

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Proposed Health Technology Appraisal**

**Tenofovir alafenamide for treating chronic hepatitis B**

**Draft scope (pre-referral)**

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of tenofovir alafenamide within its marketing authorisation for treating chronic hepatitis B.

**Background**

Hepatitis B is an infectious disease of the liver caused by the hepatitis B virus (HBV). HBV is transmitted through exposure to infected blood (mainly through contaminated needles) and sexual contact. It is also transmitted from mother to infant during, or soon after, birth. Infection with HBV may present as hepatitis B 'e' antigen (HBeAg) positive or HBeAg negative according to whether HBeAg is expressed. The presence of HBeAg is typically associated with higher rates of viral replication and therefore increased infectivity.

The majority of people infected with HBV during adulthood make a full recovery and acquire immunity from future infection. Less than 5% of infected adults will develop chronic hepatitis B, defined as viraemia and hepatic inflammation that persists for more than 6 months after acute infection with HBV<sup>1</sup>. About 20% of people with chronic hepatitis B will develop cirrhosis over 10-20 years<sup>2</sup>. Cirrhosis can progress to become 'decompensated', where the remaining liver can no longer compensate for the loss of function. There is an increased risk of hepatocellular carcinoma among people with chronic hepatitis B and cirrhosis<sup>3</sup>.

In 2002 it was estimated that about 180,000 people in the UK had chronic hepatitis B, with numbers rising up to 326,000 in recent times due to people migrating to the UK from areas with high chronic hepatitis B prevalence<sup>4</sup>. There are about 7,700 new cases of chronic hepatitis B each year.

The aim of treatment is to prevent cirrhosis, hepatocellular carcinoma and liver failure. Current treatment options for the initial treatment of adults with chronic hepatitis B include peginterferon alfa-2a (NICE TA96), entecavir (NICE TA153) and tenofovir disoproxil (NICE TA173). The HBeAG status influences treatment decisions and response. [NICE clinical guideline 165](#) incorporates these recommended technologies and offers guidance on the sequence that they should be used. Lamivudine is also used in clinical practice to treat chronic hepatitis B.

**The technology**

Tenofovir alafenamide (brand name unknown, Gilead Sciences) is a nucleotide analogue reverse transcript inhibitor (NtRTI). It is a prodrug of

tenofovir, designed to be stable in plasma and then converts into tenofovir once inside cells. It is administered orally.

Tenofovir alafenamide does not currently have a marketing authorisation in the UK for treating chronic hepatitis B. It has been studied in clinical trials compared with tenofovir disoproxil, for treating adults with HBeAG positive and negative chronic hepatitis B.

NICE TA173 recommends tenofovir disoproxil for treating chronic hepatitis B. In TA173, tenofovir disoproxil was considered cost-effective compared with other treatments recommended by NICE and/or used in clinical practice. Given that tenofovir alafenamide and tenofovir disoproxil are both prodrugs of tenofovir, a technology appraisal including the other treatments as comparators is not considered necessary. Therefore, this appraisal of tenofovir alafenamide for treating chronic hepatitis B will focus on a direct comparison with tenofovir disoproxil only.

<b>Intervention(s)</b>	Tenofovir alafenamide
<b>Population(s)</b>	<ul style="list-style-type: none"> <li>• People with HBeAG positive chronic hepatitis B</li> <li>• People with HBeAG negative chronic hepatitis B</li> </ul>
<b>Comparators</b>	Tenofovir disoproxil
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• HBeAg seroconversion rate</li> <li>• HBsAg seroconversion rate</li> <li>• virological response (HBV-DNA level)</li> <li>• histological improvement (inflammation and fibrosis)</li> <li>• biochemical response (e.g. ALT levels)</li> <li>• development of viral resistance</li> <li>• time to treatment failure</li> <li>• overall survival</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>

