

**REGIONAL DRUG AND THERAPEUTICS CENTRE
(NEWCASTLE)**

**THE USE OF ENTECAVIR IN THE
MANAGEMENT OF CHRONIC HEPATITIS B
INFECTION**

**Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH**

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ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

Subject	Date issued
The use of natalizumab in the management of multiple sclerosis	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma	June 2006
Bortezomib second-line in the management of multiple myeloma	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer (N)	March 2006
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Ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
Rituximab in combination with CVP chemotherapy for the management of follicular non-hodgkins lymphoma.	March 2006
Pemetrexed in the management of malignant pleural mesothelioma	February 2006
Pegvisomant in the management of acromegaly	January 2006
Ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
Teriparatide in the management of osteoporosis	July 2004
Adefovir dipivoxil for the treatment of chronic hepatitis B infection (N)	May 2004
An update on newer agents for the treatment of pulmonary hypertension	February 2004
Drotrecogin alfa (activated) in the management of severe sepsis (N)	December 2002
Agalsidase alfa and beta in the management of Fabry disease	July 2002
Carbamyl glutamate in the management of N-acetylglutamate synthetase deficiency	July 2002
Erythropoietin in the management of cancer related anaemia	July 2002
Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec®, STI-571), in the management of chronic myeloid leukaemia (N)	November 2001
Atypical antipsychotics in the management of dementia	June 2001
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
Verteporfin for age related macular degeneration	November 2000
Temozolomide for high grade gliomas (N)	May 2000
New drugs for rheumatoid arthritis (N)	May 2000

Ribavirin and interferon alfa for chronic hepatitis C (N)	March 2000
Low molecular weight heparins in venous thrombo-embolic disease	November 1999
Low molecular weight heparins in unstable coronary artery disease	November 1999
Octreotide	July 1999
Drug treatment of obesity (N)	July 1999
Interferon alfa in Hepatitis C (N)	May 1999
Interferon beta in MS (N)	May 1999 (update)
Topotecan for ovarian cancer (N)	December 1998 (update)
Somatotrophin for GHD in adults	December 1998 (update)
Paclitaxel in ovarian cancer (N)	December 1998 (update)
Interferon alfa for haematological malignancy	July 1998
Irinotecan for colorectal cancer (N)	July 1998
Antiretroviral therapy	July 1998
Topotecan for ovarian cancer (N)	July 1998
Dornase alfa for cystic fibrosis	July 1998 (update)
New drugs for Alzheimer's disease (N)	February 1998
Atypical antipsychotics in the management of schizophrenia (N)	February 1998
Somatropin for GHD in adults (N)	January 1998
Taxanes in breast cancer (N)	July 1997
Alglucerase for Gaucher's disease	July 1997 (update)

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by the presence of a **(N)** after the report name. Please refer to the NICE website to access the guidance for these agents/conditions.

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SUMMARY

- Hepatitis B is one of the most common infectious diseases in the world and up to 180,000 people in the UK suffer from chronic infection. Hepatitis B can lead to cirrhosis, liver failure and hepatocellular carcinoma (HCC) in 15-40% of chronically infected patients.
- Entecavir is a nucleoside analogue with antiviral activity against hepatitis B virus. It is licensed for the treatment of chronic (HBeAg-positive, HBeAg-negative and lamivudine resistant) hepatitis B infection in adults.
- Phase III randomised controlled trials have shown treatment with entecavir is superior to lamivudine in producing histological improvement, after 48 weeks of treatment in patients with HBeAg-positive, HBeAg-negative and lamivudine-refractory chronic hepatitis B infection.
- The most common adverse events with entecavir treatment are insomnia, headache, dizziness, somnolence, vomiting, diarrhoea, nausea, dyspepsia and fatigue. Post-launch studies will be scrutinised for any increase in malignancies in view of the results from carcinogenicity studies in rodents.
- Altogether the data demonstrate that there is no early safety signal for an increased rate of human cancer as a result of treatment with entecavir. However, the MHRA concluded that the long-term observational period is as yet too limited to exclude a carcinogenicity risk and close monitoring in long-term follow up studies is required.
- Entecavir may be used, within its licensed indications, as an alternative to adefovir dipivoxil for patients with compensated liver disease in whom:
 - Treatment with interferon alfa or peginterferon treatment has been unsuccessful, relapse occurs after initial treatment or treatment with either agent is not tolerated or contraindicated.
 - Lamivudine has been tried and not toleratedAdefovir dipivoxil is preferred in the treatment of lamivudine-resistant HBV infection
- Entecavir therapy should be initiated by a physician experienced in the management of chronic hepatitis B. Shared care arrangements may be suitable for patients who have been stabilised on treatment, where the GP is willing to participate and clear guidance around monitoring is provided.
- The cost of treating a patient with entecavir for 16 weeks is £1,411. This is considerably more expensive than treatment with lamivudine (£312) or adefovir dipivoxil (£1,176).
- Studies in patients with decompensated liver function and recurrent HBV post-transplantation are on-going.

