APPENDIX E

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal

Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B

Response to consultee and commentator comments on the draft scope and provisional matrix

Comments on the draft scope			
Consultee/ Commentator	**Subject in Scope**	**Comment**	**Response**
Foundation for Liver Research	Background	It is not clear in the first page on defining the HBeAg-positive and HBeAg-negative groups that the latter is only associated with viral replication when a precore mutant viral strain has developed. With this, HBeAg cannot be produced and yet viral replication is continuing as shown by high HBV DNA levels. This is the group that need treatment with antiviral agents. There is also a large group of HBeAg-negative anti HBe-positive cases in which viral replication is inactive and they are cases that have seroconverted to an inactive carrier state.	The scope was amended following the comments made by the consultee.
RCP	Interventions	Consideration should also be given to the effectiveness of combined antiviral therapies i.e. adefovir plus lamivudine to avoid the emergence of treatment resistant strains.	The scope was amended following the comments made by the consultee by broadening the description of the interventions.
SHTAC	Interventions & other considerations	Although the scope indicates that the two agents could be compared to each other it is assumed that they are to be appraised as separate agents in comparison to current treatments (e.g. lamuvidine). The scope doesn't explicitly acknowledge the fact that the two agents have	The scope was amended following the comments made by the consultee by broadening the description of the

	Current standard treatment (comparators)	been evaluated, and are likely to be used, in combination with current treatments (see below). We are assuming that the assessment will appraise them as both mono and combination therapy. Is liver transplant an appropriate comparator? We have not identified any literature in which this has been compared with either pegylated interferon or adefovir dipivoxil.	interventions. Following the comments by consultees liver transplantation was removed from the scope as a comparator.
Gilead	Background	We feel that the cited prevalence of chronic viral hepatitis of 1 per 550 population may be an underestimate – particularly if this figure includes other forms of viral hepatitis. In the "Getting Ahead of the Curve" report, the DoH state that the prevalence of CHB in the UK is around 0.3%, equating to 156,000 people in England and Wales. However, only around one third of these patients are likely to need treatment.	The scope was amended following the comments made by the consultee.
	Technologies	Based on (these) data, we feel that it would be more appropriate to phrase this sentence as: "Mild reversible nephrotoxicity occurs rarely among patients with compensated liver disease treated with 10 mg adefovir. Renal impairment is seen more commonly among patients with decompensated liver disease and those who have undergone liver transplantation, although many of these cases could have been caused by other nephrotoxic drugs or liver failure."	The scope was amended following the comments made by the consultee by including reference to dosing and dose-interval as per the SPC.
	Current standard treatment	Liver transplantation is listed as a treatment for HBeAg-positive and HBeAg-negative **compensated** CHB. However, clinical practice and current clinical guidelines would recommend this costly treatment only for patients with **decompensated** liver disease.	Following the comments by consultees liver transplantation was removed from the scope as a comparator.
RCN	Other considerations – answers to	• The treatment options that we are aware of is Interferon alfa-2b + / - Lamivudine. This combination works for some people but it is	The scope was amended following the comments made by the consultee by broadening

	queries	neither effective for all nor is it tolerated well by all people. • The protocol for initiating treatment is based on a series of viral studies and consecutive liver function tests that demonstrate a significant and progressive deterioration. Once it is established that the person has progressive liver disease and ongoing demonstrated damage, treatment is discussed. Some physicians will look to do a liver biopsy first others may not. Treatment can be commenced when it is established that the current therapy may be of benefit and the person is willing to commence, understanding the side effects and the protocol for follow up. There are dietary issues including alcohol and other substance use to cover as well as an assessment on the relative risk of depression. • If we can extrapolate the success of combination therapy in HIV as an example, it could be argued that treating Hepatitis B with a combination of drugs i.e. interferon alfa-2b and lamivudine gives a greater level of liver recovery. The combined side effects and associated morbidity for the individual must be factored in along with the usual stress on the renal system. • Other considerations: o The role of treatments in acute icteric hepatitis B (if any) in prevention of fulminant hepatitis/chronic infection o Alternative treatment for patients with depression/serious psychiatric disorders o Funding issues for vulnerable sub groups for example asylum seekers and prisoners • Suggest following appropriate subgroups to be considered: Transplant candidates; Co-infected patients; Prisoners; Injecting drug users; Pregnant/breastfeeding women; Healthcare workers.	the description of the comparators. The scope was amended following the comments made by the consultee by including an additional reference to biopsy in other considerations. The scope was amended following the comments made by the consultee by broadening the description of the current standard treatments (comparators). Acute icteric hepatitis B and funding issues for the subgroups mentioned are outside of the scope of the appraisal. Examples of subgroups have been included in the 'other considerations' section.

