Comments on ACD for Hepatitis B drugs 2005

Consultee	Section	Comment	Action
Professor H Thomas (expert)	General	In general the ACD is a masterly summary of the meeting and reaches a fair conclusion. The preliminary recommendations accommodate all the issues, but because lamivudine is not being assessed, you have not mentioned it on page 1. The reader has to read the whole document, particularly the section on cost-effectiveness, to get an indication the PEG IFN → LAM → ADEFOVIR sequence is the one that the clinician should be applying in most if not all cases. I suspect that the only way round this is for NICE to produce a management algorithm and this might best be done after entecavir has 'bedded down' in clinical practice.	The recommendations in the FAD have been revised to clarify the circumstances in which adefovir dipivoxil (alone or in combination) might be considered appropriate.
		Do you think the February 2009 review might be 'management guidelines' rather than a review of adefovir and PEG IFN? Apart from entecavir there are at least three additional drugs coming into phase 3 trial which will be licensed at about that time. This emphasises the need for guidelines even more.	The referral of clinical guidelines is a matter for ministers.
		Because of the complexity of management of these patients, it may be appropriate to suggest that where possible they are managed in the Managed Clinical Networks in Hepatology that are being developed to meet the Department of Health Hepatitis C Action plan.	This is not a matter for this technology appraisal.
	Resource impact (Section 6)	Finally, I really have no idea about the resource impact. All I can say is that we have reviewed our hepatitis B referrals for the last 2 years and they number almost 2000 cases. We are currently reviewing how many would be eligible, under the current licensed indications, for therapy.	Resource impact will be considered by the costing team.

Consultee	Section	Comment	Action
Professor G Dusheiko (expert)	General	The preliminary document is a good document that that takes into account the complexities of HBV and its treatment. Importantly the document considers the potential for resistance induced by monotherapies, and allows flexibility and scope for clinicians to grapple with the looming burden of resistant hepatitis B. This strategy will allow clinicians and funding bodies to optimise strategies for treatment while treatment algorithms are still evolving. The admissible sequences are reasonable, as pegylated interferon appears to be cost effective and efficacious. It will important in the future to assess combination therapy, albeit that these assessments should not delay the approval of the drugs under consideration. In practice it is not yet clear what percent of HBeAg positive and negative patients will accept pegylated interferon as the unalterable route of first line treatment.	No action for FAD
		The document deals with HBeAg positive and negative disease, albeit in a somewhat atypical text. It would be helpful to use more standardised nomenclature. The document is in part a health care evaluation which evaluates the economic rationale for treatment but it will be important to take into account the consequences of poor treatment strategies i.e. the opportunity cost and indirect costs to society.	

Consultee	Section	Comment	Action
Professor G Dusheiko (expert)	1.2	This statement [i.e.1.2] is problematic in both HBeAg positive and negative patients. **HBeAg positive patients** It is desirable to avoid treating patients with interferon for an unnecessary period if treatment is failing. However, the evidence for the efficacy of six months treatment with interferon is based on the use of standard interferon. The only evidence of efficacy of 6 months treatment with PEG IFN is that derived from a relatively small dose finding study of PEG interferon vs standard interferon in which patients were treated for 24 weeks. No comparison for PEG Interferon has been completed in HBeAg (and anti-HBe positive) patients. (Such comparative trials have been requested by the FDA). **Anti-HBe positive patients.** The same is true for anti-HBe positive patients. Response to treatment in anti-HBe positive patients is measured by suppression of HBV DNA and improvement in serum ALT. Relapses are relatively common after cessation of treatment in anti-HBe positive patients after six months of treatment with standard interferon. Stopping points for anti-HBe positive patients have not been determined but the bulk of evidence suggests that efficacy is improved by one year of therapy. There are no precisely determined stopping points. ALT levels may not normalise in patients with suppression of HBV DNA (effect of PEG interferon).	Section 1.2 from the ACD (regarding assessment of response/side effects and duration of therapy) is not included in the FAD
	1.4	Should read the use of currently licensed antiviral agents, i.e. standard interferon, pegylated interferon, lamivudine or adefovir.	Changed for FAD so that the antiviral agents concerned are named
		Statements are made which lack supporting evidence, including the use of six months treatment with interferon.	Not included in the FAD (see above