<p><b>Other considerations</b></p>	<p>If evidence allows, the following subgroups will be considered:</p> <ul style="list-style-type: none"> <li>• treatment history</li> <li>• people with and without cirrhosis</li> <li>• people with advanced liver disease</li> <li>• people who are intolerant to or ineligible for interferon treatment</li> </ul> <p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
<p><b>Related NICE recommendations and NICE Pathways</b></p>	<p>Related Technology Appraisals:</p> <p>Tenofovir disoproxil for the treatment of chronic hepatitis B (2009). NICE Technology Appraisal 173. Guidance on static list</p> <p>Telbivudine for the treatment of chronic hepatitis B (2008). NICE Technology Appraisal 154. Guidance on static list</p> <p>Entecavir for the treatment of chronic hepatitis B (2008). NICE Technology Appraisal 153. Guidance on static list</p> <p>Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (2006). NICE Technology Appraisal 96. Guidance on static list</p> <p>Appraisals in development (including suspended appraisals)</p> <p>Entecavir and tenofovir disoproxil fumarate for the treatment of chronic hepatitis B in adults with decompensated liver disease (Appraisal suspended).</p> <p>Related Guidelines:</p> <p>Hepatitis B (chronic): diagnosis and management. NICE guideline 165 (June 2013) Review date TBC.</p> <p>Related Public Health Guidance:</p> <p>Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012). NICE public health guidance 43 Review date December 2016</p> <p><a href="https://www.nice.org.uk/guidance/ph43">https://www.nice.org.uk/guidance/ph43</a></p> <p>Related Quality Standards:</p>

	<p>Hepatitis B (2014). NICE quality standard 65.  <a href="http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp">http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp</a></p> <p>Related NICE Pathways:  NICE Pathway: Hepatitis B (Chronic). Pathway created: September 2015.  <a href="http://pathways.nice.org.uk/pathways/hepatitis-b-chronic">http://pathways.nice.org.uk/pathways/hepatitis-b-chronic</a>  <a href="http://pathways.nice.org.uk/">http://pathways.nice.org.uk/</a></p>
<p><b>Related National Policy</b></p>	<p>NHS England (2014) Commissioning intentions 2015/16 for prescribed specialised services  <a href="https://www.england.nhs.uk/wp-content/uploads/2014/10/comms-intents-2015-16.pdf">https://www.england.nhs.uk/wp-content/uploads/2014/10/comms-intents-2015-16.pdf</a></p> <p>NHS England Manual (2014) for prescribed specialised services 2013/2014. Section 65:  <a href="http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf">http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf</a></p> <p>NHS England (2013) NHS Standard Contract – specialist liver disease service (2013)  <a href="https://www.england.nhs.uk/wp-content/uploads/2013/06/e03-speci-paedi-liver.pdf">https://www.england.nhs.uk/wp-content/uploads/2013/06/e03-speci-paedi-liver.pdf</a></p> <p>NHS England (2013) NHS Standard Contract – for hepatobiliary and pancreas  <a href="https://www.england.nhs.uk/wp-content/uploads/2013/06/a02-hepto-pancreas-adult.pdf">https://www.england.nhs.uk/wp-content/uploads/2013/06/a02-hepto-pancreas-adult.pdf</a></p> <p>Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 2 - 4.  <a href="https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf">https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf</a></p>

### Questions for consultation

What are the clinical characteristics of the population who would receive tenofovir alafenamide?

Is the proposed approach of appraising tenofovir alafenamide compared with tenofovir disoproxil only appropriate? If not, what other treatments should be included as comparators for tenofovir alafenamide?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations' appropriate?

Are there any other subgroups of people in whom tenofovir alafenamide is expected to be more clinically effective and cost effective or other groups that should be examined separately? For example, should subgroups be included based on co-infection with hepatitis C virus (HCV), hepatitis D virus (HDV) or HIV?

Where do you consider tenofovir alafenamide will fit into the existing NICE pathway, [Hepatitis B \(Chronic\)](#)?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which tenofovir alafenamide is licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider tenofovir alafenamide to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of tenofovir alafenamide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>)

### References

1. World Health Organisation (2015) Guidelines for the prevention, care and treatment of person with chronic hepatitis B infection. Accessed April 2016
2. NHS England (2014) Hepatitis B Factsheet. Accessed April 2016
3. Oakes K (2014) Chronic hepatitis B, part 1: hepatitis B: prevalence and pathophysiology. *Nursing Times*; 110: 7, 12-16.