difficulty for this recommendation is the lack of evidence on the long-term clinical effectiveness of treatment. The main conclusion that both adefovir and peginterferon are clinically-effective and cost-effective is predicated on the strong assumption that the demonstrable short-term effect of treatment on laboratory markers will translate to clinical benefits. To date there is insufficient follow-up on treated patients to support this conclusion; also, the data on the durability of therapeutic effects on laboratory markers are also very limited. Unfortunately, the adefovir registration trials will not provide this evidence as all patients initially allocated to placebo were switched to adefovir at 48 weeks, so that randomised comparisons cannot be made after this time point.

Arguably, NICE should take a cautious position until the clinical evidence becomes clearer. I have a number of specific comments on the economic model as well as some general comments.

## Economic model

1. SHTAC have made a commendable attempt at an economic analysis in the time available. However, given the state of current knowledge, requiring questionable assumptions about the model structure and input parameters, the estimates of cost-effectiveness are necessarily subject to considerable uncertainty.

2. The effect of therapy is mainly mediated through an effect on HBeAg seroconversion, which in turn influences the rate of progression to cirrhosis. The effect of HBeAg seroconversion – a 5-fold reduction in the incidence of cirrhosis – appears highly optimistic. The effect of "response" in HBeAg negative patients is even stronger, a 9-fold reduction.

3. The duration of lamivudine or adefovir therapy assumed in the model is not clear. On p.128 it is stated that treatment continues until resistance develops; on p.135 it is stated that treatment may also be stopped 6 months after HBeAg seroconversion. Some experts consider that treatment should be given indefinitely, in which case costs would increase substantially. Although NICE guidelines could presumably stipulate limited therapy this position would be hard to maintain if future evidence emerged supporting indefinite treatment.

4. The SHTAC model is one of the first models to include HBeAg negative patients. The "response" rate for HBeAg negative patients is defined as normalisation of

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ALT and HBV DNA <20,000 copies/ml. However, the effect of HBV DNA on disease progression is likely to be a continuum and the level of 20,000 copies/ml would seem arbitrary.

5. HBeAg negative patients are a very heterogeneous group, but overall they have a better prognosis than HBeAg positive patients. It is inaccurate to say they have a lower life expectancy than patients with HBeAg positive disease (p.135). I assume that the economic analysis was limited to the subgroup of HBeAg negative patients with a poor prognosis but this does not seem to be explicit.

6. It is stated that peginterferon followed by lamivudine followed by adefovir has lower costs than peginterferon followed by lamivudine followed by adefovir (p.137). However, the difference is only £59 and inconsequential. This is presumably due to the high incidence of resistance to lamivudine, such that most patients will require adefovir eventually.

7. There is a possibility that HBV DNA levels, rather than HBeAg status, may become the main driver for therapeutic decisions. The Marcellin and Lau trials show a rapid rebound in HBV DNA after the cessation of peginterferon or lamivudine. Thus the use of indefinite antiviral therapy (given continuously or intermittently) may become the clinical standard, with much higher costs than assumed in the models.

8. The marked difference is the cost-effectiveness of peginterferon in Table 38 (HBeAg positive patients) and Table 39 (HBeAg negative patients) does not seem plausible.

**Other comments**

1. I concur with the view that treatment should first to be targetted at those at high risk of disease progression in view of the slow natural course in most patients (p.152). Recent data indicates that high viral load, rather than ALT level, may be the most powerful predictor of disease progression.

2. Another argument for delaying therapy in those with a low risk of disease progression is that there will be wider availability of drugs in the future and better knowledge on how to use the therapies most effectively. While not a perfect model, some lessons can perhaps be learned from the treatment of HIV infection. Patients who received zidovudine monotherapy and rapidly acquired resistance were, with hindsight, inappropriately treated. Also, several observational studies have documented increasing rates of virological suppression with first-line therapy over time, in the era of combination therapy.

3. The spontaneous HBeAg seroconversion rate is assumed to be 9% per annum. Thus over 5 years, 38% of patients ($1-0.91^5$) will have spontaneously seroconverted, although some will have back reverted. Unless there is a clinical indication for immediate treatment, this would seem to support a policy of careful monitoring.
4. More data are needed to guide treatment policy for chronic hepatitis B. If treatment does become more widely available in the UK, the hepatology community should endeavor to collect and analyse data on the outcomes of

treatment in a systematic way. Linking the availability of drugs to a commitment to supply relevant data may be one way of achieving this. Of course, such a scheme requires funding, which the DoH should consider.

5. There is now close agreement between AASLD and EASL guidelines on indications for therapy, including biopsy evidence of active liver disease. It would seem logical that the NICE recommendation should be at least as conservative as these guidelines in terms of patient eligibility.

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