Consultee	Section	Comment	Action
Professor G Dusheiko (expert)		Fig 1A in Lau G et al NEJM 352:2682-2695, see figure 1 below) implies continued HBeAg seroconversion between 24 and 48 weeks of treatment; is this correct? Is this a late effect of early viral suppression and immunomodulation or an effect of continued viral suppression after six months? The manufacturers should be asked. Does maximal DNA reduction in the first 3 and 6 months of treatment predict loss of HBeAg loss and HBeAg seroconversion? Are the predictors of HBeAg loss and seroconversion with PEG interferon well defined? Can we specify log declines in HBV DNA at particular time points that yield acceptable negative and positive predictive values for loss of HBeAg in HBeAg-positive patients or sustained virological response in anti-HBe positive patients? ALT flares may predict response, but are imprecise measures. DNA measurements are now measured in standardised WHO units by sensitive PCR. HBV DNA may become undetectable by PCR but the sensitivity of these assays varies considerably further adding to the imprecision of this statement. The statement could read " Response to treatment in HBeAg positive patients is measured by loss of HBeAg, seroconversion to anti-HBe, concomitant suppression of HBV DNA and improvement in serum aminotransferases (ALT). Treatment response and tolerance requires assessment during therapy, to justify therapy for a full year, but there are insufficient data for PEG interferon to determine predictors of HBeAg seroconversion and appropriate stopping points for non responders."	Roche contacted and response obtained. No action for FAD. FAD does not give guidance on assessment and monitoring of treatment effects.

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Professor G Dusheiko (expert)		The document does not include a statement of the possible effect of baseline factors; these include: HBV genotype. Although there is some controversy, genotype A and B may respond better to interferon therapy than genotype C and D. ALT and DNA level at baseline, and DNA level ALT levels during therapy may predict response. Marked ALT elevations at baseline and during therapy were more frequently associated with loss of HBeAg. (Lau et al)	The influence of baseline factors is unclear and has not been addressed in the evidence submitted for this appraisal. No action for FAD
		For both HBeAg positive and HBeAg negative patients, first line therapy must take into account adverse events profiles and the need for dose modifications. Strategies for monitoring differ between PEG interferon and nucleosides/tides.	No change required
	2.1	Add by horizontal transmission among children. The immune response is complex: could read “the risk of chronic infection depends upon the nature of the immune response to the primary infection.”	Amended for FAD as suggested
	2.2	insert primary to read “primary liver cancer”	Amended for FAD as suggested
	2.3	“various” should read “well characterised serological markers in the blood.” Should read “Some variant forms of the virus do not express HBeAg (HBeAg is a viral protein not cellular protein) according to whether HBeAg is expressed. Should read persistence of HBsAg for six months is the accepted definition of chronic hepatitis B.	Amended for FAD as suggested

Consultee	Section	Comment	Action
Professor G Dusheiko (expert)	2.4.1	“phase can last for many years before progressing to active disease. In those who acquire the infection as adults the immunotolerant phase is very short (about 2-4 weeks) and represents the incubation phase of the infection. ” Delete this sentence as there is no evidence for this statement and it is invalid.	Amended for FAD as suggested
	2.4.3	Sometimes referred to as “the inactive HBsAg carrier state because patients” Inactive carrier state is the accepted nomenclature	Amended for FAD as suggested
	2.4.4	typographical error	Amended for FAD as suggested
	2.4.5	Variants of hepatitis B are recognised however, that are not associated with detectable HBsAg by current immunoassays “occult hepatitis B”	Amended for FAD as suggested
	3.2	reduction in platelet and white cell counts are common	Amended for FAD as suggested
	3.6	increases in serum creatinine	Unclear: no action

Consultee	Section	Comment	Action
Professor G Dusheiko (expert)	4.1.11	"The remaining two studies in HBeAg-positive chronic hepatitis B investigated the combination of adefovir dipivoxil with lamivudine compared with lamivudine alone. One was in treatment-naive patients (n = 112) and the other was in patients with lamivudine resistance (n = 94). In the study in treatment-naive patients (which was still ongoing at the time of this appraisal there was no advantage in adding adefovir dipivoxil to lamivudine at one year." What this latter study shows, in fact, is that although there is no additive effect on efficacy, rates of lamivudine resistance are reduced 10 fold. This is an important result.	Amended for FAD to add the following statement "However, there was an increased incidence of lamivudine resistance mutations and viral breakthrough in the group that received lamivudine alone."
	4.1.13	long term data. I have detailed this in my personal statement for both HBeAg and anti-HBe positive disease. The NICE statement does not appear to reflect recently published data in anti-HBe positive patients Hadziyannis et al NEJM 352:2673 2005. Adefovir resulted in excellent longer term suppression of HBV DNA with low rates of resistance.	Results from Hadzidyannis et al are briefly outlined in 4.1.13 of the ACD and remain in the FAD.
	4.1.15	"The experts noted that a strategy of treating chronic hepatitis B with lamivudine followed by adefovir dipivoxil for those in whom lamivudine-resistance developed reflected current practice and was appropriate for most people." This is an important statement but this reviewer would prefer "The experts noted that a strategy of treating chronic hepatitis B with lamivudine followed by adefovir dipivoxil for those in whom lamivudine-resistance developed reflected current practice. However, the experts noted that there was a subgroup of people with highly replicative HBeAg-negative disease in whom resistance could develop rapidly; in these people a strategy of using lamivudine [sic; should be adefovir] in combination with lamivudine might be appropriate.	Amended for FAD as suggested