BACKGROUND

Hepatitis B is a viral infection that can lead to cirrhosis, liver failure and hepatocellular carcinoma in 15-40% of chronically infected patients.¹ It is transmitted by sexual contact, through the use of infected blood and blood products, by reuse of contaminated needles and syringes, by vertical transmission from mother to child during, or soon after birth and by horizontal transmission among children.² Hepatitis B is one of the most common infectious diseases in the world and an estimated 180,000 people in the UK suffer from chronic infection (defined as viraemia that persists for more than six months after an acute infection).² The risk of chronic infection with hepatitis B virus depends on the initial response of the immune system,² which varies according to the age at which the infection is acquired. Almost 100% of neonates, and about 50% of young children, develop chronic hepatitis if infected with the virus.² In contrast only between 2 and 10% of people infected as adults go on to develop chronic hepatitis B.²

Natural history of chronic hepatitis B

Immunotolerant phase

This phase is usually seen in patients infected at birth or in early childhood. The hepatitis B virus (HBV) is present but the immune system does not actively fight it.² The virus replicates rapidly during this phase and the patient is highly infectious without overt clinical symptoms.² Hepatitis B viral load is high and hepatitis B 'e' antigen (HBeAg) is present but serum alanine aminotransferase (ALT) levels are normal.^{1,3} This phase usually lasts between two to four weeks in healthy adults but often can last for several decades in those infected neonatally or in early childhood.¹

Incubation

This period can range from 40-160 days (average of 60-90 days).²

Immunoreactive phase

During this phase the immune system starts to fight the virus with an associated increase in inflammation and hepatic necrosis. The HBV load increases and ALT and aspartate aminotransferase (AST) levels are persistently raised;² liver biopsy may show evidence of hepatic necrosis and inflammation.² On-going infection and inflammation can lead to progressive liver damage and cirrhosis (annual rate of progression to cirrhosis = 2-5.5%, cumulative 5 year rate = 8-20%).² The human body develops antibodies against the 'e' antigen of the virus (HBeAg seroconversion).² Among carriers with elevated ALT levels, the rate of clearance of HBeAg averages between 8% and 12% per annum; older age, higher ALT and HBV genotype B are associated with higher rates of spontaneous HBeAg clearance.³ The risk of disease progression in this seroconverted state is relatively low, with patients experiencing a relatively good quality of life.² This phase is referred to as the 'inactive HBsAg carrier state' because patients continue to express hepatitis B surface antigen (HBsAg).² The spontaneous HBeAg seroconversion rate is 5-10% per year (this varies between populations),² and most people remain in the inactive carrier state after seroconversion. Clearance of HBeAg, whether spontaneous or after antiviral therapy, reduces the risk of hepatic decompensation and improves survival.³

Moderate or high levels of persistent HBV replication, or reactivation of HBV replication following a period of quiescence, after HBeAg seroconversion leads to HBeAg-negative chronic hepatitis B (characterised by HBV DNA levels > 2,000 IU/ml and continued necroinflammation of the liver).³ Most patients with HBeAg-negative chronic hepatitis B harbour HBV variants with a mutation in the precore or core promoter region of the HBV genome.^{1,3} The infected hepatic cells do not secrete HBeAg and infection with this form of HBV is associated with a fluctuating condition and a poor prognosis.² Active disease is associated with either constantly raised ALT levels or an erratic pattern of ALT changes with 'flares' which resemble acute HBV infection and can be severe or even fatal.² Each year 8-10% of patients with HBeAg-negative HBV progress to cirrhosis of the liver and few achieve a lasting remission of their disease.²

HBsAg seroconversion

The development of antibodies against HBsAg, with clearance of HBsAg, occurs spontaneously in approximately 0.5-2% of people with chronic HBV infection in western countries.² Clearance of HBsAg is most likely to occur in the year following HBeAg seroconversion and signifies resolution of the chronic infection.²

Current treatment options

The aims of treatment are to suppress HBV replication, induce remission of liver disease and ultimately to prevent progression to cirrhosis and hepatocellular carcinoma.^{2,3} Parameters used to assess treatment response include normalisation of serum ALT, decrease in serum HBV DNA level, loss of HBeAg with or without the detection of anti-HBe, and improvement in liver histology.³

Four antiviral agents are currently available as treatments for hepatitis B infection.

Interferon alfa-2a and peginterferon alfa-2a exert their antiviral effects by inducing a state of resistance in cells, and modulating the immune system to neutralise viruses or eliminate virus infected cells.^{4,5} Peginterferon is derived by the addition of a polyethylene glycol group to interferon alfa-2a which slows the rate of absorption and excretion of interferon, in turn reducing fluctuations in serum levels.² The pegylated form is given by subcutaneous injection once a week compared with three or more times weekly for the unmodified form.² Treatment with peginterferon alfa-2a may be preferable to interferon alfa-2a.⁶ The use of these agents is limited by a response rate of less than 50% and relapse is frequent,⁶ treatment should be discontinued if there is no improvement after three to four months.² Both forms are licensed for the treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in patients with compensated liver disease (and evidence of viral replication, increased ALT and histologically verified liver inflammation or fibrosis).^{4,5} The use of interferon alfa-2a and peginterferon alfa-2a is generally contraindicated in decompensated liver disease^{4,5} but low doses can be used with great caution in such patients.⁶ Interferon alfa-2b is also licensed for the treatment of chronic hepatitis B.⁷

Lamivudine is a nucleoside analogue metabolised by both infected and uninfected cells to the active triphosphate derivative which acts as a substrate for HBV viral polymerase.⁸ The formation of further viral DNA is blocked by incorporation of lamivudine triphosphate into the chain.⁸

Lamivudine triphosphate does not interfere with normal cellular deoxynucleotide metabolism and has little effect on mammalian cell DNA content.⁸ It is licensed for the initial treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in patients with compensated liver disease (and evidence of viral replication, increased ALT and histologically verified liver inflammation or fibrosis).⁸ It is also licensed for use in patients with decompensated liver disease.^{6,8} In patients with HBeAg-positive hepatitis B virus, treatment with lamivudine is usually given until HBeAg seroconversion occurs or until HBsAg seroconversion.⁸ The optimum treatment duration for patients with HBeAg-negative hepatitis B virus is unknown, however treatment may be stopped after HBsAg seroconversion.⁸ Treatment is continued long-term in patients with decompensated liver disease.⁶ Emergence of resistance is the main problem with long-term treatment with lamivudine (> 60% of cases following three years of treatment).²

