This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.
Clevudine (Levovir) for hepatitis B

Target group

• Chronic hepatitis B.

Technology description

Clevudine (Levovir) is an oral, synthetic pyrimidine nucleoside analogue in development for the treatment of hepatitis B viral (HBV) infection. The drug inhibits hepatitis B virus DNA synthesis by causing deformation of the chain polymerisation geometry. Clevudine is administered 30mg once daily.

Innovation and/or advantages

Clevudine may have more potent activity against HBV than adefovir.

Developer

Pharmasset

Availability, launch or marketing dates, and licensing plans:

In phase III clinical trials.

Relevant guidance

• NICE technology appraisal in development. Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B. Expected May 20091.
• NICE technology appraisal. Entecavir for the treatment of chronic hepatitis B. 20082.
• NICE technology appraisal. Telbivudine for the treatment of chronic hepatitis B. 20083.
• NICE technology appraisal. Hepatitis B (chronic) - adefovir dipivoxil and pegylated interferon alpha-2a adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. 20064.
• British HIV Association (BHIVA) guideline. HIV and chronic hepatitis: co-infection with HIV and hepatitis B virus infection. 20045.

Clinical need and burden of disease

Chronic hepatitis B is defined as persistence of HBV infection for more than six months6. HBeAg positive chronic hepatitis B occurs during the early phases of chronic HBV infection and is characterised by extremely high HBV replication and persistently or intermittently increased aminotransferase levels. HBeAg negative chronic hepatitis B, represents a later phase in the course of chronic HBV infection and is a potentially severe and progressive form of chronic liver disease with very rare spontaneous remissions, frequent progression to cirrhosis and increased risk of the development of hepatocellular carcinoma7.

The World Health Organization (WHO) estimates that in the UK the prevalence of chronic hepatitis B infection is 0.3% of the general population (an estimated 160,200 cases in England and Wales)8,9. It is estimated that there are between 7,000 and 7,700 new cases of chronic hepatitis B in England and Wales each year4,10.

Existing comparators and treatments

Chronic carriers of hepatitis B virus with abnormal liver function tests should be considered for antiviral therapy. The aim is to suppress viral replication and facilitate
seroconversion. The choice of treatment is a matter of debate. Current options are only effective in around 40% of patients and they are often associated with limited efficacy, poor tolerability or resistance problems. A review of three studies indicates that 24% of patients are lamivudine-resistant after one year of treatment, rising to 30%, 49% and 66% over years two, three and four\(^a\).

The current treatment options for chronic hepatitis B are:

- Lamivudine, an oral nucleoside analogue reverse transcriptase inhibitor.
- Interferon alfa (IFN\(\alpha\)) and peginterferon alfa-2a (pegIFN\(\alpha\)) [intravenous or subcutaneous].
- Adefovir dipivoxil, an oral nucleotide reverse transcriptase inhibitor (effective in lamivudine-resistant, and IFN\(\alpha\)/pegIFN\(\alpha\)-resistant chronic hepatitis B).
- Entecavir, an oral nucleoside analogue DNA polymerase and reverse transcriptase inhibitor, licensed for the treatment of HBV with compensated liver disease.
- Telbivudine, an oral L-nucleoside analogue DNA polymerase inhibitor.

### Efficacy and safety

<table>
<thead>
<tr>
<th>Trial code</th>
<th>Study 305 (CI-PSI-5628-06-305): HBeAg positive; clevudine vs adefovir; phase III.</th>
<th>Study 306 (CI-PSI-5628-06-306): HBeAg negative; clevudine vs adefovir; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Pharmasset</td>
<td>Pharmasset</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Location</td>
<td>US, Canada, Brazil, Europe (including UK) Australia, New Zealand, Asia.</td>
<td>US, Canada, Brazil, Europe (including UK) Australia, New Zealand, Asia.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, double-blind, controlled.</td>
<td>Randomised, double-blind, controlled.</td>
</tr>
<tr>
<td>Participants in trial</td>
<td>n=376; &gt;16 years; chronic hepatitis B HBeAg positive; newly diagnosed. Randomised to adefovir 30mg or clevudine 30mg once-daily.</td>
<td>n=480; &gt;16 years; chronic hepatitis B HBeAg negative; newly diagnosed. Randomised to adefovir 30mg or clevudine 30mg once-daily.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Treatment for 48 weeks, monitoring for 96 weeks.</td>
<td>Treatment for 48 weeks, monitoring for 96 weeks.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Undetectable HBV DNA (less than 300 copies/mL) and normal liver enzymes at 48 weeks.</td>
<td>Undetectable HBV DNA (less than 300 copies/mL) and normal liver enzymes at 48 weeks.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Liver histology, hepatitis B e-antigen (eAg) seroconversion, HBV hepatic (cccDNA), eAg and surface antigen (sAg).</td>
<td>Liver histology, hepatitis B e-antigen (eAg) seroconversion, HBV hepatic (cccDNA), eAg and surface antigen (sAg).</td>
</tr>
</tbody>
</table>

---

\(^a\) Expert opinion
outcome

Secondary outcomes  Undetectable HBV DNA (<300 copies/mL) and normal liver enzymes (alanine aminotransferase [ALT]).

Key results  Median changes in HBV DNA from baseline were -4.25 and -0.48 log_{10} copies/mL at week 24 in the clevudine and placebo group respectively (p<0.0001). Viral suppression in the clevudine group was sustained after withdrawal of therapy with 3.11 log_{10} reduction at week 48. At week 24 and 48, 92.1% in the clevudine group and 16.4% in the placebo group had undetectable serum HBV DNA levels by PCR assay test (<300 copies/mL). 74.6% and 33.3% achieved ALT normalisation in the clevudine and placebo groups respectively. ALT normalisation was maintained in the clevudine group during post-treatment follow-up.

Adverse effects  Clevudine was generally well tolerated.

---

### Estimated cost and cost impact

The cost of clevudine is currently not known. The monthly cost of current alternative treatments for chronic HBV infection is\(^b\):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Dose</th>
<th>Approximate monthly cost per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Zeffix (GSK)</td>
<td>100mg daily</td>
<td>£78</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Hepsera (Gilead)</td>
<td>10mg daily</td>
<td>£315</td>
</tr>
<tr>
<td>Interferon alpha (SC)</td>
<td>IntronA (Schering-Plough)</td>
<td>5-10 million IU 3 times per week</td>
<td>£259-£518</td>
</tr>
<tr>
<td></td>
<td>Roferon-A (Roche)</td>
<td>2.5-5 million IU/m² 3 times per week</td>
<td>£271-£542</td>
</tr>
<tr>
<td>PegInterferon alpha (SC)</td>
<td>Pegasys (Roche)</td>
<td>180 μg once weekly</td>
<td>£528</td>
</tr>
</tbody>
</table>

---

### Potential or intended impact – speculative

**Patients**

- Yes: Reduced morbidity
- Yes: Improved quality of life for patients and/or carers
- No: None identified

- No: Reduced mortality or increased survival
- No: None identified

- No: Quicker, earlier or more accurate diagnosis or identification of disease
- No: None identified

**Services**

- No: Increased use
- Yes: Service reorganisation required
- No: Staff or training required

- Yes: Decreased use
- No: None identified

**Costs**

- Yes: Increased unit cost compared to alternative: depends on comparative price.
- No: None identified

- Yes: Increased costs: more patients coming for treatment
- No: None identified

- No: New costs:
- Yes: Increased costs: capital investment needed

- No: Savings:
- No: Other:

---

\(^b\) British National Formulary No.55, March 2008.
References