Consultee	Section	Comment	Action
Professor G Dusheiko (expert)	4.2 general	Interferon therapy has been considered cost effective. All other strategies are considered to be dominated. However, certain strategies have been excluded. Combination therapy has not been modelled and therefore the analysis failed to differentiate the cost effectiveness of monotherapy vs combination therapy. This should not delay acceptance of the treatments under considerations but future models should include combination therapy. Health economic analysis should ideally explore starting with a combination of LAM + ADV given the growing evidence of a lack of resistance with combination therapies.	Additional analysis performed to consider combination therapy was presented at the second committee meeting.
		Several analyses are included. The NICE assessment group model assumed that patients begin with a treatment involving either IFN or PEG. A further analysis assumes that there is no initial treatment with IFN or PEG, and the patient begins either with LAM or ADV and goes through the same pathways as above (LAM alone; LAM followed by ADV [LAM then ADV]; ADV alone until ADV failure; followed by LAM [ADV then LAM]).	
		The model thus explored a sequential strategy of PEG leading to failed PEG, then LAM until failure, ADV until failure and then treatment with LAM – but such patients would already resistant to LAM.	Not true. Paths in the AG model are PEG then LAM then ADV or PEG then ADV then LAM.
		Note also: the sequential strategy of lamivudine followed by adefovir for lamivudine resistance is clinically incorrect; There is a looming body of evidence to suggest that lamivudine should be continued together with adefovir after lamivudine resistance in order to suppress wild type HBV; this is not included in the model, although was suggested by previous reports.	Cost for continued lamivudine were considered in the model although this is not explicitly stated in the assessment report

Consultee	Section	Comment	Action
Professor G Dusheiko (expert)		A sequential strategy does not fully examine the biological costs of resistance- flares in hepatitis with the propagation of wild type virus – which would occur episodically with resistance- and would lead to disease punctuated by at flares that are injurious to the liver.	The Committee considered the dangers of resistance flares, particularly in patients at high risk. This is reflected in the FAD
		It is clear that a high proportion of patients with high levels of replication or poor primary response will develop resistance. Resistance has cost implications and the concept of sequential treatment may become increasingly difficult to justify. There are externality costs to resistance leading to increases in the population with resistant strains.	The guidance does not rule out combination therapy where this is considered appropriate.
African & Caribbean Med Soc	General	I found the papers comprehensive. Although there may a drug-resistance concern there seems to be good evidence that adefovir dipivoxil and pegylated interferon alfa-2a are clinically effective and cost effective in reducing biochemical virological and histological outcomes from chronic hepatitis B infection. The treatment should be used in cases where there is benefit. It is encouraging to note that race did not impact on outcomes of treatment and that there is scope to treat patients co-infected with HIV etc.	No action required. Note that people with HIV co-infection are outside the scope of this guidance

Consultee	Section	Comment	Action
NHSQIS I	General	The recommendations have changed since the original consultation [on the Assessment report]. The initial document [assessment report] proposed that chronic HBV treatment should follow the sequence of PEG-interferon as preferred first line, followed by lamivudine monotherapy for those patients who fail to respond or relapse following treatment, with adefovir being used as monotherapy for patients who develop lamivudine resistance. The contribution of expert clinicians in the management of HBV has shifted the recommendations awat from lamivudine monotherapy to one whidch suggest the choice of antiviral should be based on individual patient characteristics including the potential for lamivudine resistance to develop. This is very sensible advice as I suspect the future use of lamivudine monotherapy will decline sharply because of the superiority of adefovir (resistance rate 6% vs. 60% after 3 years treatment) as monotherapy. The key question now is whether combination therapy with adefovir and lamivudine is superior to adefovir alone. The main implication for Scotalnd is that the current SMC recommendation for adefovir is that it should be used only for the treatment of lamivudine resistant HBV. This will become untenable when the NICE guidelines are published.	No action required
NHSQIS II	General	As far as I am aware, this is a comprehensive review of the evidence which reaches reasonable conclusions on which to base recommendations to the NHS in Scotland.	No action required

