Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B

Technology appraisal guidance
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1 Guidance

This guidance was partially updated by NICE clinical guideline 165 in June 2013. See About this guidance for more information.

This guidance does not apply to people with chronic hepatitis B known to be co-infected with hepatitis C, hepatitis D or HIV.

1.1 Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications.

1.2 This recommendation has been replaced by recommendation 1.5.13 in NICE clinical guideline 165.

1.3 This recommendation has been replaced by recommendation 1.5.14 in NICE clinical guideline 165.

1.4 This recommendation has been replaced by recommendation 1.5.15 in NICE clinical guideline 165.
2 Clinical need and practice

2.1 Chronic hepatitis B is defined as viraemia and hepatic inflammation that persists for more than 6 months after acute infection with hepatitis B virus. Hepatitis B virus 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. The risk of chronic infection with hepatitis B virus depends on the nature of the immune response to the initial infection. This varies according to the age at which the infection is acquired. Almost 100% of neonates, and about 50% of young children, develop chronic hepatitis B if infected with hepatitis B virus. In contrast, only about 2–10% of people who are infected as adults go on to develop chronic hepatitis B.

2.2 The Department of Health estimates that about 180,000 people in the UK have chronic hepatitis B. There are about 7700 new cases of chronic hepatitis B each year. Of these, around 300 people were infected within the UK; the remainder (mainly immigrants to the UK) were infected abroad, generally in areas of high prevalence where the virus is frequently transmitted from mother to child.

2.3 People with active chronic hepatitis B are at increased risk of liver cirrhosis (scarring of the liver tissue that may progress to liver failure) and primary liver cancer (hepatocellular carcinoma).

2.4 The diagnosis of chronic hepatitis B is based on the presence of well-characterised serological markers in the blood. Hepatitis B viral DNA (HBV DNA) is present in both acute and chronic hepatitis B. Hepatitis B surface antigen (HBsAg) is a viral protein detectable in the blood in both acute and chronic infection. Chronic hepatitis B is defined as persistence of HBsAg for 6 months or more after acute infection. Hepatitis B 'e' antigen (HBeAg) is an indicator of viral replication, although some variant forms of the virus do not express HBeAg (see section 2.5.5 below). Active infection can be described as HBeAg-positive or HBeAg-negative according to whether HBeAg is secreted.

2.5 The natural history of chronic hepatitis B can be divided into phases, each of which may last many years.
2.5.1 **Immunotolerant phase.** People who are affected at birth or in early childhood initially enter an 'immunotolerant' phase during which the immune system does not actively fight the virus. The virus replicates rapidly during this phase, but the person usually has no symptoms. The person is highly infectious, and may infect other members of the family and community. This phase can last for many years before progressing to active disease.

2.5.2 **Incubation.** The incubation period for hepatitis B infection ranges from 40–160 days, with an average of 60–90 days.

2.5.3 **Active chronic hepatitis B.** The first stage of active disease involves a period of increasing inflammatory hepatic necrosis as the immune system begins to fight the virus. This stage of the disease is characterised by elevated levels of viral DNA in the blood, persistently raised levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and evidence of hepatic necrosis and inflammation on biopsy. The liver damage caused by infection and inflammation may eventually lead to cirrhosis of the liver. Progression to cirrhosis occurs at an annual rate of 2–5.5%, with a cumulative 5-year rate of progression of 8–20%.

2.5.4 **HBeAg seroconversion.** In people infected with an HBeAg-positive form of the virus, the next stage of the infection occurs when inflammation becomes sufficiently intense to cause lysis of infected hepatocytes. This produces a 'flare' of the disease with symptoms resembling acute hepatitis B, and leads to the development of antibodies against the 'e' antigen. This is referred to as 'HBeAg seroconversion'. The seroconverted disease state is associated with good quality of life and a relatively low risk of disease progression. It is referred to as the 'inactive HBsAg carrier state' because patients continue to express hepatitis B surface antigen (HBsAg). The spontaneous seroconversion rate is 5–10% per year, although this varies among populations. Once seroconversion has taken place, most people remain in the inactive HBsAg carrier state. However, increasing viraemia and recurrent hepatitis after seroconversion indicate the emergence of the HBeAg-negative strain of the virus.

2.5.5 **HBeAg-negative chronic hepatitis B.** In recent years a form of the virus that does not cause infected cells to secrete HBeAg has been discovered (sometimes called the 'precore mutant' strain). People can be infected with the so-called HBeAg-negative form of the virus from the beginning, or the viral mutation can emerge later in the course of infection in people initially infected with the
HBeAg-positive form of the virus. The prevalence of HBeAg-negative hepatitis varies geographically; it is more common in Asia and the Mediterranean region than in Northern Europe. Infection with HBeAg-negative chronic hepatitis B is associated with a fluctuating course and a poor prognosis. Active disease is associated with either persistent elevation of ALT or an erratic pattern of ALT changes with flare-ups resembling acute hepatitis B that can be severe or even fatal. Few patients with HBeAg-negative chronic hepatitis B achieve a lasting remission. Progression to cirrhosis of the liver has been estimated to occur in 8-10% of people with HBeAg-negative chronic hepatitis B each year.

