National Institute for Health and Clinical Excellence

Telbivudine for the treatment of chronic hepatitis B

Responses to comments from consultees and commentators on the draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Royal College of Pathologists	None	Noted
	Roche	None	Noted
	Royal College of Nursing	None	Noted
	British Association for Sexual Health (BASHH)	None	Noted
	British Association for the Study of the Liver	It is a very timely and appropriate for Telbivudine for the treatment of chronic hepatitis B to be reviewed by NICE	Comments noted.
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted
	Novartis	None	Noted
Wording	Royal College of Pathologists	Current treatment options for patients with HBV infection are not ideal. There is a need for new drugs. This is therefore a very appropriate topic	Comments noted.
	Roche	None	Noted
	Royal College of Nursing	None	Noted

Section	Consultees	Comments	Action
	British Association for Sexual Health (BASHH)	This is a well worded document. BASHH initially commented for the hepatitis b guidelines from nice that these would need rapid review with the development of new agents and forthcoming launch of entecavir and telbivudine. we would therfore welcome this review	Comments noted.
	British Association for the Study of the Liver	Yes	Noted
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted
	Novartis	No change in wording needed	Noted
Timing Issues	Royal College of Pathologists	No comment	Noted
	Roche	Current suggested timelines seem appropriate.	Comments noted.
	Royal College of Nursing	This seems totally appropriate if not overdue.	Comments noted.
	British Association for Sexual Health (BASHH)	This is a well worded document. BASHH initially commented for the hepatitis b guidelines from nice that these would need rapid review with the development of new agents and forthcoming launch of entecavir and telbivudine. we would therfore welcome this review	Comments noted.
	British Association for the Study of the Liver	The suggested timing is appropriate	Comments noted.
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted
	Novartis	Yes it is appropriate.	Noted

Section	Consultees	Comments	Action
Additional comments on the draft remit	Royal College of Pathologists	No	Noted
	Roche	None	Noted
	Royal College of Nursing	None	Noted
	British Association for Sexual Health (BASHH)	The draft remit does not include HIV patients. We believe that this should be outside the remit of the present consultation but that reference should be made to the current BHIVA guidelines It is essential that three aspects of hepatitis b are examined 1 e antigen positive v e antigen negative 2 sequencing of therapy and the neccesity for resistance testing 3 combination therapy	Comments noted. The scope has been amended to include these subgroups. In line with the Technology Appraisal No. 96, this STA will not specifically consider people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or HIV.
	British Association for the Study of the Liver	None	Noted
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	Telbivudine will be a useful addition to the armamentarium of drugs available to treat chronic hepatitis B infection but should not be appraised in isolation. The whole management of chronic HBV infection needs to be re examined in the light of increasing evidence that sequential monotherapy for HBV is inappropriate	Comments noted. From the scoping workshop, consultees agreed on a single technology appraisal (STA).

Section	Consultees	Comments	Action
	Novartis	We are unable to edit the field entitled "appropriateness" above. Our comments are as follows: We agree that an appraisal of the current Hepatitis B treatments is relevant, and we fully support NICE's proposal to review telbivudine in a technology appraisal. In particular, we believe that this is a priority issue, with the magnitude of the problem of chronic Hepatitis B often being underestimated, and in light of the limitations of current treatment options.	Comments noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Royal College of Pathologists	I would strongly dispute the wording of the last sentence of the second paragraph (Infection with HBeAg-negative ….). In the UK, the considerable majority of anti-HBe positive carriers have quiescent infection with low or undetectable levels of HBV DNA, and therefore an excellent prognosis. Indeed, this underlies the rationale for treatment of HBeAg positive patients in order to render them anti-HBe positive! Also the penultimate sentence of the first paragraph under the heading "Treatment" looks odd to me. No-one in the UK routinely genotypes patients with HBV infection, and I am not aware that therapy regimens are tailored at all according to genotype. I wonder if there is some confusion here with chronic HCV infection?	Comments noted. The text has been amended to refer to mutant strains of the virus that do not produce 'e' antigen at all. References to tailoring treatment to HBV genotypes have been amended.
	Roche	Although side effects limited the long term use of standard interferons, the 48 weeks of treatment with peginterferon alfa 2a is not due side effects rather that is the optimum period of treatment required for obtaining potential clinical benefits.	Comments noted.
	Royal College of Nursing	None	Noted
	British Association for Sexual Health (BASHH)	None	Noted
	British Association for the Study of the Liver	Accurate	Noted
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted

Section	Consultees	Comments	Action
	Novartis	We agree that this is an accurate summary. We believe, however, that the background section should reflect the future direction of successful chronic Hepatitis B therapy. We suggest to add the following paragrapg: Maximizing profound viral suppression early in the course of treatment- within first 24 weeks- and maintaining it would be a significant step forward toward minimizing serious long-term sequelae. Understanding the relationship of persistently raised viral loads with the disease progession to cirrhosis, hepatocellular carcinoma or hepatic failure are important when assessing prognosis and the potential place of specific therapies in the successful treatment of chronic Hepatitis B virus (HBV) infection. Ideally, one or more agents are needed to quickly and profoundly suppress HBV viral replication and result in HBeAg seroconversion, and prevent or at least significantly slow disease progression.	Comments noted. The scope is intended to provide a brief background to the decision problem. This level of detail is not required.
The technology/ intervention	Royal College of Pathologists	No comment	Noted
	Roche	Yes	Noted
	Royal College of Nursing	None	Noted
	British Association for Sexual Health (BASHH)	None	Noted
	British Association for the Study of the Liver	Accurate	Noted
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted

Section	Consultees	Comments	Action
	Novartis	At present, the scope does not precisely describe the way in which telbivudine works. We would suggest the wording to be altered as follows: Telbivudine (Novartis Pharmaceuticals/Idenix) is a nucleoside analogue which specifically targets the HBV DNA polymerase, resulting in competitive inhibition of the HBV polymerase and termination of the growing chains of HBV DNA. Telbivudine preferentially inhibits HBV second-strand DNA synthesis. This mode of action is a theoretical rationale for the clean preclinical profile observed with telbivudine.	Comments noted. The draft scope has been amended to reflect these issues.
Population	Royal College of Pathologists	What about HIV co-infected patients?	Comments noted. In line with the Technology Appraisal No. 96, this STA will not specifically consider people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or HIV.
	Roche	It should be made clear that data in 'e' antigen positive and negative patient groups should be analysed separately as the main goals of treatment (although similar) and efficacy will vary between these 2 subgroups. Currently due to the lack of clinical outcomes in various Hepatitis B genotypes no reference should be made to these.	Comments noted. Subgroups of patients will be considered depending on the availability of good quality clinical evidence.
	Royal College of Nursing	Yes, this seems appropriate.	Comments noted.

Section	Consultees	Comments	Action
	British Association for Sexual Health (BASHH)	The draft remit does not include HIV patients. We believe that this should be outside the remit of the present consultation but that reference should be made to the current BHIVA guidelines It is essential that three aspects of hepatitis b are examined 1 e antigen positive v e antigen negative 2 sequencing of therapy and the neccesity for resistance testing 3 combination therapy	Comments noted. In line with the Technology Appraisal No. 96, this STA will not specifically consider people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or HIV.
	British Association for the Study of the Liver	The population is defined appropriately	Comments noted.
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted
	Novartis	The population is defined appropriately.	Comments noted.
Comparators	Royal College of Pathologists	What about entecavir?	Comment noted. The draft scope has been amended appropriately.

Section	Consultees	Comments	Action
	Roche	The inclusion of standard (non pegylated) interferon seems unnecessary as these are rarely used in the treatment of chronic hepatits B. On mentioning pegylated interferon it should be made clear that this refers to peginterferon alfa-2a, as peginterferon alfa-2b does not have a license for the treatment of Hepatitis B. It should be noted that no direct comparative data comparing telbivudine with pegylated interferon is available; therfore the choice of a uniform outcome measure is important (please see outcomes section below)	Comments noted. Despite non-pegylated interferon alfa-2a is rarely used in routine clinical practice, it remains a valid licensed comparator to telbivudine. See section 2.2.3.1 of the Guide to Methods of Technology Appraisal. The comparator section clearly states 'peginterferon alfa-2a' A uniform outcome measure is most desired though various randomised clinical trials on chronic hepatitis B have reported treatment effects using various clinical outcome measures.
	Royal College of Nursing	None	Noted
	British Association for Sexual Health (BASHH)	standard of care re nice guidelines is lamivudine or peg interferon BASHH have previously expressed their concern over lamivudine monotherapy due to the high rate of resistance that develops to this agent and the cross resistance to newer agents that develops	Comments noted.
	British Association for the Study of the Liver	Yes	Noted
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted

Section	Consultees	Comments	Action
	Novartis	Yes, although we would suggest that entecavir be added to the list as an additional treatment option for chronic Hepatitis B. We feel that it would be appropriate to evaluate both telbivudine and entecavir in relation to current standard treatments. There is no head-to-head data for these two new agents, as lamivudine is presently the standard treatment agent for chronic Hepatitis B. Liver transplantation may also be considered an alternative treatment option for advanced liver disease patients. Defining "best alternative care" is difficult due to the many variables associated with chronic Hepatitis B treatment and disease progression, and widely differing protocols from hospital to hospital.	Comments noted. Following discussion at the scoping workshop, it was agreed that these treatments should be appraised separately through the STA process to facilitate the timely production of guidance. Liver transplantation is considered as the option in decompensated liver disease. This appraisal focuses on adults with compensated liver disease. Comment noted. See section 2.2.3.1 of the Guide to Methods of Technology Appraisal.
Outcomes	Royal College of Pathologists	No comment	Noted
	Roche	The outcomes suggested encompass clinical factors of treatment success; however the weighting to each especially in the context of 'e' antigen positive versus antigen negative disease should be discussed. The appraisal should also consider the definition of 'treatment failure', as different clinical studies had varying criteria. The outcomes could also be categorised into 'active treatment' - where the goal is seroconversion or 'suppression' - where the long term clinical goal is viral load suppression and prevention of ongoing liver damage.	Comments noted. As much as there are subtle differences in the definition of treatment failure, the broad meaning does not change as long as this is clearly specified in the clinical trial protocols.
	Royal College of Nursing	None	Noted

