National Institute for Health and Clinical Excellence

Tenofovir disoproxil fumarate for the treatment of hepatitis B

Comments received on the draft scope

Comment 1: The draft remit

Section	Consultee	Comment	Action
Appropriateness	Hepatitis B Foundation UK	As liver cancer is increasing due to the impact of viral hepatitis bothe B and C then it is highly appropraite that this topic is refered to NICE	Comment noted
Appropriateness	Gilead Sciences	Tenofovir disoproxil fumarate (TDF) is an appropriate topic to refer to NICE. TDF is currently used by HIV/ID clinicians in HIV/HBV coinfected patients and as a result of experience and available data there is an impetus to use TDF in HBV mono infected patients. Furthermore, in clinical trials TDF has shown superiority over adefovir, one of the most commonly used drugs to treat HBV monoinfection.	Comment noted
Appropriateness	The Foundation for Liver Research	Yes, but value of Tenofovir needs to be related to that of the increasing list of anti HBV viral agents available, including Entecavir and Telbivudine which are already under appraisal by NICE.	Following consultation it was agreed that this technology should be appraised through the STA process. All relevant comparators will be considered.
Appropriateness	British Association for Sexual Health and HIV (BASHH)	this is an important exercise but should take place as part of the review of all hep b drugs	Following consultation it was agreed that this technology should be appraised through the STA process. All relevant comparators will be considered.

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Appropriateness	BASHH	it is also needed s many physicians on the basis of recent data may feel this is the time to switch from 3tc therapy to an alternative therapy including dual therapy	Comment noted
Appropriateness	Department of Health (DOH)	This is certainly an appropriate topic for referral to NICE, who have undertaken, or are in the process of undertaking, appraisals on four other oral viral suppressive agents active against hepatitis B replication (with others to come).	Comment noted
Appropriateness	Bristol Myers-Squibb	Long term data on the clinical effectiveness/efficacy and resistance is important for any appraisal of drugs for hepatitis B. Indeed, a minimum of 2 years of data was available for both of the hepatitis B drugs currently being appraised by NICE. The clinical efficacy and resistance data available for tenofovir is likely to be available only for one year. Therefore, we would suggest that this appraisal is delayed until such time that longer term data is available so as to ensure a consistent approach in this clinical area.	During consultation the majority view was that an appraisal of this technology is appropriate at this time.
Wording	Hepatitis B Foundation UK	YES	Comment noted.
Wording	Gilead Sciences	The wording of the draft remit and draft scope is appropriate.	Comment noted
Wording	BASHH	yes	Comment noted
Wording	Bristol Myers-Squibb	The title of the draft remit should include the word 'chronic' and read as 'Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B'.	The final remit has now been received and the scope has been amended accordingly.
Timing Issues	Hepatitis B Foundation UK	There are young mostly male patients who have developed resistance to all other therapies available And a timely appraisal may mean that their infection does not proceed to liver damage and or liver cancer and end stage liver disease	Comment noted

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Timing Issues	BASHH	this is an important exercise but should take place as part of the review of all hep b drugs	Following consultation it was agreed that this technology should be appraised through the STA process. All relevant comparators will be considered.
Timing Issues	BASHH	it is also needed as many physicians on the basis of recent data may feel this is the time to switch from 3tc therapy to an alternative therapy including dual therapy	Comment noted
Timing Issues	Gilead Sciences	An expedited review of tenofovir disoproxil fumarate may be warrented on a clinical and therapeutic basis, in order to provide more timely guidance for its use.	Comment noted
Timing Issues	The Foundation for Liver Research	Clinical factors - there are already occasions to use Tenofovir rather than Lamivudine or Adefovir. Combination of two anti HBV viral agents is increasingly being considered and is particularly important with HIV coinfected subjects. So there is in my view urgency to proceed with this appraisal.	Comment noted. It was agreed at the scoping workshop that HIV co-infected patients should not be included because they were not in the registration trials for tenofovir and the course of hepatitis B disease is different for co-infected individuals.
Additional Comments	Gilead Sciences	The product name, Viread, has been spelt incorrectly	The scope has been amended accordingly.