2.5.6 **HBsAg seroconversion.** The development of antibodies against HBsAg, with clearance of HBsAg, occurs spontaneously in about 0.5–2% of people with chronic hepatitis B each year in western countries. In countries where hepatitis B is endemic, the rate is much lower – between 0.05 and 0.08% per year. Clearance of HBsAg is most likely to occur in the year following HBeAg seroconversion. It signifies resolution of the chronic infection. Variants of hepatitis B (known as ‘occult hepatitis B’) that are not associated with detectable HBsAg by current immunoassays have been recognised.

2.5.7 The aim of treatment is to prevent progression to cirrhosis or hepatocellular carcinoma. Treatment may be given as a finite course (circumscribed therapy) – with the intention of allowing the immune system to respond and control the infection without the need for further drug treatment – or as long-term viral suppressive therapy. Long-term therapy is needed if short-term therapy is unsuccessful.

2.5.8 The first drugs to be licensed for the treatment of chronic hepatitis B were alfa interferons. Interferons are natural proteins that activate the immune system in response to viral infection. Three recombinant interferon products have UK marketing authorisation for the treatment of chronic hepatitis B: IntronA (interferon alfa-2b, Schering-Plough), Roferon-A (interferon alfa-2a, Roche) and Viraferon (interferon alfa-2b, Schering-Plough). Interferon alfa-2a is usually given at a dose of 2.5–5 million units per square metre of body surface area by subcutaneous injection three times a week for 4–6 months. Interferon alfa-2b is given at a dose of 5–10 million units three times a week for 4–6 months. The side effects of interferons can be severe and this means that they are not suitable for long-term treatment in chronic hepatitis B. Interferons are contraindicated in decompensated liver disease. There are no data on long-term
maintenance therapy with an alfa interferon and the treatment is not licensed for this.

2.5.9 Lamivudine (Zeffix, GlaxoSmithKline) is a nucleoside reverse transcriptase inhibitor antiviral drug. The dose in adults is 100 mg per day. It can be given both as a circumscribed course of treatment or as long-term viral suppressive therapy. In HBeAg-positive chronic hepatitis B, treatment is usually given for a year with the aim of bringing about HBeAg seroconversion. In HBeAg-negative chronic hepatitis B, a circumscribed course of therapy is less likely to lead to long-term control of the infection, and long-term treatment is often needed. The main problem with long-term antiviral treatment is the emergence of resistance. Resistance to lamivudine occurs in more than 60% of cases after 3 years' treatment.
3 The technologies

Peginterferon alfa-2a

3.1 Peginterferon alfa-2a (Pegasys, Roche) has UK marketing authorisation for the treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in adults with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis. Peginterferons are formed by attaching strands of polyethylene glycol (PEG) to the interferon molecules. This slows the rate of absorption and excretion of interferon, reducing the fluctuations in serum level that occur with unmodified interferon. Peginterferons are administered once a week, compared with three or more times a week for the unmodified form.

3.2 Peginterferons have a range of adverse effects similar to those of interferons. These include influenza-like symptoms such as fever, chills, myalgias, arthralgias and headache, which are most likely to occur at the start of treatment and seldom require discontinuation of treatment. Depletion of platelets and white blood cells is common. Other adverse effects include depression, anxiety or emotional lability, which may be severe. Cardiovascular adverse effects include hypertension or hypotension, arrhythmias, oedema, myocardial infarction or stroke. Interferons are contraindicated in chronic hepatitis with decompensated cirrhosis of the liver. For full details of side effects and contraindications, see the ‘Summary of product characteristics’.

3.3 A prefilled syringe containing 180 micrograms of peginterferon alfa-2a costs £132.06 (excluding VAT, ‘British national formulary’, 50th edition [‘BNF’50]). The usual dose is 180 micrograms once a week. Costs may vary in different settings because of negotiated procurement discounts.

Adefovir dipivoxil

3.4 Adefovir is structurally related to the purine base adenine. It is converted intracellularly to the diphosphate, which inhibits the synthesis of hepatitis B virus DNA through competition for the enzyme reverse transcriptase and incorporation into the viral DNA. Adefovir is not well absorbed after oral administration so is given by mouth as the prodrug adefovir dipivoxil.
3.5 Adefovir dipivoxil (Hepsera, Gilead) has 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 ALT levels and histological evidence of active liver inflammation and fibrosis
- decompensated liver disease.

3.6 The most commonly reported adverse effects for adefovir dipivoxil are gastrointestinal effects including nausea, flatulence, diarrhoea and dyspepsia. Increases in serum creatinine are common but usually mild to moderate. However, cases of renal impairment and acute renal failure have been reported. For full details of side effects and contraindications, see the 'Summary of product characteristics'.

3.7 A pack containing 30 days' supply of adefovir dipivoxil 10 mg tablets costs £315.00 (excluding VAT, 'BNF'50). Costs may vary in different settings because of negotiated procurement discounts.
Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 **Clinical effectiveness**

Peginterferon alfa-2a

4.1.1 The Assessment Group found three randomised controlled trials investigating peginterferon alfa-2a in chronic hepatitis B. Two trials were in people with HBeAg-positive chronic hepatitis B, and the third was in people with HBeAg-negative chronic hepatitis B.