British Liver Trust	Title Technologies & Interventions Other considerations Background & current treatment	The title of the Appraisal makes it sound as if the combination of adefovir and pegylated interferon alfa-2a is being assessed, whereas they are two entirely different treatments. The 40kd version of pegylated interferon is being assessed but not the 12kd version. The potential burden of monitoring patient response while undergoing therapy (along with unwanted effects and toxicity of the agents) should be included in the 'other considerations'. Two categories of hepatitis B (HBeAg positive and HBeAg negative) have been delineated whereas in clinical practice it is more realistic to evaluate the HBV DNA quantitatively and correlate this to the liver biopsy findings.	The objective of the scope was amended following the comments made by the consultee. The 12kd version has no marketing authorisation in the UK for chronic hepatitis B. If evidence allows this will be included in the outcome measures currently listed in the scope such as health related quality of life and adverse effects of treatment. Following further expert advice it was decided not to amend the scope.
Roche	Background Current standard treatment	In the Background section, the prevalence of chronic viral hepatitis B is estimated at 1 per 550 of the population (0.002%). The World Health Organisation, however, estimates the UK prevalence of chronic hepatitis B infection to be 0.3%. • Based on UK market share (sales figures 2003) and conversations with UK clinicians treating Hepatitis B, the most common treatment for patients with HBeAg- negative & compensated liver disease is lamivudine (approx 80%). We therefore recommend that lamivudine is the main added as an important comparator for this patient population. • We would also like to point out that based on UK expert opinion, neither interferon alfa-2a nor interferon alfa-2b are commonly used for the HBeAg- negative population. Therefore, interferon alfa-2a and	The scope was amended following the comments made by the consultee. The scope was amended following the comments made by the consultee by including lamivudine in the HBeAg-negative patient groups. Following further expert advice it was decided not to amend the scope.

	Other considerations & Outcomes	interferon alfa-2b may not be relevant comparators for this appraisal. • To describe liver transplantation as a "current standard treatment" for those patients with compensated liver disease is not an accurate reflection of UK treatment practice. Such patients are not at an advanced enough stage of disease progression to warrant such an intervention. Therefore we recommend removal of liver transplantation as a standard treatment for those patient groups with compensated liver disease. • Finally, pegylated interferon alfa-2a will not be licensed for use in patients with decompensated liver disease, only compensated disease (SPC). Therefore pegylated interferon alfa-2a should be removed from this population sub-group for both the HBeAg-negative and positive populations. Additional outcome measures which are of critical importance in this disease area are: • Durability of response • S-antigen loss • S-antigen seroconversion.	Following the comments by consultees liver transplantation was removed from the scope as a comparator. The scope already reflects this. The scope was amended following the comments made by the consultee by including HBsAg in the outcomes related to virological response. Durability of response is already covered by 'time to treatment failure'.
DoH	Background Technologies	• Would you consider amending the wording to say o "*HBV is transmitted horizontally by blood to blood contact (e.g. the sharing of blood contaminated needles and injecting equipment used by drug users) and sexual transmission.*" o Hep B is no longer transmitted by blood products in the UK. • Would you clarify whether "*prevalence of chronic viral hepatitis*", should read "*prevalence of chronic hepatitis B*"? Our view is that the connection between adefovir and renal impairment is dose related, and is much less of a problem with currently	The scope was amended following the comments made by the consultee. The scope was amended following the comments made by the consultee. The scope was amended following the comments made

	Current standard treatment (comparators) Other considerations & outcomes	recommended dosage. Would you consider clarifying this? Would you clarify whether liver transplantation would be a current standard treatment for patients with compensated liver disease as opposed to decompensated liver disease in either the HBeAg positive or negative categories? Would you also consider seeking views on establishing satisfactory end-points for treatment, particularly in HBeAG negative cases where, in perhaps a majority of cases, viral suppression may only be maintained as long as treatment is continued?	by the consultee. Following the comments by consultees liver transplantation was removed from the scope as a comparator. Following the comments by the consultee a sentence was included in the 'other considerations' section.
BASL	Other considerations & outcomes	BASL would like to suggest that the scope also includes the use of these agents in patients co-infected with the HIV (Human Immunodeficiency Virus).	The scope was amended following the comments made by the consultee.
Hepatitis Nurse Specialist Forum	Other considerations	Appropriate subgroups to be considered. • Chronic hepatitis B in HIV co-infected patient, as well as this group of patients who develop YMDD mutant HBV stains • Chronic hepatitis B and hepatitis delta virus super-infection • Chronic hepatitis B and chronic hepatitis C co-infection • Treatment of chronic hepatitis B post liver transplantation	The scope was amended following the comments made by the consultee.

Statement of 'no comment' received from:

- NHS Quality Improvement Scotland
- Schering-Plough Ltd
- Welsh Assembly Government

No response was received from the other potential consultees and commentators