Comment 2: The draft scope

Section	Consultee	Comment	Action
Background information	Hepatitis B Foundation UK	You state "The prevalence of chronic hepatitis B is estimated at between 0.2% and 0.3% of the UK general population (an estimated 106,800 to 160,200 cases in England and Wales). It is estimated that there are between 7,000 and 7,700 new cases of chronic hepatitis B in England and Wales each year." The estimated prevalence appears to be based on figures in the Department of Health's (2002) Getting Ahead of the Curve: A Strategy for Infectious Diseases. These figures are now out of date since they do not take account of the recent enormous increase in migrants from countries of intermediate and high chronic hepatitis B virus (HBV) prevalence. In Rising Curve: Chronic Hepatitis B Infection in the UK, Hepatitis B Foundation UK estimates that there are around 326,000 people with chronic HBV infection in the UK (November 2007).	The prevalence information in the scope has been amended accordingly.
Background information	Gilead Sciences	In the report 'Rising Curve - Chronic Hepatitis B Infection in the UK' published by the Hepatitis B Foundation in November 2007, the number of people in the UK with Chronic HBV infection was estimated at 325,000.	The prevalence information in the scope has been amended accordingly
Background information	BASHH	i think a summary of the toxicity data should be included	The scoping document only provides a very brief summary of the condition and its management.
Background information	BASHH	no mention of hiv has been mentioned where there is most evidence for the long term efficacy and toxicity of tenofovir for hepatitis b	It was agreed at the scoping workshop that this patient population should not be included because they were not in the registration trials for tenofovir and the course of hepatitis B disease is different for co-infected individuals.

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Background information	DOH	We feel that the meaning of "HBeAg negative chronic hepatitis" should be more clearly defined. In our view, not all individuals who are chronically infected with hepatitis B (and are HBeAg negative) will have a poor prognosis or have a 8-10% progression rate to cirrhosis.	The scoping document only provides a very brief summary of the condition and its management.
Background information	DOH	In our opinion, the majority of the "new cases" of chronic hepatitis B in England and Wales each year will not derive from infections acquired in the UK, but will be established chronic infections in those, migrating to the UK from countries with a higher prevalence of hepatitis B. We feel that these are likely to have been acquired by mother to baby (vertical) transmission or by horizontal transmission during early childhood, rather than through adult risk behaviours.	The background section of the scope has been amended.
Background information	Bristol Myers-Squibb	In general, the background is appropriate. However, there are differences from the wording of the remit used in Entecavir's final scope. For example, the estimated prevalence of chronic hepatitis B (CHB) is stated as 0.2-0.3% with number of cases being between 106,800-160,200. Whereas in the entecavir scope, the estimates of prevalence were higher at 180,000 in the UK. Both of these figures may be underestimates, as the recent Rising Curve report estimated the prevalence to be 325,000 in the UK. It is unclear why different estimates have been used and whether this is a change of approach or an inconsistency. Further, the incidence of CHB between those who were infected within the UK and those infected abroad has not been distinguished as it was for Entecavir's scope. Please provide source of this data and why it deviates from Entecavir's scope.	The scope has been amended accordingly.
The technology/ intervention	Hepatitis B Foundation UK	YES	Comment noted

