# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Multiple Technology Appraisal

## Entecavir and tenofovir disoproxil fumarate for the treatment of chronic hepatitis B in adults with decompensated liver disease

## Draft scope

### Remit/appraisal objective

To appraise the clinical and cost effectiveness of entecavir and tenofovir disoproxil fumarate within their licensed indications for the treatment of chronic hepatitis B in adults with decompensated liver disease.

### Background

Hepatitis B is an infectious disease of the liver caused by the hepatitis B virus (HBV). It is transmitted through blood to blood contact (for example through sharing of blood-contaminated needles by drug users) and sexual contact. It is also transmitted from mother to infant during, or soon after, birth. Infected individuals develop an acute infection, which may or may not result in symptoms. The majority of those infected during adulthood make a full recovery and acquire immunity from future infection. Only about 2-10% 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. In contrast almost 100% of infected neonates and about 50% of infected young children will develop chronic hepatitis B if infected with HBV.

Chronic hepatitis B can lead to liver disease, including cirrhosis (where scarring, fibrosis and irregular bumps replace smooth liver tissue). Liver disease can be compensated (where residual liver function is retained) or decompensated (where liver function is lost and the liver fails). Clinical and laboratory information are used to determine disease severity and the level of decompensation. In addition, classification systems such as the Child-Pugh score, can assess the prognosis of people with liver disease, and determine the necessity of liver transplantation. Generally, patients with a Child-Pugh score greater or equal to 7 (out of a possible score of 15) are considered to have decompensated liver disease.

In 2002, approximately 180,000 people in the UK were estimated to be living with chronic hepatitis B and there are between 7,000 and 7,700 new cases of chronic hepatitis B each year..Since then, there has been a significant increase in migration to the UK from countries of medium to high HBV prevalence, and it is estimated there could now be over 325,000 people in the UK with chronic HBV infection. Approximately 20% of people with untreated chronic hepatitis B with compensated liver disease will decompensate over 5 years. If untreated, the survival of patients with decompensated liver disease is poor (only 14-35% of people will be alive at 5 years). People with

decompensated disease may also develop serious complications, including ascites, encephalopathy and oesophageal varices.

There is no NICE guidance for the treatment of chronic hepatitis B in people with decompensated liver disease. Current treatment options for this indication which have a UK marketing authorisation include lamivudine (an oral nucleoside analogue reverse transcriptase inhibitor) and adefovir dipivoxil (an oral nucleotide analogue reverse transcriptase inhibitor). These agents act by inhibiting the viral DNA polymerase responsible for HBV replication. They can be given either as a circumscribed course of treatment or as long-term viral suppressive therapy. People with advanced liver disease will require liver transplantation if their disease is not controlled by antiviral therapy.

## The technologies

Entecavir

Entecavir (Baraclude, Bristol-Myers Squibb) is an oral nucleoside analogue which works by inhibiting the viral DNA polymerase responsible for hepatitis B virus replication, without inhibiting human cellular polymerases.

Entecavir does not currently have a UK marketing authorisation for the treatment of chronic hepatitis B in patients with decompensated liver disease. Clinical studies for this indication in patients either previously untreated, or refractory to lamivudine, are currently in progress.

Entecavir has a UK marketing authorisation for the treatment of chronic HBV infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate (Viread, Gilead Sciences) is an oral nucleotide analogue. It works by blocking the enzyme reverse transcriptase, which is responsible for HBV replication.

Tenofovir disoproxil fumarate does not have a UK marketing authorisation for the treatment of chronic hepatitis B in patients with decompensated liver disease. It is being studied in a three arm clinical trial comparing tenofovir disoproxil, emtricitabine plus tenofovir disoproxil fumarate, and entecavir in adults with decompensated liver disease.

It has a UK marketing authorisation for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

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| **Intervention(s)** | • Entecavir<br>• Tenofovir disoproxil fumarate |
| **Population(s)** | Adults with chronic hepatitis B with decompensated liver disease. |
| **Comparators** | • Entecavir and tenofivir disoproxil fumarate, within their licensed indications, will be compared with each other<br>Entecavir and tenofovir disoproxil fumarate will be compared with:<br>• Lamivudine<br>• Adefovir dipivoxil<br>• Lamivudine plus adefovir dipivoxil |
| **Outcomes** | The outcome measures to be considered include:<br>• virological response (HBV-DNA)<br>• time to loss of virological response<br>• biochemical response (for example ALT, bilirubin, albumin and prothrombin time)<br>• development of viral resistance<br>• development of complications (for example jaundice, ascites, portal hypertension, oesophageal varices, haematemesis, encephalopathy)<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective. |

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| **Other considerations** | Guidance will only be issued in accordance with the marketing authorisation.<br><br>If evidence allows, the appraisal will consider sequential use of antiviral drugs and combination therapy.<br><br>If evidence allows, subgroups by treatment-resistant disease, time to transplant and time to surgical management of hepatocellular carcinoma (HCC) will be considered. If evidence allows, HBeAg-positive and HBeAg-negative disease will be considered separately.<br><br>In line with previous guidance, this MTA will not specifically consider people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or HIV. |
| **Related NICE recommendations** | Related Technology Appraisals:<br><br>Technology Appraisal 96, Feb 2006, 'Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B'. Review date March 2012.<br><br>Technology Appraisal 153, Aug 2008, 'Entecavir for the treatment of chronic hepatitis B'. Review date March 2012.<br><br>Technology Appraisal 154, Aug 2008, 'Telbivudine for the treatment of chronic hepatitis B'. Review date March 2012.<br><br>Technology Appraisal 173, July 2009, 'Tenofovir disoproxil fumarate for the treatment of hepatitis B' Review date March 2012. Review date March 2012 |

Have the most appropriate comparators for the treatment of chronic hepatitis B in adults with decompensated liver disease been included in the scope? Are the comparators listed routinely used in clinical practice?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?

Do you consider the technology 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 the technology 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