Adefovir dipivoxil is a nucleotide analogue that is converted to the active compound (adefovir diphosphate) in mammalian cells.⁹ Adefovir diphosphate is incorporated into HBV DNA resulting in termination of the viral DNA chain.⁹ It is licensed for use in patients with HBeAg-positive or HBeAg-negative chronic HBV with compensated or decompensated liver disease (and evidence of viral replication, persistently elevated serum ALT and histological evidence of active liver inflammation and fibrosis).⁹ The National Institute for Health and Clinical Excellence (NICE) have recommended the use of adefovir dipivoxil if treatment with interferon-alfa or peg-interferon alfa-2a is not tolerated, the response is unsatisfactory or a relapse occurs after successful initial treatment.² It is also recommended for use in combination with lamivudine where resistance to lamivudine is present or likely to occur.² Treatment with adefovir dipivoxil is continued long-term in patients with decompensated liver disease or cirrhosis.⁶

Entecavir (Baraclude[®] Bristol-Myers Squibb Pharmaceuticals Ltd) is licensed for the treatment of chronic HBV infection (HBeAg-positive and HBeAg-negative) in adults with compensated liver disease.¹⁰ Entecavir is another example of a nucleoside analogue with anti-viral activity against HBV. It is converted to the active form (entecavir triphosphate) which inhibits HBV replication at three different steps; the priming of the HBV DNA polymerase, reverse transcription of the negative strand HBV DNA from the pregenomic RNA, and synthesis of the positive strand HBV DNA.¹¹ This results in the termination of the viral DNA chain and cessation of further viral replication.¹¹ The purpose of this report is to evaluate the efficacy and safety of the nucleoside analogue entecavir for the treatment of chronic hepatitis B infection.

EFFICACY

Three randomised, controlled, phase III clinical trials have been published comparing treatment with entecavir and lamivudine in patients within distinct disease categories.

HBeAg-positive chronic hepatitis B

One 52 week double-blind, randomised, double-dummy trial compared entecavir (0.5 mg daily, n = 354) with lamivudine (100 mg daily, n = 355), in nucleoside-naïve patients.¹² All patients had HBeAg-positive chronic hepatitis B infection with compensated liver function defined as:

- bilirubin \leq 42.8 micromol/L.
- prothrombin time \leq 3 seconds longer than normal, or international normalised ratio (INR) \leq 1.5.
- serum albumin level \geq 30 g/L.
- no history of variceal bleeding or hepatic encephalopathy.

Patients with co-existing infection with hepatitis C, hepatitis D, human immunodeficiency virus (HIV), or other liver disease were excluded from this trial. Patients administered interferon alfa, thymosin (alpha), or antiretroviral agents with activity against HBV within 24 weeks before randomisation were also excluded. Patients were classed as nucleoside naïve if they received < 12 weeks treatment of lamivudine prior to being admitted to the trial.

The primary efficacy outcome measure was the proportion of patients with histological improvement defined as an improvement in the Knodell necroinflammatory score of greater than or equal to two points, with no worsening in the Knodell fibrosis score (Appendix 1), at week 48. Liver biopsy specimens were evaluated by a central, independent histopathologist who was unaware of each patient's treatment assignment, biopsy sequence and clinical outcome.¹² At baseline, 314 patients in each group had adequate baseline liver-biopsy specimens with a Knodell necroinflammatory score of greater than or equal to two at baseline which equates to 89% of the intention to treat (ITT) population. A further 67 patients were excluded due to the collection of biopsies at week 48 that could not be evaluated (n = 22 and 45 in the entecavir and lamivudine groups). At week 48, 226 patients (72%) in the entecavir group showed histologic improvement compared with 195 patients (62%) taking lamivudine (difference estimate = 9.9, 95% confidence interval [CI] 2.6 to 17.2, p = 0.009).¹³ The mean Knodell inflammatory score reduced from baseline in both groups by 3.8 and 3.5 points respectively.

Several other measures of disease severity and progression were used as planned secondary end points in this trial. Both groups showed a marked reduction in HBV DNA load (reflecting viral load). The mean change in HBV DNA from baseline was -6.9 log₁₀ copies/ml (\pm 2.0) with entecavir treatment compared with -5.4 log₁₀ copies/ml (\pm 2.6) with lamivudine (difference estimate -1.52, 95% CI -1.78 to -1.27, p < 0.001). Compared with 36% of the group receiving lamivudine, 67% of the entecavir group achieved a viral load < 300 copies/ml (p < 0.001). Similar proportions of patients in the entecavir and lamivudine groups showed an improvement in Ishak fibrosis score (Appendix 2) of 39% and 35%, respectively (p = 0.41).

HBeAg loss and seroconversion rates were similar in each of the treatment groups (21% of entecavir group and 18% of the lamivudine group, $p = 0.33$). Normalisation of ALT levels can also be used as a marker of treatment efficacy. In this trial 68% of patients in the entecavir group achieved an ALT level of < 1 times the upper limit of normal (ULN), compared with 60% of the group treated with lamivudine (difference estimate = 8.4, 95%CI 1.3 to 15.4, $p = 0.02$). The results are reported as a proportion of patients with adequate biopsies available at week 48 rather than a proportion of the ITT population or those with an adequate baseline biopsy. This may have allowed the introduction of bias to the results. At week 48, 74 patients in the entecavir group (21%) and 67 patients in the lamivudine group (19%) had a protocol-defined response (HBV DNA < 0.7 MEq per ml and HBeAg loss). These patients were followed up 24 weeks after the cessation of treatment where 61 patients in the entecavir group and 49 patients in the lamivudine group maintained this protocol defined response (17% and 14% of the ITT populations, respectively).

Lamivudine-refractory HBeAg-positive chronic hepatitis B

Treatment of patients with lamivudine-refractory HBeAg-positive chronic hepatitis has also been investigated ($n = 286$).¹³ One phase III, randomised, controlled trial compared high-dose entecavir (1 mg daily, $n = 141$) with lamivudine (100 mg daily, $n = 145$). Inclusion criteria specified on-going treatment with lamivudine and proven lamivudine-refractory disease with compensated liver function.