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The technology/ intervention	Gilead Sciences	Tenofovir disoproxil fumarate is a nucleotide analogue not a nucleoside analogue	The scope has been amended accordingly.
The technology/ intervention	BASHH	i think a summary of the toxicity data should be included	The scoping document only provides a very brief summary of the condition and its management
The technology/ intervention	BASHH	no mention of hiv has been mentioned where there is most evidence for the long term efficacy and toxicity of tenofovir for hepatitis b	It was agreed at the scoping workshop that this patient population should not be included because they were not in the registration trials for tenofovir and the course of hepatitis B disease is different for co-infected individuals
Population	Hepatitis B Foundation UK	Patients tend to develop resistance to hepatitis B anti-viral therapy and so there will be a group of patients at any given time for whom another therapy is vital as they will have developed resistance to all other that are on other	Comment noted
Population	Gilead Sciences	Considering the subgroups HBeAg-positive and HBeAg-negative disease seperately is appropriate.	Comment noted
Population	Gilead Sciences	HIV/HBV coinfected patients should be considered as a separate group.	It was agreed at the scoping workshop that this patient population should not be included because they were not in the registration trials for tenofovir and the course of hepatitis B disease is different for co-infected individuals
Population	Gilead Sciences	When comparing data it should be ensured that baseline histology and viral loads are taken into account when comparing outcomes.	Comment noted

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Population	The Foundation for Liver Research	One group of patients not included are those who had a liver tranpslant and in whom recurrence of HBV has to be prevented by long-term antiviral drug therapy.	The scope now specifies that If evidence allows, the appraisal will seek to identify subgroups of individuals for whom the technology is particularly clinically and cost-effective
Population	The Foundation for Liver Research	. HIV coinfected subjects present a particularly difficult group and should be included in the appraisal.	It was agreed at the scoping workshop that this patient population should not be included because they were not in the registration trials for tenofovir and the etiology of hepatitis B is different for co-infected individuals
Population	BASHH	hiv should be considered seperately and may fall outside of the remit of this guidance (since Tenofovir is also used as an anti-HIV agent)	It was agreed at the scoping workshop that this patient population should not be included because they were not in the registration trials for tenofovir and the course of hepatitis B disease is different for co-infected individuals
Population	BASHH	Patients failing lamivudine/telbivudine/adefovir/entacavir mono-therapies should be considered seperately	The scope now specifies that if evidence allows, the appraisal will seek to identify subgroups (e.g. people with …..treatment resistant disease…) of individuals for whom the technology is particularly clinically and cost- effective

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Population	BASHH	Cirrhotic patients/patients with advanced liver disease i.e. de-compensated disease/post-transplant patients should also be considered	The scope now specifies that if evidence allows, the appraisal will seek to identify subgroups of individuals for whom the technology is particularly clinically and cost-effective
Population	DOH	Given the use of tenofovir in the treatment of HIV infection, could you please consider its place in treating patients with HIV/hepatitis B co-infection.	It was agreed at the scoping workshop that this patient population should not be included because they were not in the registration trials for tenofovir and the course of hepatitis B diseaseis different for co-infected individuals
Population	Bristol Myers-Squibb	The consideration of the HBeAg-positive and HBeAg-negative patients separately in an appraisal relating to CHB is appropriate. However, an important sub-group to consider is treatment resistant patients, as the treatment pathway and costs/outcomes differ from treatment-naïve patients.	Comment noted. The scope now specifies that if evidence allows, the appraisal will seek to identify subgroups (e.g. people with …..treatment resistant disease…) of individuals for whom the technology is particularly clinically and cost-effective
Comparators	Hepatitis B Foundation UK	Yes these are the other therapies available but resistance is an issue and prescribing choice is limited by this	Comment noted.
Comparators	Gilead Sciences	Interferon alfa 2a and interferon alfa 2b are rarely used for the treatment of HBV and it may be inappropriate to use these as standard comparitors	Comment noted. It was agreed at the scoping workshop that although these drugs are rarely used in clinical practice, they are licensed to treat chronic hepatitis B and therefore should be included.