Section	Consultees	Comments	Action
	British Association for Sexual Health (BASHH)	None	Noted
	British Association for the Study of the Liver	Yes	Noted
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted
	Novartis	Yes, we agree, but would suggest adding predictors of outcome as an important criterion/tool in ensuring successful Hepatitis B treatment. Current evidence shows that the magnitude of early viral suppression with antiviral nucleoside analogues influences subsequent efficacy outcomes (i.e. the outcome measures already listed in the draft scope). Such measures will allow clinicians to modify treatment in the short term, increasing the likelihood of achieving the most favourable outcome in the long term.	Comments noted.
Economic analysis	Royal College of Pathologists	No comment	Noted
	Roche	None	Noted
	Royal College of Nursing	no clear on time horizon	Noted
	British Association for Sexual Health (BASHH)	long term consequenses including economic consequences rather than short term benefits should be examined for lamivudine monotherapy	Comments noted.
	British Association for the Study of the Liver	Appropriate	Noted
	British Association for the Study of the Liver Nurse Forum	None	Noted

Section	Consultees	Comments	Action
	British Infection Society	None	Noted
	Novartis	Yes, we agree (no change needed).	Noted
Other considerations	Royal College of Pathologists	No comment	
	Roche	The appraisal may also consider advice for clinicians who choose not to treat certain patients and thus which criteria should be used in these patients for follow-up and when to implement treatment. The use of liver biopsies in managing patient care should be considered and also the increased cost in doing so.	Comments noted. Watchful waiting is appropriately done for patients with chronic hepatitis B and treatment is often initiated with evidence of liver disease obtained through biopsies.
	Royal College of Nursing	None	Noted
	British Association for Sexual Health (BASHH)	See above	Noted
	British Association for the Study of the Liver	None	Noted
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted
	Novartis	None that we want to add.	Noted
Questions for consultation	Royal College of Pathologists	The answer is "Yes"	Noted
	Roche	None	Noted
	Royal College of Nursing	None	Noted
	British Association for Sexual Health (BASHH)	See above	Noted
	British Association for the Study of the Liver	N/A	Noted

Section	Consultees	Comments	Action
	British Association for the Study of the Liver Nurse Forum	Telbivudine should be appraised alongside other treatments for chronic hepatitis B in a multiple technology appraisal.	Following discussion at the scoping workshop, it was agreed that these treatments should be appraised separately through the STA process to facilitate the timely production of guidance. *Following a search for information relevant to this appraisal (TA96) and the recent referral of the Single Technology Appraisals for entecavir for (chronic) hepatitis B and telbivudine for (chronic) hepatitis B the Institute proposes that the decision to review the original guidance is deferred until February 2009. At this point we are likely to know the outcome of the appraisals of entecavir and telbivudine. We will then look again at the evidence base to ascertain the need for a review of the guidance.*
	British Infection Society	None	Noted.

Section	Consultees	Comments	Action
	Novartis	Considering the current treatment strategies and variety of drugs used, we agree with NICE's proposal that telbivudine should be appraised alongside other treatments for chronic Hepatitis B in a multiple technology appraisal (MTA). This new agent needs to be compared to several other existing treatment options, thus an MTA is more appropriate. Moreover we believe that one set of guidelines covering all treatment options for Hepatitis B would be more appropriate for clinicians as well as less confusing to the NHS. Since NICE intends to review Guidance No 96 for Hepatitis B (chronic) -adefovir dipivoxil and pegylated interferon alpha-2a- in February 2007, we suggest that telbivudine (and entecavir) be included in this review. In summary, one comprehensive guidance document will facilitate implementation of the recommendations.	Following discussion at the scoping workshop, it was agreed that these treatments should be appraised separately through the STA process to facilitate the timely production of guidance. *Following a search for information relevant to this appraisal (TA96) and the recent referral of the Single Technology Appraisals for entecavir for (chronic) hepatitis B and telbivudine for (chronic) hepatitis B the Institute proposes that the decision to review the original guidance is deferred until February 2009. At this point we are likely to know the outcome of the appraisals of entecavir and telbivudine. We will then look again at the evidence base to ascertain the need for a review of the guidance.*
Additional comments on the draft scope.	Royal College of Pathologists	No comment	Noted
	Roche	None	Noted
	Royal College of Nursing	None	Noted
	British Association for Sexual Health (BASHH)	None	Noted

Section	Consultees	Comments	Action
	British Association for the Study of the Liver	None	Noted
	British Association for the Study of the Liver Nurse Forum	None	Noted
	British Infection Society	None	Noted
	Novartis	No additional comments.	Noted

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit	Novartis	Yes	Noted
Current or proposed marketing authorisation	Novartis	Confidential information removed	Noted

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

- British National Formulary
- NHS Quality Improvement Scotland
- Foundation for Liver Research
- Gilead Sciences Limited
- Bury PCT
- British Pain Society
- Welsh Assembly