Lamivudine-refractory disease was defined as:

- persistently detectable HBV DNA after at least 36 weeks of treatment with lamivudine
- recurrence of detectable HBV DNA on two determinations (after achieving undetectable HBV DNA on lamivudine)
- recurrence and persistence of HBV replication after discontinuing lamivudine provided that lamivudine had been reintroduced and maintained ≥ 12 weeks prior to screening
- documented YMDD mutation and hepatitis B viraemia on lamivudine regardless of duration of therapy.

Patients co-infected with hepatitis C, hepatitis D or HIV, other liver disease or those treated with a nucleoside/nucleotide analogue with activity against hepatitis B virus other than lamivudine (> 12 weeks or given within six months prior to randomisation) were excluded from this trial. This study included two co-primary end points: histological improvement shown in patients at 48 weeks compared to baseline (defined as an improvement of greater than or equal to two points on the Knodell necroinflammation score and no worsening of fibrosis), and a composite end point of serum hepatitis B viral DNA < 0.7 MEq/ml and ALT $< 1.25 \times$ ULN. At baseline 124 patients (88% of ITT population) randomised to entecavir treatment were classed as having an evaluable biopsy specimen (Knodell necroinflammatory score \geq two). The corresponding figure in the lamivudine group was 116 patients, equating to 80% of ITT population. Of the entecavir subgroup, histological improvement was seen in 68 patients treated with entecavir compared with 32 patients in the lamivudine group ($p < 0.0001$).

Similarly, the composite end point was achieved in significantly more of the entecavir group (77 patients, 55% of ITT population) than the lamivudine group (6 patients, 4% of ITT population, $p < 0.0001$). The question of whether or not lamivudine is a suitable comparator in this trial population should be considered. The inclusion criteria for this trial stated the patients would have lamivudine-refractory chronic HBV and would therefore have been candidates for adefovir dipivoxil treatment following NICE guidance.

Secondary end points studied in this trial included the proportion of patients with HBV DNA < 300 copies/ml at week 48 (19% in the entecavir group compared with 1% in the lamivudine group, $p < 0.0001$) and ALT normalisation defined as $\leq 1.0 \times \text{ULN}$ (61% and 15% respectively, $p < 0.0001$). The mean \log_{10} change in HBV DNA from baseline, was $-5.11 \log_{10}$ copies/ml (± 2.23) compared with $-0.48 \log_{10}$ copies/ml (± 1.97) with lamivudine ($p < 0.0001$). The difference in the percentage of patients achieving HBeAg seroconversion was not statistically significant (8% and 3% respectively, $p = 0.06$). Within this study, two patients exhibited a confirmed virologic rebound during the first year of treatment due to emergence of an entecavir-resistant mutant viral strain.

HBeAg-negative chronic hepatitis B

A phase III, double-blind, randomised, controlled trial evaluated entecavir treatment in patients with HBeAg-negative chronic hepatitis B.¹⁴ Subjects received entecavir 0.5 mg daily ($n = 325$) or lamivudine 100 mg daily ($n = 313$) for a minimum of 52 weeks. The primary end point was the proportion of patients with histological improvement at week 48 compared with baseline (demonstrated by an improvement in histological biopsy results defined as an improvement by two or more points in the Knodell necroinflammatory score and no worsening in the Knodell fibrosis score). To allow assessment of histological improvement, an adequate biopsy specimen at baseline, and week 48, as well as a Knodell necroinflammatory score of greater than or equal to two were required ($n = 265$ and 250 in the entecavir and lamivudine groups). The published results are reported as a proportion of these subgroup populations rather than a proportion of the ITT population.

Histologic improvements were seen in 208 patients in the entecavir subgroup (70%) and 287 of patients in the lamivudine subgroup (61%, $p = 0.01$). However, the mean reduction in the necroinflammatory score was similar in both groups (3.9 and 3.2 respectively).

Secondary end points included the reduction of hepatitis B viral DNA to undetectable levels (90% of entecavir group, 72% of lamivudine group, $p < 0.001$) and ALT normalisation to the upper limit of normal or less (78% of entecavir group, 71% of lamivudine group, $p = 0.045$). The mean change in HBV DNA level from baseline was $-5.0 \pm 1.7 \log_{10}$ copies/ml with entecavir compared with $-4.5 \pm 1.9 \log_{10}$ copies/ml with lamivudine ($p < 0.001$).

The use of entecavir in combination with standard lamivudine therapy has been studied in one unpublished open-label trial ($n = 859$). The limited data from this complex cross-over trial suggest the combination of entecavir (1 mg daily) and lamivudine (100 mg daily) did not provide any additional benefit over entecavir monotherapy.¹⁰ It is currently recommended that lamivudine is discontinued when patients are switched to entecavir treatment to decrease the risk of entecavir resistance.³

ADVERSE EFFECTS

General adverse events

The most common adverse events with at least a possible relation to entecavir treatment were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%).¹¹

In a safety cohort of 2,399 patients 15 deaths have been reported (9 in entecavir groups). The overall incidence of serious adverse events was low at 5% in the entecavir treatment group compared with 8% in the lamivudine treatment group.¹⁰ The development of lactic acidosis in patients with chronic hepatitis B has been linked to treatment with nucleoside analogues. In the safety population there has been one reported case, which was deemed to be unrelated to treatment with entecavir.¹⁰ However, as this is a class effect, the risk of development of lactic acidosis cannot be ruled out and treatment should be discontinued if rapidly elevating ALT levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology occur.¹¹ There is a lack of clinical trial data for the use of entecavir in patients co-infected with human immunodeficiency virus (HIV) who are not receiving highly active anti-retroviral therapy (HAART).¹⁵ One case report details the selection of a HIV variant containing the M184V resistance substitution during entecavir treatment in a HIV/HBV co-infected patient who was not simultaneously receiving HAART. This information led to the European Medicines Agency (EMA) advising healthcare professionals that there appears to be a risk of developing HIV resistance with entecavir treatment in HIV/HBV co-infected patients not receiving HAART.¹⁵ Until reassuring data become available, the EMA recommend that entecavir should only be considered in this setting under exceptional circumstances.¹⁵