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Comparators	BASHH	clearly this will be compared with adefovir bit also should be compared with other single agent therapies .the use of truvada should be discussed although ftc- emtricitabine -is not licensed for hepatitis b	Comment noted. It was agreed at the scoping workshop that travada and emtricitabine were not valid comparators because they are rarely used to treat chronic hepatitis B in clinical practice and they are not licenced for chronic hepatitis B.
Comparators	DOH	In our view, the most obvious comparators are the other four oral agents (lamivudine, adefovir, entecavor and telbivudine), rather than the interferons (as the guidance suggests).	It was agreed at the scoping workshop that interferons are are licensed to treat chronic hepatitis B and therefore should be included
Comparators	Bristol Myers-Squibb	The comparators stated are standard treatments, except for interferon alfa-2a and 2b as they are not commonly used in treatment practice in the UK. It is not possible to describe one of these treatments as 'best' alternative care' as choice of therapy depends on population being treated (i.e. treatment naïve, treatment-resistant, HBeAg positive or HBeAg negative).	Comments noted. Comment noted. It was agreed at the scoping workshop that although these drugs are rarely used in clinical practice, they are licensed to treat chronic hepatitis B and therefore should be included
Outcomes	Hepatitis B Foundation UK	The issue of restisance should be covered	The outcome measure – development of viral resistance is included in the scope.
Outcomes	Gilead Sciences	A definition of virological response (HBV DNA) is required. Undetectable viral load may be the most appropriate definition (<400 IU/ml).	It was agreed at the scoping workshop that it would be innappropriate to define viral response at the scoping stage of the appraisal, but it was acknoledged that most of the identified trials would probably used <400 IU/ml.

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Outcomes	BASHH	Yes Transplantation should be considered an outcome measure	Comments noted. Following consultation, transplantation was not included as an outcome in the scope. However transplantation may be considered in the economic modelling of lifetime costs and consequences of treating chronic hepatitis B
Outcomes	DOH	We feel that these are generally appropriate; the development of viral resistance being particularly important.	Comment noted
Outcomes	DOH	We also feel however, that survival may be difficult to assess in the shorter term.	Though the clinical trials may not report survival, it remains an important secondary outcome measure for chronic hepatitis B. Furthermore, survival is key to economic modelling of lifetime costs and consequences of treating chronic hepatitis B
Outcomes	Gilead Sciences	These outcomes are consistent with that of Entecavir's final scope and would capture the most important health-related benefits. .	Comment noted
Outcomes	Gilead Sciences	However, survival is not an endpoint generally used in chronic hepatitis B trials and may not be appropriate in this context	Though the clinical trials may not report survival, it remains an important secondary outcome measure for chronic hepatitis B. Furthermore, survival is key to economic modelling of lifetime costs and consequences of treating chronic hepatitis B.
Economic analysis	Hepatitis B Foundation UK	This drug is needed as soon as possible so they a population of young (mostly men) can control their viral load and resume work and contribute to GDP	Comment noted

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Economic analysis	Gilead Sciences	Although a time horizon for the economic evaluation reflecting the chronic nature of hepatitis B is appropriate, it may also be helpful to conduct a separate analysis at 1, 3 and 5 years given the rapidly evolving nature of the field and the availability of an increasing number of therapies in the area.	Comment noted
Economic analysis	BASHH	appropriate The economical analysis may want to take into account progression to hepatic transplant and the costs associated with this.	Comments noted
Economic analysis	Bristol Myers-Squibb	As resistance rates with existing hepatitis B drugs has been shown to rise over time, caution should be exercised in extrapolating outcomes such as resistance from 1 yr data for economic modelling purposes.	Comment noted
Equality	Hepatitis B Foundation UK	Most of those who have viral hepatitis will have been born abroard or their mother was born abroad. Many will be migrant workers. Without a range of treatment these peole will not be offered an equal health care	Comment noted. The appraisal committee as part of its legal obligations will take into account the need to eliminate unlawful discrimination and promote equality of oportunity when making recommendations.
Equality	BASHH	should be aware that adefovir and tenofovir are both made by Gilead and the potential impact on pricing of tenofovir being passed, whether positively or negatively, on both hepatitis and hiv care	Comment noted
Other considerations	Gilead Sciences	The appraisal should consider the timing of the intervention (for example, is it appropriate for patients to undergo a biopsy prior to receiving treatment)	Comment noted