4.1.2 In HBeAg-positive chronic hepatitis B, the most useful measure of response is HBeAg loss or seroconversion because this signals transition to the inactive carrier state, which is associated with a relatively benign outcome. The rate of HBeAg seroconversion was reported in both studies of peginterferon alfa-2a in HBeAg-positive chronic hepatitis B.

4.1.3 One trial was an open-label study in which 194 participants were randomised to one of three doses of peginterferon alfa-2a or interferon alfa-2a. Treatment was for 24 weeks, and was followed by 24-weeks' treatment-free follow-up. The rate of HBeAg seroconversion was higher in the patients treated with peginterferon alfa-2a (32% for all three doses combined) than in patients treated with interferon alfa-2a (25%), but the difference was not statistically significant. ALT levels were also more likely to return to the normal range in the people treated with peginterferon alfa-2a (36% for all three doses combined compared with 25% for interferon alfa-2a). This difference was also not statistically significant. The only statistically significant difference between treatment and control in this trial was for the rate of 'combined response', defined as HBeAg loss, HBV DNA normalisation and ALT normalisation (24% for all three treatment doses combined compared with 12% for control, p = 0.036).

4.1.4 The second trial in patients with HBeAg-positive chronic hepatitis B was a comparison of peginterferon alfa-2a with lamivudine, in which 814 people were randomised to peginterferon alfa-2a plus placebo, peginterferon alfa-2a plus lamivudine, or lamivudine alone. The study was partially double blind in that
those who were receiving peginterferon alfa-2a were blinded as to whether they were receiving lamivudine. Treatment was for 48 weeks, and was followed by 24-weeks’ treatment-free follow-up. The rate of HBeAg seroconversion at week 72 was significantly higher in the patients treated with peginterferon alfa-2a plus placebo (32%) than in those treated with lamivudine alone (19%), \( p < 0.001 \). Addition of lamivudine to peginterferon alfa-2a did not improve the HBeAg seroconversion rate over peginterferon alfa-2a alone: the rate in the group that received both lamivudine and peginterferon alfa-2a was 27%.

Normalisation of ALT occurred in a higher proportion of the group taking peginterferon alfa-2a than of the group taking lamivudine alone (41% versus 28%, \( p = 0.002 \)). Again, adding lamivudine to peginterferon alfa-2a did not improve the response rate for this endpoint (ALT normalisation 39%).

4.1.5 In HBeAg-negative chronic hepatitis B, a major objective of treatment is suppressing viral replication and preventing progressive liver disease. In clinical trials these outcomes have usually been expressed in terms of decrease in the levels of HBV DNA found in the serum and ALT normalisation.

4.1.6 The only study of peginterferon alfa-2a in HBeAg-negative chronic hepatitis B was a three-way comparison of peginterferon alfa-2a plus placebo, peginterferon alfa-2a plus lamivudine, and lamivudine alone (\( n = 537 \)). Treatment was for 48 weeks and was followed by 24-weeks’ treatment-free follow up (72 weeks in total). The study had two predetermined primary measures of efficacy: the normalisation of ALT levels and the suppression of HBV DNA levels to less than 20,000 copies/ml. At week 72, the percentage with normalised ALT was significantly higher in the groups treated with peginterferon alfa-2a than in the lamivudine group (59% with peginterferon alfa-2a monotherapy and 60% for peginterferon alfa-2a plus lamivudine, versus 44% for lamivudine; \( p = 0.004 \) and \( p = 0.003 \) respectively). For the outcome of virological response (HBV DNA < 20,000 copies/ml) at week 72, the percentage of patients who had a response was significantly higher in the groups treated with peginterferon alfa-2a than in the lamivudine group (43% for peginterferon alfa-2a monotherapy and 44% for peginterferon alfa-2a plus lamivudine, versus 29% for lamivudine; \( p = 0.007 \) and \( p = 0.003 \) respectively).

4.1.7 Treatment-resistance mutations were detected in 32 people (18%) in the lamivudine group and one person (< 1%) in the peginterferon alfa-2a plus lamivudine group (\( p < 0.001 \)).
Adefovir dipivoxil

4.1.8 The assessment report included five randomised controlled trials of adefovir dipivoxil in chronic hepatitis B. Four of the studies were conducted in people with HBeAg-positive chronic hepatitis B and one was in people with HBeAg-negative chronic hepatitis B.

4.1.9 The largest study (n = 515) was a comparison of two doses of adefovir dipivoxil (10 mg and 30 mg) with placebo in people with HBeAg-positive chronic hepatitis B and compensated liver disease. The primary endpoint was histological improvement (defined in terms of a reduction in Knodell necroinflammatory score). Histological improvement was seen in 59% of patients in the adefovir dipivoxil 30 mg group, 53% of patients in the adefovir dipivoxil 10 mg group and 25% of patients in the placebo group (p < 0.001 for both comparisons with placebo). The HBeAg seroconversion rates were 14% for the adefovir dipivoxil 30 mg group, 12% for the adefovir dipivoxil 10 mg group and 6%, for the placebo group. The rates of ALT normalisation were 55% for the 30 mg, 48% for the 10 mg and 16% for the placebo group.