Resistance

Long-term treatment with lamivudine results in the emergence of lamivudine resistant infection in more than 60% of cases following three years of treatment.² Treatment with adefovir dipivoxil can lead to development of gene mutations in the hepatitis B virus, which in turn confers resistance to adefovir dipivoxil. The probability of developing these adefovir-associated resistance mutations in all patients has been estimated as 0% at 48 weeks and 25% at 240 weeks.⁹

Entecavir inhibits HBV replication at three different steps (the priming of the HBV DNA polymerase, the reverse transcription of the negative strand HBV DNA from the pregenomic RNA, and the synthesis of the positive strand HBV DNA) and has a similar method of action to adefovir. Data from clinical trials (duration \leq 96 weeks) have shown a relatively low incidence of entecavir resistance. In order to explore this further, a four year assessment of entecavir-resistance in nucleoside naïve patients and those with lamivudine resistant infection was conducted.¹⁶ The cumulative probability of a virologic breakthrough was 0.8% in nucleoside naïve patients and 39.5% in patients with lamivudine resistant infection.¹⁶ However, this data is based on relatively small numbers and is available only in abstract form and therefore cannot be fully evaluated.

Treatment of patients with HBeAg-negative, lamivudine-resistant chronic hepatitis B infection has not been studied.

Neoplasms

The key safety concern with entecavir relates to its possible carcinogenetic potential based on the findings in the rodent carcinogenicity studies.¹⁰

Overall, neoplasms occurred with similar frequency in both the pooled entecavir and lamivudine treatment groups (1.1% and 1.0%, respectively).¹⁰ The incidence rates were also of similar magnitude (8.5 and 7.8 per 1,000 patient-years of observation, respectively).¹⁰ As would be expected, the most common carcinoma in the overall patient population was hepatocellular carcinoma. The incidence rates (3.5 and 3.4 per 1,000 patient-years of observation, respectively) were consistent with published data in this patient group.¹⁰ There were a small number of additional non-hepatocellular carcinoma malignancies reported in the treatment groups, none of which occurred with elevated frequency in the entecavir treatment group (excluding skin cancer which occurred in four patients in the entecavir group and one patient in the lamivudine group).¹⁰ Most of the patients presented with risk factors for cancer.¹⁰

Two epidemiological studies (commissioned by the manufacturer of entecavir) assessed the incidence rates of cancer and liver cancer in patients infected with chronic hepatitis B virus.¹⁰ In a retrospective study conducted in the United States, patients with chronic hepatitis B infection showed a significant increase in the incidence rate of malignancy compared with non-infected people (9.70 per 1,000 person-years, relative risk of 2.59, 95% CI 2.19 to 3.03).¹⁰ The other study, carried out in Taiwan, showed a comparative increase in rate of malignancy in HBsAg-positive patients (6.53 per 1,000 person-years), which represented a relative increase of 1.7 (95% CI 1.4 to 1.9).¹⁰ The rate of hepatocellular carcinoma in infected patients was increased in both study cohorts as would be expected; however the incidence rate differed (US study = 4.95 per 1,000 person-years, 95% CI 3.95 to 6.11; Taiwan study = 3.60 per 1,000 person-years, 95% CI 3.06 to 4.21). As these patient populations were followed up for 8-11 years the results are not comparable with the entecavir study population.¹⁰

Within the safety cohort, 28 malignant neoplasms have so far been identified (as of December 2004).¹⁰ Nineteen of these patients were treated with entecavir (1.3% of treatment group, n = 1,497) compared with nine in the lamivudine group (1.0% of treatment group, n = 899). This translates into an incidence rate of 8.8 per 1,000 person-years with entecavir and 7.4 per 1,000 person-years with lamivudine. When the malignancies were evaluated, there were no demonstrable differences in incidence rates between the two treatments. The EMEA concluded that 'altogether the data demonstrate that there is no early safety signal for an increased rate of human cancer as a result of treatment with entecavir. However, the observational period is too limited to exclude a carcinogenicity risk and close monitoring in long-term follow up studies is required'.¹⁰

DOSAGE, ADMINISTRATION AND COST

Entecavir is an oral therapy which is licensed for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis.¹¹

In nucleoside-naïve patients the licensed dose is 0.5 mg once daily with or without food. Patients with lamivudine-refractory disease require a higher dose of 1 mg once daily taken on an empty stomach.¹¹ The optimal duration of treatment is currently unknown.

However, the summary of product characteristics (SPC) recommends that treatment discontinuation may be considered where HBeAg seroconversion occurs in patients with HBeAg-positive hepatitis B (confirmed by HBeAg loss and HBV DNA loss with anti-HBe detection on two consecutive serum samples at least three to six months apart) or until HBsAg seroconversion or there is loss of efficacy.¹¹ In patients with HBeAg-negative disease, treatment should be administered at least until HBsAg seroconversion occurs or there is loss of efficacy.¹¹ With prolonged treatment (> two years) regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.¹¹

Entecavir is not currently licensed for the treatment of patients with decompensated liver disease, or in patients co-infected with hepatitis C, hepatitis D or HIV.