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Other considerations	BASHH	toxicity	The scope specifies that an outcome to be considered is adverse affects of treatment
Other considerations	BASHH	pregnancy and women of child bearing age- tenofovir is presently not reccomended in european guidelines for women who wish or are pregnant	Comment noted
Other considerations	DOH	In our view, given the potential risks of antiviral resistance to these various agents, the question of using these drugs sequentially (as opposed to combination therapy) requires very careful consideration, since - in theory at least - the former could lead to the emergence of possible multiple drug resistant strains.	Comment noted (see other considerations section)
Other considerations	Bristol Myers-Squibb	To ensure consistency with other ongoing NICE appraisals, the use of tenofovir in populations co-infected with hepatitis C, hepatitis D or HIV needs to be considered as separate sub-groups. This is not explicit in Tenofovir's scope but is explicit in the entecavir and telbivudine STAs and TA96. Please clarify if these co-infected populations will be considered in this appraisal.	It was agreed at the scoping workshop that this patient population should not be included because they were not in the registration trials for tenofovir and the course of hepatitis B disease is different for co-infected individuals
Additional comments	Hepatitis B Foundation UK	It would be helpful if NICE Referenced its background material so that we could check from whence the facts are gleaned.We as a patient group and indeed manufactures are oblidged to do just that.	Comment noted.

Section	Consultee	Comment	Action
Additional comments	DOH	Given the issues about resistance to antiviral therapy for hepatitis B, we wonder whether you are aware of a Conference, Resistance to Antiviral Therapies for Hepatitis B and C Virus, organised by - amongst others - the European Association for the Study of the Liver (EASL), the American Association for the Study of the Liver (AASLD) etc. The conference is to be held in Paris on 14 -16 February 2008, and includes sessions on the molecular development of HBV resistance to all five oral agents currently under discussion; treatment indications and efficacy, definitions of treatment endpoints, treatment failure and resistance and on the management and prevention of HBV resistance - all of which, in our view, seem to be pertinent to these discussions. The preliminary timetable can be found on: www.easl.ch/hepatitis-conference/ -	Comment noted

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Additional comments	Health Protection Agency	The HPA recognises that Tenofovir is a potent drug used successfully and safely for a number of years in the treatment of HIV. The HPA believes that should the Department of Health instruct the National Institute of Clinical Excellence (NICE) to move forward with the appraisal, then NICE should consider the use of Tenofovir as a first line drug of choice for the treatment of Hepatitis B, although this must not be as a monotherapy. Combined nucleoside/nucleotide therapy has to be considered as the principle therapy of choice to avoid the risk of developing viruses with stable, resistance driven mutations. Currently for Hepatitis B the available treatments consist of drugs only targeting the viral polymerase and the HPA recognises the increasing number of Hepatitis B patients harbouring viruses with drug driven polymerase mutations, rendering these treatments ineffective. The HPA has developed data showing that drug induced polymerase mutations also affect antigenicity of Hepatitis B Surface Antigen which may potentially hamper immunisation efficacy.	Comments noted (see other considerations section). The Institute can only issue guidance within marketing authorisation for the technology.
Questions for consultation	DOH	We welcome the consultation question regarding appropriate combinations regimens.	Comment noted
Questions for consultation	Bristol Myers-Squibb	There is no current evidence to support the use of Tenofovir in combination therapy. As such, it will not be appropriate to consider combination regimens with Tenofovir.	Comments noted.
Questions for consultation	Bristol Myers-Squibb	There is evidence of renal impairment and bone problems with the use of Tenofovir and it may not be suitable to use Tenofovir in populations with renal and bone problems.	Comments noted.