Consultee	Section	Comment	Action
NHSQIS III	General	Summaries of clinical and cost effectiveness appear reasonable. Athough we have few data, I suspect very few patients with chronic hepatitis B in Scotland are currently being treated with antiviral therapy. As indicated, the major burden will be urban immigrant communities form Asia and the number requiring treatment will probably remain relatively small, especially in rural areas. Therefore I would suggest that any treatment should be initiated and monitored by Hepatologists of Infectious Disease clinicians with experience of treating other forms of viral hepatitis. The provisional recommendations appear reasonable. It seems that a finite period of PEG-IFN is the best initial therapy for most patients. Alhough generally a sequential change to lamivudine then adefovir once resistance develops, may be the current strategy for most, I agree that we have little data on the optimum sequencing of oral therapy or combined therapy. Therefore I agree that we should continue to assess individuals on a case by case basis approach whilst awaiting further published data.	The FAD recommends that treatment is initiated 'an appropriately qualified healthcare professional with expertise in the management of viral hepatitis'
RCP	Section 1.4	Provisional recommendations reasonable but the phraseology of 1.4 is ambiguous. Is the 'antiviral agents in this sentence meant to embrace PEG-IFN? We believe it does and should but think this should be made clearer.	Guidance in the FAD no longer used the phrase 'antiviral drugs'.
	Section 9	In view of the multiplicity of new antiviral drugs emerging and in current clinical trial, and the risk of drug-resistant HBV emerging as an infectious strain, we believe that the use of antiviral agents in combination should have an interim review before February 2009	FAD recommends a review date of 2007.
SHTAC	Section 1.1	Specify Peginterferon alfa-2a, to avoid confusion with pegylated interferon alfa-2b (not licensed)	Amended for FAD as suggested

Consultee	Section	Comment	Action
SHTAC	2.4.4	Typo on line 6. Should be HBeAg-negative	Amended for FAD as suggested
	4.1.3	1. The rate of HBeAg seroconversion should be 32% not 34% as quoted (NB. The figure of 34% applies to the rate of HBeAg *loss*). 2. It should be mentioned that the only statistically significant difference between pegylated and non-pegylated interferon alfa in this trial was for the combined outcome of HBeAg loss + HBV DNA normalisation + ALT normalisation (24% for all doses of PEG combined, versus 12% for IFN, p=0.03).	Amended for FAD as suggested
	4.1.4	At the end of the paragraph suggest adding the response rate for the lamivudine and pegylated interferon group, 39%	Amended for FAD as suggested
	4.1.10	The p value quoted is p <0.05. The p value in the trial publication was p=0.005. It would be more accurate to quote the trial publication (and in keeping with the rest of the ACD which tends to report actual p values rather than whether below or above a given threshold of significance). It would also be worth quoting the p value for the adefovir dipivoxil and placebo group (compared with lamivudine) which was p=0.018.	In consultation with SHTAC, decided not to change.
Gilead	1.3	We believe that adefovir dipivoxil should be an *initial* option for the treatment of chronic hepatitis B, and longer term data could have been reviewed for the efficacy, safety and tolerability of adefovir dipivoxil by the Appraisal Committee. Clinical data up to 144 weeks in HBeAg-negative patients has been published in the New England Journal of Medicine (Hadziyannis, et al; June 2005), and in HBeAg-positive patients as a peer reviewed abstract for the annual meeting of the Digestive Disease Week (Marcellin, et al; May 2005). Electronic copies of these studies have been attached as part of this response.	Considered by committee. Sequences involving interferon were cost effective therefore no change.

Consultee	Section	Comment	Action
Gilead	4.3.9	If adefovir dipivoxil was considered as an *initial* option for treatment the reference to interferon as an initial treatment would be unnecessary.	
	4.1	We do agree that the summaries are reasonable interpretations, but this would be improved with the inclusion of longer term data for HBeAg-positive and negative patients as discussed in the first section of this response. We note with interest that the ACD presents the key findings of the Roche economic evaluation, noting only that "nothing is said about later choices for those people for whom the interferon preparation has not been clinically effective".	Hadziyannis results are already briefly outlined. Marcellin data will not be added in the light of their status (abstract only)
	4..2	The ACD currently makes no mention of other weaknesses highlighted in the Evaluation Report, such as: "overall, the Roche analysis, which ignores the sequential nature of treatment options, appears to be of limited usefulness in the totality of this appraisal". In addition, it should be noted that the Roche model considers data on a comparison of adefovir dipivoxil 208 weeks versus pegylated interferon alfa 48 weeks, where no clinical data is available.	No change. Not all details of the 200 page AR are in the 20 page ACD. .
	Implementation	Missing from the ACD: the need for suitable infrastructure and additional services to ensure that treatment of CHB is managed optimally and equitably. The facilities and clinical nurse specialists to diagnose CHB, assess disease severity and monitor response and resistance to treatment must be made accessible to centres across the UK. In particular, relatively few centres currently have the facilities or funding necessary to manage the side effects and adherence to peginterferon for chronic hepatitis B, as well as to test for mutations conferring drug resistance. While the forthcoming NICE guidance is likely to ensure that adefovir dipivoxil and peginterferon are available to all patients who need them, implementation by the NHS will also require appropriate facilities and infrastructure.	No action required for guidance – this is a resource issue. Resource impact will be considered by costing team

Consultee	Section	Comment	Action
Gilead	Guidance	Overall, Gilead Sciences does agree that the provisional recommendations are sound, with the addition of our comments as set out in this response. For adults requiring treatment for chronic hepatitis B, due to the complex nature of the disease and the requirement for prolonged treatment in a considerable proportion, we believe that physicians and patients need greater choice in their initial options for treatment.	No action
	Review date	Lastly, we have no specific issue with the proposed review date of February 2009, particularly as this will give time for emerging data, new products and development of clinical consensus in this evolving field.	Other consultees have indicated that the review date should be earlier.