Comparative cost of treatment

TABLE 1 Treatment	Route	Dose	Cost of 16 weeks treatment*
Interferon alfa-2a (Roferon A [®])	SC	9 million IU three times a week	£2,169
Peginterferon alfa-2a (Pegasys [®])	SC	180 micrograms once a week	£2,113
Interferon alfa 2b (Intron A [®])	SC	10 million IU three times a week	£2,074
Entecavir (Baraclude [®])	Oral	0.5mg or 1mg daily	£1,411
Adefovir dipivoxil (Hepsera [®])	Oral	10 mg daily	£1,176
Lamivudine (Zeffix [®])	Oral	100 mg daily	£312

*Excluding VAT. Data from MIMS March 2007

PLACE IN TREATMENT

Adefovir dipivoxil and pegylated interferon alfa-2a were assessed by the National Institute of Health and Clinical Excellence (NICE) in February 2006.² Adefovir dipivoxil was recommended in the following situations:

- Where treatment with interferon alfa or peginterferon treatment has been unsuccessful, relapse occurs after initial treatment, or treatment with either agent is not tolerated or contraindicated.
- Where lamivudine has been tried and either not tolerated or resistance has developed, or where lamivudine resistance is likely to develop rapidly and development of lamivudine resistance is likely to have an adverse outcome (e.g. if a flare of the infection is likely to precipitate decompensated liver disease)

Entecavir is being considered for inclusion on the NICE work-programme at the time of writing. It may be seen as an alternative to adefovir dipivoxil in adults with chronic hepatitis B (HBeAg-positive and HBeAg-negative) in whom prolonged oral treatment is required.

As with adefovir dipivoxil it should not normally be given before treatment with lamivudine. It should be reserved as monotherapy for patients with decompensated liver disease in whom:

- Treatment with interferon alfa or peginterferon treatment has been unsuccessful, relapse occurs after initial treatment or treatment with either agent is not tolerated or contraindicated.
- Lamivudine has been tried and not tolerated

Unlike lamivudine and adefovir dipivoxil, entecavir is not licensed for the treatment of patients with decompensated liver disease. The optimum length of treatment with entecavir is not known and sustainability of response after discontinuation of treatment has still to be fully established.

A recent economic analysis conducted in the United States compared entecavir treatment with lamivudine and adefovir dipivoxil.¹⁷ The study assessed the use of entecavir and adefovir as 'salvage' therapy (i.e. treatment after resistance to lamivudine has developed). The results demonstrated that adefovir dipivoxil was more effective and less expensive than entecavir in this situation.¹⁷

The Scottish Medicines Consortium (SMC) has accepted entecavir for use within NHS Scotland in accordance with its licensed indications. The cost-utility analysis provided by the manufacturer estimated that entecavir treatment was associated with an incremental cost per Quality Adjusted Life Years (QALY) of £12,000 and £15,000 for treatment naïve HBeAg positive and HBeAg negative patients, respectively.¹⁸

Prescribers should also be aware of local commissioning group decisions which may influence the place of entecavir in the treatment of chronic hepatitis B infection.

ARRANGEMENTS FOR PRESCRIBING

Entecavir therapy should be initiated by a physician experienced in the management of chronic hepatitis B.¹⁰ Hepatic and renal function tests should be conducted on a regular basis with dosage adjustments recommended for patients with renal impairment.¹¹ Patients should also be regularly monitored for virological and serological parameters associated with hepatitis B. If treatment is discontinued, regular monitoring of hepatic function should continue for at least six months thereafter.¹¹ Monitoring of the patient's response to treatment and determination of treatment duration should be undertaken by the initiating physician. The use of shared care arrangements for patients receiving treatment for chronic hepatitis B was endorsed by recent NICE guidance on peginterferon alfa-2a and adefovir dipivoxil.² It is reasonable, therefore, to employ this type of arrangement for patients treated with entecavir who have been stabilised on treatment, where the GP is willing to participate and clear guidance around monitoring is provided (shared care arrangements should be in place prior to initiation of prescribing).

FUTURE DEVELOPMENTS

Studies in patients with decompensated liver function in whom treatment with entecavir is being compared with adefovir dipivoxil are on-going.¹⁰

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APPENDICES

APPENDIX 1. KNODELL NECROINFLAMMATORY AND FIBROSIS INDEX¹⁹

Histology Activity Index (HAI) – Knodell Index

Periportal ± Bridging Necrosis	Score	Intralobular Degeneration and Focal Necrosis	Score	Portal Inflammation	Score	Fibrosis	Score
None	0	None	0	No portal inflammation	0	No fibrosis	0
Mild piecemeal necrosis	1	Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in 1/3 of lobules or nodules)	1	Mild (sprinkling of inflammatory cells in <1/3 of portal tracts)	1	Fibrous portal expansion	1
Moderate piecemeal necrosis (involves <50% of the circumference of most portal tracts)	3	Moderate (involvement of 1/3-2/3 of lobules or nodules)	3	Moderate (increased inflammatory cells in 1/3-2/3 of portal tracts)	3	Bridging Fibrosis (portal-portal or portal-central linkage)	3
Marked piecemeal necrosis (involves >50% of the circumference of most portal tracts)	4	Marked (involvement of >2/3 of lobules or nodules)	4	Marked (dense packing of inflammatory cells in >2/3 of portal tracts)	4	Cirrhosis	4
Moderate piecemeal necrosis <i>plus</i> bridging necrosis	5						
Marked piecemeal necrosis <i>plus</i> bridging necrosis	6						
Multilobular necrosis	10						
Total HAI (Knodell Score) = __/22							

Adapted from: Knodell RG, et al. Formulation and Application of a Numerical Scoring System for Assessing Histological Activity in Asymptomatic Chronic Active Hepatitis. *Hepatology* 1981;1(5):431-5