4.1.10 Another study (n = 59) investigated adefovir dipivoxil in people with HBeAg-positive chronic hepatitis B, genotypic evidence of lamivudine-resistance, raised ALT and a serum HBV DNA level of at least $10^6$ copies/ml despite ongoing treatment with lamivudine. The patients were randomised to adefovir dipivoxil 10 mg, lamivudine 100 mg, or the addition of adefovir dipivoxil to ongoing lamivudine treatment. The primary endpoint was time-weighted change from baseline in serum HBV DNA level. Reductions in this endpoint were seen in all recipients of adefovir dipivoxil. HBV DNA levels were 'undetectable' (< 1000 copies/ml) in 26% of patients receiving adefovir dipivoxil plus placebo, in 35% of patients receiving adefovir dipivoxil plus lamivudine, and in none of the patients receiving lamivudine plus placebo (p = 0.005). ALT was normalised in 53% of the adefovir dipivoxil plus lamivudine group and 47% of adefovir dipivoxil group, compared with 5% (1/19) of the lamivudine group (p = 0.001 and p = 0.004, respectively)

4.1.11 The remaining two studies in HBeAg-positive chronic hepatitis B investigated the combination of adefovir dipivoxil with lamivudine compared with lamivudine alone. One was in treatment-naive patients (n = 112) and the other was in patients with lamivudine resistance (n = 94). In the study in treatment-
naive patients (which was still ongoing at the time of this appraisal) there was no advantage in adding adefovir dipivoxil to lamivudine at 1 year in terms of virological, serological or biochemical outcome. However, there was a higher incidence of lamivudine-resistance mutations and viral breakthrough in the group that received lamivudine alone. In the other study of patients with lamivudine resistance, adefovir dipivoxil plus lamivudine was more effective than lamivudine alone in terms of both virological and ALT responses. HBV DNA level fell to $10^5$ copies/ml or less in 85% of those taking adefovir dipivoxil plus lamivudine, compared with 11% of patients taking lamivudine alone ($p < 0.001$). ALT was normalised in 37% of those taking the combined treatment, compared with 9% of those taking lamivudine ($p = 0.003$).

4.1.12 One study compared adefovir dipivoxil with placebo in people with HBeAg-negative chronic hepatitis B. This was a double-blind study in which 185 people were randomised in a 2:1 ratio to adefovir dipivoxil or placebo for 48 weeks. The primary endpoint was histological improvement defined in terms of a reduction in Knodell necroinflammatory score with no worsening of fibrosis. A total of 167 patients (91%) had assessable pre-treatment and post-treatment liver biopsy specimens. Significantly more patients had histological improvement in the adefovir dipivoxil group than in the placebo group (64% versus 33%, $p < 0.001$). At week 48, 51% of the adefovir dipivoxil group had undetectable HBV DNA levels (< 400 copies/ml), compared with no one in the placebo group ($p < 0.001$), and 72% had normalised ALT levels compared with 29% in the placebo group ($p < 0.001$).

4.1.13 Long-term follow-up data have been published recently. After week 48, 123 people who had been assigned to adefovir dipivoxil in the initial study were randomised to continue adefovir dipivoxil at a dose of 10 mg daily or to switch to placebo. Of the 61 patients who had initially been randomised to placebo, 60 switched to treatment with adefovir dipivoxil 10 mg daily. At week 96, HBV DNA was undetectable in 71% of the group continuing with adefovir dipivoxil, compared with 8% of the placebo group. In the group who received adefovir dipivoxil for 48 weeks having previously received placebo for 48 weeks, HBV DNA was undetectable in 76% of patients. The cumulative incidence of resistance to adefovir dipivoxil among all patients was 3% at 96 weeks and 5.9% at 144 weeks. This trial will continue until all patients have completed 5 years' follow-up.
Evidence from clinical experts

4.1.14 The Committee heard from the clinical experts that the decision to treat chronic hepatitis B was determined by the degree of fibrosis and/or necroinflammation on liver biopsy, combined with evidence of active viral replication (HBV DNA levels) and the persistent elevation of serum ALT. Treatment was not necessarily indicated for people with minimal elevation of ALT (1.5–2.0 times the upper limit of normal) and low necroinflammatory scores on liver biopsy. However, these people should be carefully monitored because the disease can change rapidly from a quiescent to an active state.

4.1.15 The experts expressed concern about the development of viruses with mutations rendering them resistant to antiviral drugs. Lamivudine resistance develops in a high proportion of patients on monotherapy, and could limit the options for future treatment through cross-resistance to related drugs. The experts noted that a strategy of treating chronic hepatitis B with lamivudine followed by adefovir dipivoxil for those in whom lamivudine-resistance developed reflected current practice. However, the experts noted that there was a subgroup of people with highly replicative disease in whom resistance could develop rapidly; in these people, a strategy of using adefovir dipivoxil in combination with lamivudine might be appropriate.

4.1.16 In principle, the use of combination therapies should minimise the risk of developing resistant variants, although long-term follow-up data from studies are lacking. The clinical experts stressed the need for further research on the long-term effectiveness of combination regimens in preventing resistance.

4.2 Cost effectiveness

4.2.1 The Committee considered evidence from four economic models: one by the Assessment Group, one by each of the two manufacturers involved, and one published analysis by Kanwal and colleagues (which was published after the Assessment Report’s deadline for inclusion). The models have similar structures and parameters, and their results are in broad agreement.