Consultee	Section	Comment	Action
Roche	General	Roche believes the references made to conventional interferon (interferon alfa) throughout the ACD may be incorrectly interpreted by readers of the guidance as implying that interferon alfa (in addition to peginterferon alfa-2a) is also being recommended as an initial treatment option. For example, Section 1.3 states: "*adefovir dipivoxil is recommended as an option for the treatment of CHB in adults, if treatment with **interferon alfa** or peginterferon alfa has been unsuccessful*". Section 4.3.9 states the following: "*The committee concluded that it was inappropriate to recommend adefovir as an option for the treatment of CHB where prolonged oral antiviral treatment is required. It was also persuaded that this should only be after the use of **an interferon** as initial treatment unless this was contraindicated*". Furthermore section 7.3.3 states that: "*adefovir is considered an option for treatment when treatment with **interferon alfa or** peginterferon alfa has been unsuccessful…or treatment with **an interferon** is poorly tolerated or contraindicated*". Such positioning does not reflect the evidence base presented in the Assessment Report or Overview document prepared by the NICE Technical Team which states that a treatment sequence containing interferon alfa as an initial treatment option is dominated by a treatment sequence where peginterferon alfa 2a is the initial treatment.	The Committee noted that in the randomised controlled trial comparing peginterferon alfa-2a and standard interferon alfa did not find a statistically significant difference versus placebo for the primary endpoint (see 4.1.3 in FAD). The Committee accepted that current evidence suggests that peginterferon alfa may be more effective than standard interferon, but that this had not been unequivocally established.
	Cost effectiveness	Section 4.2.7 and 4.2.8 of the ACD states that treatment sequences that include interferon alfa as an initial treatment option are either dominated or extendedly dominated. Consequently, we would suggest that the references to interferon alfa where these imply that interferon alfa can be considered as an initial treatment option need to be removed.	This is not entirely true. In HBeAg-positive chronic hepatitis B, the sequence IFN-LAM-ADEFOVIR is cost effective relative to lamivudine alone (4.2.7).

Consultee	Section	Comment	Action
Roche	1.3 and 4.3.9	The current guidance relating to the use of adefovir and lamivudine does also not appropriately reflect the available evidence base. Page 21 of the ACD states: "*In most of the analyses, strategies in which adefovir dipivoxil is used before lamivudine or without lamivudine in the sequence are dominated by the alternative strategies*". In addition page 23 states: "*However, when considering the use of adefovir dipivoxil in the various treatment sequences, the committee heard the most cost effective option was for it to be used after failure of lamivudine or following the emergence of virus resistance to lamivudine*" Consequently, for the guidance to state that adefovir dipivoxil is a treatment option directly after peginterferon alfa-2a appears again to contradict the available evidence base. Furthermore, the cost per QALY of such a treatment strategy (PEG, ADF, LMV) in all patients, as stated on page 15 of the Appraisal Committee Overview document, is listed as £160,000. This treatment strategy (PEG, ADF, LMV) is *dominated* from a cost effectiveness perspective within the HBeAg negative population when compared to several alternative treatment strategies (PEG, PEG + LAM, PEG + LMV + ADF) as stated on page 17 of the ACD overview. To address this point, Roche would suggest that the Committee give consideration to inserting the phrase "**and lamivudine**" into section 1.3 prior to the phrase "…*has been unsuccessful in producing a response…*".	The recommendations in the FAD have been revised to clarify the circumstances in which adefovir dipivoxil (alone or in combination) might be considered appropriate.

Consultee	Section	Comment	Action
	1.3	Section 1.3 currently states that adefovir dipivoxil may be used where: "*treatment with an interferon is poorly tolerated or contraindicated*". Currently the wording of this recommendation may imply that adefovir dipivoxil should be an initial treatment option for chronic hepatitis B if tolerability is considered an issue prior to the commencement of treatment with peginterferon alfa 2a. However, the evidence base summarised within the ACD demonstrates that any treatment sequence where adefovir dipivoxil is the initial treatment option is not a cost effective strategy. Consequently, Roche suggests that the phrase "***has been proven to be***" be inserted into section 1.3 prior to the words "*poorly tolerated…*".	Not considered necessary to add 'has proven to be' to current wording.
		This technology appraisal and the evidence base which has been analysed during the appraisal relates to the drug peginterferon alfa-2a, which is currently the only peginterferon alfa treatment licensed for the treatment of chronic hepatitis B. However, throughout the ACD the term "peginterferon alfa" is used. Roche believes that the use of this term may imply to readers of the guidance that the use of peginterferon alfa-2b, which is not licensed for the treatment of chronic hepatitis B, may be endorsed by the guidance. Roche therefore requests that the term "peginterferon alfa-2a" is utilised consistently and comprehensively throughout the ACD in order to avoid possible misinterpretation and off-license use of peginterferon alfa-2b, which is unsupported by the available evidence base.	FAD amended as suggested