APPENDIX 2. ISHAK NECROINFLAMMATORY AND FIBROSIS INDEX¹⁹

Modified HIA grading – Ishak Necroinflammatory Index							
Periportal or Periseptal Interface Hepatitis (piecemeal necrosis) (A)	Score	Confluent Necrosis (B)	Score	Focal (spotty) Lytic Necrosis, Apoptosis, and Focal Inflammation* (C)	Score	Portal Inflammation (D)	Score
Absent	0	Absent	0	Absent	0	None	0
Mild (focal, few portal areas)	1	Focal confluent necrosis	1	One focus or less per 10x objective	1	Mild, some or all portal areas	1
Mild/moderate (focal, most portal areas)	2	Zone 3 necrosis in some areas	2	Two to four foci per 10x objective	2	Moderate, some or all portal areas	2
Moderate (continuous around <50% of tracts or septa)	3	Zone 3 necrosis in most areas	3	Five to ten foci per 10x objective	3	Moderate/marked, all portal areas	3
Severe (continuous around >50% of tracts or septa)	4	Zone 3 necrosis + occasional portal-central (P-C) bridging	4	More than ten foci per 10x objective	4	Marked, all portal areas	4
		Zone 3 necrosis + multiple P-C bridging	5				
		Panacinar or multiacinar necrosis	6				
Total Modified HAI = ___/18							
*Does not include diffuse sinusoidal infiltration by inflammatory cells.							
<i>Additional features which should be noted but not scored:</i> <ul style="list-style-type: none"> ▪ Bile-duct inflammation and damage ▪ Lymphoid follicles ▪ Steatosis, mild moderate or marked ▪ Hepatocellular dysplasia, large- or small-cell ▪ Adenomatous hyperplasia ▪ Iron or copper overload ▪ Intracellular inclusions (eg. PAS-positive globules, Mallory bodies) 						<i>Immunohistochemical findings</i> Information on viral antigens, lymphocyte subsets or other features, when available, should be recorded and may be semi-quantitatively expressed	

ISHAK FIBROSIS INDEX¹⁹

Modified Staging: architectural changes, fibrosis and cirrhosis*	Score
Change	
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3
Fibrous expansion of portal areas with marked bridging [portal to portal (P-P) as well as portal to central (P-C)]	4
Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6
*Additional features which should be noted but not scored: Intra-acinar fibrosis, perivenular ('chicken wire' fibrosis) and phlebosclerosis of terminal hepatic venules.	
Adapted from:	
<ol style="list-style-type: none"> 1. Ishak K, et al. Histological grading and staging of chronic hepatitis. <i>J Hepatol</i> 1995;22:696-699. 2. Knodell RG, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. <i>Hepatology</i> 1981;1(5):431-5 	

APPENDIX 3. SUMMARY OF MAJOR CLINICAL TRIALS OF ENTECAVIR.

Key: ALT - alanine aminotransferase; CT - controlled trial; DB - double blinded; DD - double dummy; DNA - deoxyribonucleic acid; HBsAg - Hepatitis B surface antigen; HBV - hepatitis B virus; HIV - human immunodeficiency virus; INR - international normalised ratio; MC - multi-centre; PCR - polymerase chain reaction; PT - prothrombin time; R - randomised; ULN - upper limit of normal; URTI - upper respiratory tract infection.

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Chang T-T et al. (BEHoLD A1463022) ¹²	DB, DD, R, CT, MC	Entecavir 0.5 mg once daily or lamivudine 100 mg once daily for a minimum of 52 weeks	354 355 received at least one dose of study drug However 357 patients were initially randomised to treatment with entecavir 358 patients to lamivudine.	HBsAg-positive men and women aged 16 and over, compensated liver function (bilirubin \leq 42.8 micromol/L), PT \leq 3 seconds longer than normal or INR \leq 1.5, serum albumin level \geq 3.0 g/dL. Detectable HBsAg for \geq 24 weeks before screening, evidence of chronic hepatitis on baseline liver-biopsy specimen obtained within 52 weeks before randomisation, evidence of HBV DNA by any commercial assay at least 4 weeks before screening, HBV DNA level of at least 3 MEq/ml at screening, serum ALT level 1.3 to 10.0 times the ULN at screening.	Co-infection with hepatitis C, hepatitis D or HIV, other liver disease, use of interferon alfa, thymosin (alpha) or antiviral agents with activity against HBV within 24 weeks before randomisation, prior lamivudine therapy (duration > 12 weeks), alpha fetoprotein level > 100 ng/ml, history of ascites requiring diuretics or paracentesis and previous treatment with entecavir. History of variceal bleeding or hepatic encephalopathy.	Proportion of patients with histological improvement defined as: \geq 2 point improvement in the Knodell necro-inflammatory score with no worsening in the Knodell fibrosis score at week 48 (relative to baseline).	340 patients treated with entecavir and 321 patients treated with lamivudine completed 52 weeks of treatment. In each group 314 had an adequate baseline biopsy and at week 48, biopsies from 292 and 269 could be evaluated. Primary endpoint- 226 patients (77%) on entecavir showed histologic improvement compared with 195 (72%) on lamivudine. Mean Knodell inflammatory scores were similarly reduced from baseline in both groups (3.8 with entecavir and 3.5 with lamivudine). Secondary outcomes: Ishak fibrosis score improvement: entecavir 39%, lamivudine 35% (p = 0.41). ALT level normalised: entecavir 68%, lamivudine 60% (p = 0.02). HBV DNA undetectable (< 300 copies/ml by PCR assay). Entecavir 236 (67%), lamivudine 129 (36%), p < 0.001. No significant difference in the number of patients with: <input type="checkbox"/> Loss of HBsAg (22% vs. 20%, p = 0.45) <input type="checkbox"/> HBsAg seroconversion (21% vs. 18%, p = 0.33) <input type="checkbox"/> HBsAg loss (2% vs. 1%, p = 0.52)	Most frequent adverse effects (number of patients not defined): Headache URTI Nasopharyngitis Cough Pyrexia Upper abdominal pain Fatigue Diarrhoea <small>(No specific data detailing incidence of these adverse events)</small> Discontinuation rate due to an adverse effect was significantly lower in the entecavir group (<1% vs. 3% in lamivudine group, p = 0.02).