Assessment Group model

4.2.2 The Assessment Group model presents analyses for people with HBeAg-positive disease and HBeAg-negative disease separately, and also as a single
group, with proportions of people with HBeAg-positive disease and HBeAg-
negative disease determined from the parameters of the model.

4.2.3 Results are presented for peginterferon alfa-2a (48 weeks' treatment) 
compared with interferon alfa-2a (24 weeks for HBeAg-positive disease or 
48 weeks for HBeAg-negative disease), and for adefovir dipivoxil compared with 
lamivudine. The incremental cost-effectiveness ratios (ICERs) for these two 
comparisons in HBeAg-positive and HBeAg-negative groups combined were 
£6100 and £16,500 per quality-adjusted life year (QALY) respectively. However, 
this analysis assumes that, if the first therapy does not produce a sustained 
response, people receive no further treatment other than best supportive care, 
whereas in practice people may go on to receive treatment with an alternative 
agent. The Assessment Group therefore produced an analysis that considered 
more clinically relevant scenarios in which people could receive a sequence of 
drug treatments as necessary.

4.2.4 It is assumed that all patients are first given a course of treatment with either 
interferon alfa-2a (for 24 or 48 weeks, depending on HBeAg status) or 
peginterferon alfa-2a for 48 weeks. If HBeAg or HBsAg seroconversion occurs 
on one of the interferons, the patients are assumed to take no further antiviral 
medication; if not, they proceed to one of the following sequences of treatment, 
which form the basis of the comparison:

- best supportive care, that is, no further antiviral medication
- lamivudine, then best supportive care on seroconversion or development of resistance
- adefovir dipivoxil, then best supportive care on seroconversion or development of resistance
- lamivudine, then adefovir dipivoxil on development of resistance, then best supportive 
care on seroconversion or development of resistance.

4.2.5 The Assessment Group analysis also reports ICERs for the use of lamivudine 
then best supportive care without first using an interferon, and of adefovir 
dipivoxil then best supportive care without first using an interferon. It did not 
report on sequences of both lamivudine and adefovir dipivoxil that were not 
preceded by an interferon. However, because of the underlying assumptions 
used in the model, these ICERs can be inferred from the equivalent comparisons 
for sequences including peginterferon alfa-2a or interferon alfa-2a.
4.2.6 Comparing these sets of sequences generated a large number of ICER estimates. However, some of the strategies can be excluded from consideration using the notion of dominance or extended dominance. This means that when strategies A, B and C (in order of increasing cost) are compared, if the ICER for B compared with A is higher than that for C compared with A, and if the benefits of B are less than those of C, then B is excluded.

4.2.7 For HBeAg-positive disease, the treatment sequences that are not excluded by extended dominance are as follows:

- lamivudine then best supportive care (estimated ICER £3500 per QALY compared with best supportive care)
- interferon alfa-2a then lamivudine then adefovir dipivoxil then best supportive care (estimated ICER £9900 per QALY compared with lamivudine then best supportive care)
- peginterferon alfa-2a then lamivudine then adefovir dipivoxil then best supportive care (estimated ICER £18,800 per QALY compared with interferon alfa-2a then lamivudine then adefovir dipivoxil then best supportive care)
- peginterferon alfa-2a then adefovir dipivoxil then lamivudine then best supportive care (estimated ICER £57,000 per QALY compared with peginterferon alfa-2a then lamivudine then adefovir dipivoxil then best supportive care). Note that this treatment sequence did not appear in the Assessment Report, but was prepared by the Assessment Group for the Appraisal Committee before its first meeting.

4.2.8 For HBeAg-negative disease, the treatment sequences that are not excluded by extended dominance are as follows:

- peginterferon alfa-2a then best supportive care (estimated ICER £3000 per QALY compared with best supportive care)
- peginterferon alfa-2a then lamivudine then best supportive care (estimated ICER £4900 per QALY compared with peginterferon alfa-2a then best supportive care)
- peginterferon alfa-2a then lamivudine then adefovir dipivoxil then best supportive care (estimated ICER £18,000 per QALY compared with peginterferon alfa-2a then lamivudine then best supportive care).
Manufacturer's model (Roche)

4.2.9 The model submitted by Roche reports a number of estimated cost effectiveness results, all involving either interferon alfa-2a or peginterferon alfa-2a, for HBeAg-positive and HBeAg-negative disease separately. Nothing is said about later choices for people for whom the interferon has not been clinically effective. The estimated ICERs for people with HBeAg-positive disease are as follows:

- peginterferon alfa-2a for 24 weeks compared with interferon alfa-2a for 24 weeks (ICER £2700 per QALY)
- peginterferon alfa-2a for 48 weeks compared with interferon alfa-2a for 24 weeks (ICER £13,900 per QALY)
- peginterferon alfa-2a for 48 weeks compared with lamivudine for 48 weeks (ICER £5300 per QALY)
- peginterferon alfa-2a for 48 weeks compared with lamivudine for 208 weeks (ICER £5900 per QALY)
- peginterferon alfa-2a for 48 weeks compared with adefovir dipivoxil for 48 weeks (ICER £1400 per QALY)
- peginterferon alfa-2a for 48 weeks compared with adefovir dipivoxil for 208 weeks (dominant, that is, greater benefit at lower cost than adefovir dipivoxil)
- peginterferon alfa-2a for 48 weeks compared with no treatment (ICER £2800 per QALY).