Consultee	Section	Comment	Action
Roche	1.4	The provisional guidance is not explicit in defining the term “anti viral agent”; consequently there is ambiguity within the ACD as to what agents certain of the recommendations actually relate to. For example, section 1.4 states: “*The appropriate strategy and sequencing of the anti-viral agents should be assessed on a case by case basis*”. It is possible to classify peginterferon alfa-2a as an anti-viral agent. Section 1.4 may be interpreted as permitting adefovir or lamivudine to be utilised prior to pegylated interferon alfa 2a. To address this ambiguity, Roche would suggest that the term “nucleoside analogue” or “oral anti-viral agent” should replace the term “anti-viral agent” throughout the guidance for those readers who may assume the term anti-viral agent refers only to adefovir and lamivudine.	Guidance in the FAD no longer used the phrase ‘antiviral drugs’.
Roche	1.2 and 4.3.3	The licensed indication in the SPC for peginterferon alfa-2a states that the treatment duration is 48 weeks. All phase III randomised control trial evidence of efficacy, safety and tolerability for peginterferon alfa-2a relates to this treatment duration. Consequently it is unclear what evidence base has been utilised by the Committee to substantiate the recommendation in section 4.3.3 that peginterferon alfa 2a “may be stopped after 4-6 months”.	This section has been removed from the FAD

Consultee	Section	Comment	Action
BASHH	General	We are in agreement that all the currently available evidence has been taken into account in the evaluation report and the ACD. However, we urge the committee to bear in mind that data for combination suppressive therapies and their effect on reducing the emergence of resistance may be available in the future, and the guidance will need to be reviewed in light of new data at the earliest opportunity to prevent wide-spread emergence of resistance. New drugs, too, will be available in the near future – Entacavir has already been approved by the FDA for the treatment of therapy-naïve and lamivudine-refactory HBV. We, therefore, suggest that a further review of treatment strategies and treatment options be carried out sooner than that proposed in February 2009.	FAD recommends a review date of 2007.
	Resource implications	In taking into account resource impact and implications for the NHS the need for a) clinical nurse specialists to supervise therapy (especially for pegylated-interferon) b) resources for frequent patient monitoring (both for side-effects and treatment response) c) resources for growth-factor support for some patients on pegylated-interferon (G-CSF for neutropenia and erythropoietin for anaemia) The current experience from the treatment of HCV suggests that in order to maximise treatment benefits and resource allocation, development of local and regional treatment networks should be encouraged.	This is a resource issue. No action required for guidance. Resource impact will be considered by costing team.

Consultee	Section	Comment	Action
BASHH	Preamble	We are in agreement with the broad strategy and provisional recommendations. We would stress the importance of re-affirming that these recommendations would not apply to patients co-infected with HIV and that current guidance on the treatment of HIV/HBV co-infection in the UK is available on the BHIVA website (http://www.bhiva.org/guidelines/2004/HBV/index.html).	Already in preamble to guidance in bold.
	1.4	We agree that the appropriate strategy and sequencing for the use of antiviral agents should be assessed on a case-by-case basis. We a the need for HIV-testing in all HBV-infected patients but especially for those about to start on lamivudine therapy since the use of this drug alone may jeopardise future treatment options for HIV.	No action, as this is not a guideline and lamivudine is not the subject of the appraisal.
DoH		The indications for initiating treatment for chronic hepatitis B seem rather vague. Would it be possible for you to be any more specific? Should patients for whom treatment is not recommended continue to be monitored? Would you consider spelling out the criteria for "evidence of active viral replication"? Should HBV DNA levels play any part? Is a histological diagnosis of moderate or severe hepatitis (as with chronic hepatitis C) the necessary indication? Is a liver biopsy always necessary?	Monitoring and diagnosis are outside the scope of a technology appraisal The indications for treatment, including the necessity for histological diagnosis, are set out in the SPC for each drug.
	1.2	In paragraph 1.2, could you clarify what is meant by "conventional assay" – a term not described, and not used elsewhere in this document? Does this refer to the older insensitive hydridisation assays (usually reporting levels as pg/ml and which probably do not detect HBV DNA levels (much) below 10^6 copies/ml) or to the much more sensitive HBV DNA amplification assays (as used in the study results quoted later in the document). Are these latter assays recommended for monitoring patients on long tern treatment whose HBV DNA levels fall below the hybridisation assay threshold?	This paragraph has been removed for the FAD.