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Lai CL et al. (BEHoLD - AI463027) ¹³	R, DB, CT, MC	Entecavir 0.5 mg once daily or lamivudine 100 mg once daily for a minimum of 52 weeks	296 287 received at least one dose of study drug	HBeAg-negative men and women aged 16 years and over, compensated liver function (bilirubin \leq 42.8 μ mol/L), PT \leq 3 seconds longer than normal or INR \leq 1.5, serum albumin level \geq 3.0 g/dL. Detectable HBsAg for \geq 24 weeks before screening, evidence of chronic hepatitis on baseline liver-biopsy specimen obtained within 52 weeks before randomisation, evidence of HBV DNA by any commercial assay at least 2 weeks before screening, undetectable HBeAg, detectable anti-HBe, serum HBV DNA \geq 0.7 MEq/ml at screening, serum ALT level 1.3 to 10.0 times the ULN at screening.	Co-infection with hepatitis C, hepatitis D or HIV, other liver disease, use of interferon alfa, thymosin (alpha) or antiviral agents with activity against HBV within 24 weeks before randomisation, prior lamivudine therapy (>12 weeks), alpha fetoprotein level >100 ng/ml, history of ascites requiring diuretics or paracentesis, previous treatment with entecavir. History of variceal bleeding or hepatic encephalopathy.	Proportion of patients with histologic improvement: defined as improvement by \geq 2 points in the Knodell necroinflammatory score and no worsening in the Knodell fibrosis score at week 48 (relative to baseline).	Week 48: Biopsy specimens obtained in 296 and 287 patients (entecavir and lamivudine groups respectively) Histologic improvement: entecavir - 208 patients (70%) lamivudine - 174 patients (61%), $p = 0.01$ Mean Knodell necroinflammatory score reduction: 3.9 - entecavir, 3.2 - lamivudine (from baseline). Secondary endpoints: Undetectable HBV DNA (<300 copies/ml by PCR assay): 90% of entecavir group, 72% of lamivudine group ($p < 0.001$) ALT normalisation ($\leq 1.0 \times$ ULN): 78% of entecavir group compared with 71% of lamivudine group ($p = 0.045$).	Mean exposure was 56 weeks for entecavir and 56 for lamivudine Figures are based on ITT population of entecavir ($n = 325$) and lamivudine ($n = 313$) groups respectively. Any adverse events: 246 (76%) and 248 (79%), $p = 0.30$ Serious adverse events: 21 (6%) and 24 (8%), $p = 0.64$ ALT (> 2 baseline and > 10x ULN); 3 (< 1%) and 5 (2%), $p = 0.50$ Discontinuation rates due to adverse events were not significantly different in the two groups (2% and 3%, $p = 0.44$). Other frequent adverse events (mostly mild to moderate severity): Headache URTI Upper abdominal pain Influenza Nasopharyngitis Dyspepsia Fatigue Back pain Arthralgia / myalgia Diarrhoea Insomnia Cough Nausea (No specific data detailing incidence of these adverse events)

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Sherman et al. (BEHoLD AI463026) 14	DB, DD, R, CT, MC	Entecavir 1 mg once daily or lamivudine 100 mg once daily for a minimum of 52 weeks	141 145 received at least one dose of study drug However, 147 patients were initially randomised to treatment with entecavir, 146 patients to lamivudine.	HBsAg-positive men and women > 16 years of age, receiving on-going lamivudine and refractory to that treatment, ALT levels 1.3 – 10 times the ULN, HBV DNA levels > 3.0 MEq/ml at screening. Compensated liver function with total serum bilirubin < 42.75 µmol/L, PT < 3 seconds longer than the normal control, INR < 1.5, serum albumin > 3.0 g/dL. Evidence of chronic hepatitis upon liver biopsy at screening or within 12 months of randomisation and following clinical evidence of incomplete response to lamivudine.	History of variceal bleeding, ascites requiring diuretics or paracentesis, encephalopathy. Coinfection with hepatitis C, hepatitis D or HIV, other forms of liver disease, prior therapy with a nucleos(t)ide analogue with activity against HBV other than lamivudine for > 12 weeks duration or given within 6 months prior to randomisation, use of interferon alpha or thymosin-alpha 1 within 6 months prior to randomisation, alpha-fetoprotein >100 ng/ml, prior treatment with entecavir.	2 co-primary endpoints: Histologic improvement: > 2 point decrease in the Knodell necroinflammatory score and no worsening of the Knodell fibrosis score on the week 48 liver biopsy specimen compared with baseline. Composite end point defined as serum HBV DNA < 0.7 MEq/mL, ALT < 1.25 times ULN at week 48.	Week 48: Biopsy specimens obtained in 124 and 116 patients (entecavir and lamivudine groups, respectively) Histologic improvement: entecavir - 68 patients (55%) lamivudine - 32 patients (28%) p < 0.0001. Mean Knodell necroinflammatory score reduction: entecavir – 3.0, lamivudine - 0.7 from baseline, Composite end point: entecavir - 77 patients (55%), lamivudine - 6 patients (4%), p<0.0001	Mean exposure to study therapy was 63 weeks for entecavir and 52 weeks for lamivudine. Entecavir and lamivudine adverse effects are reported respectively: Any adverse event: 85%, 81% Serious adverse event: 10%, 8% ALT flares (2x baseline and 10x ULN) : <1%, 11% Fatalities: <1%, 1% Other frequent adverse events (>10%) of patients in either group: URTI (18%, 11%) Increased ALT (4%, 10%) Headache Fatigue Upper abdominal pain Cough Nausea Nasopharyngitis Fewer entecavir-treated patients discontinued due to adverse events (1% compared with 7% in lamivudine group).