4.2.10 The ICERs for people with HBeAg-negative disease are as follows:

- peginterferon alfa-2a for 48 weeks compared with lamivudine for 48 weeks (ICER £3200 per QALY)
- peginterferon alfa-2a for 48 weeks compared with lamivudine for 208 weeks (ICER £1900 per QALY)
- peginterferon alfa-2a for 48 weeks compared with no treatment (ICER £1500 per QALY).
Manufacturer's model (Gilead)

4.2.11 The model submitted by Gilead presents estimated cost-effectiveness ratios for a number of single treatments and treatment sequences. However, the cost effectiveness of adefovir dipivoxil compared with best supportive care is not reported. The interferons are not considered as treatment options, and the analyses are for a combined population of people with HBeAg-positive and HBeAg-negative disease. The estimated ICERs are as follows:

- lamivudine then adefovir dipivoxil (when lamivudine resistance emerges) compared with best supportive care – ICER £6700 per QALY
- lamivudine then adefovir dipivoxil (when lamivudine resistance emerges) compared with lamivudine then best supportive care (when lamivudine resistance emerges) – ICER £9200 per QALY
- adefovir dipivoxil then lamivudine (when adefovir dipivoxil resistance emerges) compared with best supportive care – ICER £8200 per QALY
- adefovir dipivoxil then lamivudine (when adefovir dipivoxil resistance emerges) compared with lamivudine then best supportive care (when lamivudine resistance emerges) – ICER £11,400 per QALY
- adefovir dipivoxil then lamivudine (when adefovir dipivoxil resistance emerges) compared with lamivudine then adefovir dipivoxil (when lamivudine resistance emerges) – ICER £29,400 per QALY.

Published model

4.2.12 The published model (Kanwal and colleagues) evaluated a ‘do nothing’ strategy (equivalent to best supportive care), interferon alfa, lamivudine, adefovir dipivoxil, and lamivudine then adefovir dipivoxil. For HBeAg-positive disease, the estimated ICERs for the non-dominated strategies are as follows:

- interferon alfa compared with best supportive care – ICER $2300 (£1300 at an exchange rate of $1.75 per £1) per QALY
- lamivudine then adefovir dipivoxil, compared with interferon alfa – ICER $16,600 (£9500) per QALY
4.2.13 In the analysis for HBeAg-negative disease, lamivudine then adefovir dipivoxil (as salvage therapy after resistance to lamivudine develops) is both cheaper and more effective than all other treatment options.

Overall results of the models

4.2.14 The models show that interferon alfa or peginterferon alfa-2a therapies followed by lamivudine then adefovir dipivoxil, where necessary, appear to be cost effective relative to alternative strategies. In most of the analyses, strategies in which adefovir dipivoxil is used before lamivudine, or without lamivudine, in the sequence are dominated by the alternative strategies. The exceptions are Gilead’s estimated ICER of £29,400 per QALY for adefovir dipivoxil then lamivudine, compared with lamivudine then adefovir dipivoxil, and the Assessment Group’s estimated ICER of £57,000 per QALY (for HBeAg-positive patients) for peginterferon alfa-2a then adefovir dipivoxil then lamivudine, compared with peginterferon alfa-2a then lamivudine then adefovir dipivoxil.

4.3 Consideration of the evidence

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B, having considered evidence on the nature of the condition and the value placed on the benefits of adefovir dipivoxil and peginterferon alfa-2a by people with chronic hepatitis B, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee considered that peginterferon alfa-2a was clinically and cost effective compared with interferon alfa therapy for the treatment of chronic hepatitis B on the basis of the cost effectiveness modelling. However, given that the difference in the rates of HBeAg seroconversion and ALT normalisation (HBeAg-positive chronic hepatitis B) compared with standard interferon alfa-2a were not statistically significant, the Committee was not persuaded that the potential advantages of peginterferon alfa-2a over standard interferon had been conclusively proven. The Committee concluded, therefore, that...
peginterferon alfa-2a should be considered as an alternative to interferon alfa for the management of chronic hepatitis B during the initial phase of treatment.

4.3.3 The experts stated that the effects of initial treatment with peginterferon alfa-2a in achieving a good response were different for HBeAg-positive and HBeAg-negative disease. The Committee was persuaded, however, that the response to peginterferon alfa-2a as measured by HBeAg seroconversion (in the case of HBeAg-positive disease) or an adequate reduction in viral load (in the case of HBeAg-negative disease) was clinically important in both cases. Thus the Committee concluded, on this basis, that peginterferon alfa-2a should be recommended as an option in first-line therapy for both HBeAg-positive and HBeAg-negative chronic hepatitis B.

4.3.4 The Committee next considered the use of the oral antiviral agents (specifically adefovir dipivoxil) for the long-term treatment of both HBeAg-positive and HBeAg-negative chronic hepatitis B. The Committee considered the cost-effectiveness analysis presented by the assessment team on the use of adefovir dipivoxil compared with lamivudine in the long-term treatment of chronic hepatitis B. In addition the Committee discussed the cost-effectiveness analysis of the various treatment sequences that could be used over the entire disease process. It was apparent that adefovir dipivoxil was cost effective when compared directly with lamivudine for long-term therapy, if it was assumed that a switch could not be made to the alternative treatment if resistance developed. However, when considering the use of adefovir dipivoxil in the various treatment sequences, the Committee heard that the most cost-effective option was for it to be used following the emergence of viral resistance to lamivudine.