Consultee	Section	Comment	Action
DoH	1.2, 4.3.3 and 4.3.4	In paragraphs 1.2 and 4.3.3/4, for cases where an appropriate response to pegylated interferon has been obtained at six months, could you clarify how long treatment should continue for HBeAg positive chronic hepatitis (following HBeAg/antiHBe seroconversion) or HBeAg negative chronic hepatitis (following a suitable initial fall in the level of HBV DNA), or how this should be determined. Would the optimum duration of treatment differ for the two types?	1.2 and 4.3.3 removed for the FAD
	1.4 and 4.3.9;	Paragraphs 1.4 and 4.3.9 state that the likelihood of the emergence of virus resistance should form part of the assessment for the appropriate sequencing for the use of antiviral agents. Would you consider explaining how this should be determined, as we believe this could assist clinicians involved in prescribing treatment?	This recommendation is based on expert opinion.
	2.4.1 to 2..4.4	Would it be possible to clarify the language in paragraphs 2.4.1 to 2.4.4 inclusive? E.g. the incubation period of hepatitis B infection ranges from 40 to 160 days, with an average of 60-90 days; and the use of the term “HBeAg-negative strain of the virus” may be confusing given that infection with wild-type virus can go through both HBeAg positive and negative phases, and the inactive carrier state is, by definition, HBeAg negative). Would it be possible a clearer distinction be drawn between HBeAg positive chronic hepatitis, HBeAg negative chronic hepatitis and the inactive carrier state; giving some idea of the relative proportions of each in the infected population in the UK.	Added to FAD 2.4.2 FAD amended as suggested

Consultee	Section	Comment	Action
DoH		We believe there are concern about treatment options that result in the emergence of drug resistant strains, particularly as this could result in cross-resistance with other similar drugs currently under development and hence limit therapeutic options in the future. Would you consider including recommendations on how resistance may be avoided, including on the possible use of combination therapy (as for tuberculosis and HIV)?	As above (2 boxes up) new section 4.3.10
	Section 8	Would it be possible for the guidelines from EASL and the US to be mentioned in this section?	This section is for related NICE guidance only
		On page 17 of the '*Overview*' document under the heading 'transmission of drug resistant strains' it should be remembered that it is the estimated 3,780 new acute infections in England and Wales each year that result in the estimated 269[i] chronic carriers. Thus, the true incidence of hepatitis B infection is estimated at around 7.4 per 100 [sic] persons per year, so the general transmission rate in England and Wales may not be as low as surmised in this paragraph. However, there may be other factors involved in possible transmission of drug resistant strains.	Incidence changed to 7.4 per 100,000 on querying with DoH. This comment therefore loses its force. No action taken.

Consultee	Section	Comment	Action
RCN	General	All relevant evidence to date has been considered, and recent publications this year have supported this data and suggested no licensed alternatives. The recommendations for the use of Pegylated interferon and Adefovir Dipivoxil based on clinical and cost-effective data are appropriate reflecting the current clinical trial data and recommended regimes falling within less than £30,000 per QALY. This in turn provides clinicians and their patients with additional and more effective treatment options. The provisional recommendations support current expert opinion and clinical trial results. To date there has been little consensus on the treatment for chronic hepatitis B. This proposal provides guidance for first and second line therapies with the flexibility for alternate regimes in difficult to treat groups. It supports further research in the use of combination therapies. However, there is no acknowledgement of new compounds currently in development.	No action for FAD

Consultee	Section	Comment	Action
RC Path	General/ assessment report	I have a comment concerning the costing of treatment options. Whilst appendices 14 and 15 indicate that allowance is made for several HBV DNA viral load measurements before, during and after the various therapeutic regimens under consideration, there is no mention of antiviral resistance testing. It may be that an increase of HBV DNA whilst on therapy is an acceptable surrogate for the emergence of antiviral resistance, although there are other possible explanations (failure of compliance to therapy being the most obvious one). However, by analogy with what has happened in HIV medicine, my guess would be that clinicians will refer samples for analysis of resistance mutations. There are very few laboratories with the capabilities to do the relevant tests in the UK at present, although with the development of line-probe assays, it is likely that many more laboratories will be able to take this on. It is, however, an expensive technology. Resistance testing for HIV currently costs about £300 per sample. Equivalent costs for HBV may be less than this, but will certainly be in three figures. Whilst there may only be a trickle of such assays requested initially, in the longer term, especially if drugs are used in sequential monotherapy rather than in combination, there may be a need to do pre-treatment resistance testing – I note that the British HIV Association are now recommending HIV resistance testing in all newly diagnosed patients before initiation of therapy, a situation that has arisen following the recognition of widespread transmission of drug-resistant variants.	No action for FAD.