4.3.5 The Committee heard the concerns of the clinical experts about the potential impact of the development of resistant viral mutations on future treatment options, based on the current experience of lamivudine use. The experts also stated that adefovir dipivoxil was less likely than lamivudine to result in viral resistance over the short term. They also expressed the view that viral resistance may be encouraged by the use of single agents and discussed with the Committee the possibility of recommending combination therapies for long-term treatment.

4.3.6 The Committee was persuaded that it was likely that drug-resistance might be attenuated by using antiviral drugs in combination. The Committee felt unable
to recommend routine use of combination therapies in the absence of trial
evidence on the effect of combination therapy on drug resistance and its cost
effectiveness. However, the Committee considered that it was not appropriate
under these circumstances to recommend the use of adefovir dipivoxil only
after resistance had already developed to another antiviral agent. It was
persuaded by the expert testimony that it was possible to identify groups of
people for whom lamivudine resistance is more likely to occur rapidly (for
example, those with highly replicative disease), and those for whom
development of lamivudine resistance is likely to have an adverse outcome (for
example, those in whom a flare up of the infection may precipitate
decompensated liver disease). Consequently it was sympathetic to the experts'
view that it was appropriate to use adefovir dipivoxil for patients in whom the
development of lamivudine-resistance would be considered particularly
hazardous. The Committee was also sympathetic to the experts' view that under
these circumstances the use of adefovir dipivoxil alone or in combination with
lamivudine might be appropriate.

4.3.7 The Committee concluded that it was appropriate to recommend adefovir
dipivoxil as an option for the treatment of chronic hepatitis B for patients in
whom prolonged oral antiviral treatment is required. It was also persuaded that
this should be only after the use of an interferon as initial treatment unless this
was contraindicated. The Committee was mindful that in the Assessment
Group's economic model, the sequence of therapy with adefovir dipivoxil before
lamivudine was not cost effective compared with the alternative of lamivudine
followed by adefovir dipivoxil. The Committee was, however, persuaded that the
decision to use adefovir dipivoxil (alone or in combination with lamivudine)
would need to be made on a case-by-case basis. This should take into account
various factors including HBeAg status, stage of disease process (for example
the presence of compensated or decompensated cirrhosis) and the presence of,
or likelihood of the emergence of, virus resistance.

4.3.8 The Committee accepted consultee advice that drug treatment should be
initiated only by a healthcare professional with expertise in the management of
viral hepatitis, but that the task of continuing and monitoring therapy could be
undertaken by general practitioners under shared-care arrangements.
5 Recommendations for further research

5.1 There is considerable concern about viral resistance in the long-term treatment of chronic hepatitis B. Further research is needed on the role of combination therapy with antiviral drugs in reducing the development of resistance to treatment. There is at least one ongoing study comparing lamivudine alone with lamivudine in combination with adefovir dipivoxil in treatment-naive people with chronic hepatitis B.
6 Implications for the NHS

6.1 Since the final appraisal determination was issued, NICE has carried out more detailed costing analysis to support implementation of the guidance. The following costing tools are available from the NICE website.

- A national costing report, which estimates the overall resource impact associated with implementation.
- A local costing template: a simple spreadsheet that can be used to estimate the local cost of implementation.
7 Implementation and audit

7.1 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within 3 months of this guidance being published. This means that, if a patient has chronic hepatitis B and the doctor responsible for their care thinks that adefovir dipivoxil or peginterferon alfa-2a is the right treatment, it should be available for use, in line with NICE’s recommendations.

7.2 All clinicians who care for people with chronic hepatitis B should review their current practice and policies to take account of the guidance set out in section 1.

7.3 Local guidelines, protocols or care pathways that refer to the care of people with chronic hepatitis B should incorporate the guidance.

7.4 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in appendix C.

7.4.1 For an adult with chronic hepatitis B (HBeAg-positive or -negative), peginterferon alfa-2a is considered as an option for the initial treatment, within its licensed indications.

7.4.2 For an adult with chronic hepatitis B (HBeAg-positive or -negative) adefovir dipivoxil is considered as an option for treatment, within its licensed indications, if:

- treatment with interferon alfa or peginterferon alfa-2a has been unsuccessful, or
- a relapse occurs after successful initial treatment, or
- treatment with interferon alfa or peginterferon alfa-2a is poorly tolerated or contraindicated.

7.4.3 Adefovir dipivoxil is not normally given before treatment with lamivudine.

7.4.4 Adefovir dipivoxil is normally used either alone or in combination with lamivudine when:

- treatment with lamivudine has resulted in viral resistance, or
• Lamivudine resistance is likely to occur rapidly and development of lamivudine resistance is likely to have an adverse outcome.

7.4.5 Drug treatment with peginterferon alfa-2a and adefovir dipivoxil is initiated by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis.