Consultee	Section	Comment	Action
RC Path	Guidance	My primary concern here [with the provisional recommendations] is with the recommendation for use of lamivudine and adefovir dipivoxil as sequential single therapeutic agents. When lamivudine was first introduced as a means of suppressing HBV replication, there was no alternative but to use it as a single agent. A parallel exists here with the introduction of azidothymidine (AZT) as therapy for patients with HIV infection. However, the emergence of adefovir as a second agent able to suppress HBV replication (and the likely emergence of yet other agents in the near future), with no apparent cross-resistance to lamivudine, completely changes the situation. The development of HIV replication inhibitors other than AZT has led to the successful use of combination therapy, and the precept that it is unjustifiable ever to treat an HIV-infected individual with a single agent. The same underlying principles should apply to the treatment of HBV (and any other viral) infection where the emergence of drug-resistant, but fully replication competent and pathogenic variants is well documented. The suggestion that HBV infected patients might first be treated with one agent (lamivudine) until such time as resistance emerges, at which point adefovir may be added to the regimen, seems positively perverse in the light of our extensive experience of the factors associated with the emergence of antibiotic and antiviral resistance. The apparent lower rate of emergence of adefovir resistant variants (as opposed to lamivudine resistant variants) should not be interpreted as a mitigating factor in this policy – rates of 18% resistance emerging after 3 or 4 years of therapy are not insignificant. There is also the issue of onward transmission of drug-resistant variants to consider, a problem of increasing frequency and significance in the area of HIV infection.	The guidance does not rule out combination therapy where this is considered appropriate. However there was insufficient evidence for the committee to conclude that combination therapy should be recommended in all cases.

Consultee	Section	Comment	Action
RC Path	Cost effectiveness	I fully appreciate that the Appraisal panel can only consider evidence that is available to them, and that there are precious few data on the use of combination lamivudine and adefovir therapy available for scrutiny. I also note and welcome that this important issue is acknowledged in point 4.1.16, further elaborated in points 4.3.7 to 4.3.9, with a recommendation for further research in this area in point 5.1. However, I think it is a shame that the cost-effectiveness analyses did not include use of the regimen of combination adefovir and lamivudine, and it seems to me, in point 6.2, that the expectation (and implied recommendation) is that most adefovir will indeed be prescribed only after the emergence of lamivudine resistance following single-agent therapy with lamivudine. I re-iterate, as a clinical virologist with no personal experience of treating patients with HBV infection, that from first principles alone, this seems to be a perverse use of precious therapeutic agents.	Further modelling was carried out to consider combination regimens and this was presented to the Committee at the FAD meeting. This was based on the very optimistic assumption that there was no resistance associated with the use of combination therapy. However in the absence of data on resistance rates, the Committee felt that it did not have enough evidence to make a recommendation along the lines suggested by Prof Irving.

Consultee	Section	Comment	Action
RC Path		The study is evaluating the role of adefovir and pegylated interferon in the treatment of chronic hepatitis B. The effectiveness of these has been demonstrated in various studies by improvement in biochemical, virological and histological parameters. Histologically there was improvement in necroinflammatory scores and fibrosis arm liver biopsy interpretation. Individual expert opinion also stressed the value of liver biopsy in both fibrosis and necroinflammatory and in the decision to treat chronic hepatitis and points out that currently only liver biopsy will allow assessment of hepatic fibrosis. I agree that these views accurately reflect the role of histopathology in determining the decision to treat with these drugs. I do however feel that this role could have been emphasised rather more in the Appraisal Committee's preliminary recommendations given that liver biopsy is an important parameter in the initial decision to treat and that in 1.4 ''the appropriate strategy ..... should take into account a number of factors including the stage of the disease process''.	No action for FAD. The SPCs for the drugs specify the need for histological diagnosis.

Consultee	Section	Comment	Action
Foundation for Liver Research	4.3.4	All in all the document represents a reasonable assessment of the present day situation with the exception of 4.3.4 where I believe the overall view of consultant hepatologists would be that for HBeAg-negative disease, pegylated interferon was not an appropriate therapy with the long duration of treatment that was needed. These people have to be maintained on therapy, probably for a lifetime, to avoid the damaging exacerbations of HBV reactivation. This is unacceptable in terms of side effects and for this group of patients, lamivudine has been widely used but should probably be replaced by adevovir, particularly in those who develop resistance to lamivudine. For the HBe Ag positive cases there is one paper that suggests a higher seroconversion rate with pegylated interferon than with lamivudine or adefovir and on that basis the recommendation would hold, although in my clinical experience most patients will take the option of the lower response with an oral antiviral rather than the side effect of pegylated interferon.	Sequences including interferons were cost effectinve in both HBeAg-negative and HBeAg-positive chronic hepatitis B. No action for FAD.

No comment:
GSK (commentator)

[i] The estimate in the paper by Hahne et al was 269. This has, perhaps not unreasonably, been rounded up to 300 in the ACD document, but now appears as 350 in the Overview.