7.5 Local clinical audits also could include measures related to the existence of clear, long-term management plans for people with chronic hepatitis B; the provision of written information to patients on the transmission and outcomes of the disease; the regularity of ALT level checks; the clinical supervision of the patients’ care; and the coordination of data collection for local audits with national audits that may include these patients.
8 Related NICE guidance

8.1 Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance no. 75 (2004).
9 Review of guidance

9.1 Because new drugs and drug combinations are likely to be licensed in the next 18 months, it is proposed that the guidance on this technology is considered for review in February 2007.

Andrew Dillon
Chief Executive
February 2006
Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor A E Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain
Independent Patient Advocate

Professor Gary Butler
Professor of Paediatrics, University of Reading and Royal Berkshire Hospital

Dr Karl Claxton
Health Economist, University of York
Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (TA96)

Dr Richard Cookson
Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice, University of East Anglia

Professor Christopher Eccleston
Director, Pain Management Unit, University of Bath

Professor Terry Feest
Professor of Clinical Nephrology, Southmead Hospital

Ms Alison Forbes
Health Consultant Associate, Eden Insight

Professor John Geddes
Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston
Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin
Health Outcomes Manager, Johnson & Johnson Medical

Dr Elizabeth Haxby
Lead Clinician in Clinical Risk Management, Royal Brompton Hospital

Dr Rowan Hillson
Consultant Physician, Diabeticare, The Hillingdon Hospital

Dr Catherine Jackson
Clinical Lecturer in Primary Care Medicine, Alyth Health Centre, Angus

Mr Muntzer Mughal
Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust

Ms Judith Paget
Chief Executive, Caerphilly Local Health Board

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Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (TA96)

Dr Katherine Payne
Health Economist, The North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson
Independent Research Consultant

Mrs Kathryn Roberts
Nurse Practitioner, Hattersley Group Practice, Cheshire

Professor Philip Routledge
Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Dr Debbie Stephenson
Head of HTA Strategy, Eli Lilly and Company

Professor Andrew Stevens (Vice-Chair)
Professor of Public Health, University of Birmingham

Dr Cathryn Thomas
General Practitioner, Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham

Dr Norman Vetter
Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Dr Paul Watson
Medical Director, Essex Strategic Health Authority

Dr David Winfield
Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.
Alastair Fischer
Technical Lead, NICE project team

Janet Robertson
Technical Advisor, NICE project team

Alana Miller
Project Manager, NICE project team
Appendix B. Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Southampton Health Technology Assessment Centre (SHTAC), University of Southampton:


B. The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, the Assessment Report and the Appraisal Consultation Document. Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination:

I) Manufacturers/sponsors:

- Gilead Sciences
- Roche Products.

II) Professional/specialist and patient/carer groups:

- African Caribbean Medical Society
- British Association for Sexual Health and HIV
- British Association for the Study of the Liver
- British Liver Trust
- British Society of Gastroenterology
- Chinese National Healthy Living Centre
- Health Protection Agency
- Hepatitis Nurse Specialist Forum
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
III) Commentator organisations (without the right of appeal):

- British National Formulary
- NHS Quality Improvement Scotland
- GlaxoSmithKline
- Foundation for Liver Research (formerly the Liver Research Trust)
- MRC Clinical Trials Unit
- Southampton Health Technology Assessment Centre (SHTAC).

C. The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on adefovir dipivoxil and peginterferon alfa-2a by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the Appraisal Consultation Document:

- Professor Geoffrey Dusheiko, Professor of Medicine, Royal Free University College School of Medicine – nominated by the Royal College of Physicians
- Professor Howard Thomas, Professor of Medicine, Imperial College London – nominated by the British Association for the Study of the Liver.
Appendix C. Detail on criteria for audit of the use of adefovir dipivoxil and peginterferon alfa-2a for chronic hepatitis B

Possible objectives for an audit

An audit could be carried out to ensure that adefovir dipivoxil and peginterferon alfa-2a are being used appropriately for the treatment of people with chronic hepatitis B.

Possible patients to be included in the audit

An audit could be carried out on a reasonable number of people being treated for chronic hepatitis B, for audit purposes, for example, patients seen over 6 months, excluding people with chronic hepatitis B who are known to be co-infected with hepatitis C, hepatitis D or HIV.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of adefovir dipivoxil and peginterferon alfa-2a for chronic hepatitis B are as follows.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Standard</th>
<th>Exception</th>
<th>Definition of terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. For an adult with chronic hepatitis B (HBeAg-positive or -negative),</td>
<td>100% of adults with chronic hepatitis B (HBeAg-positive or -negative)</td>
<td>A. The person has a contraindication to peginterferon alfa-2a</td>
<td>Clinicians will need to agree locally on how consideration of the options for treatment is documented for audit purposes.</td>
</tr>
<tr>
<td>peginterferon alfa-2a is considered as an option for initial treatment</td>
<td></td>
<td>A contraindication is decompensated cirrhosis of the liver. See the 'Summary of product characteristics' for details of contraindications.</td>
<td></td>
</tr>
</tbody>
</table>
### 2. For an adult with chronic hepatitis B (HBeAg-positive or -negative), adefovir dipivoxil is considered as an option for treatment, in accordance with its licensed indications, if:
- treatment with interferon alfa or peginterferon alfa-2a has been unsuccessful or
- a relapse occurs after successful initial treatment or
- interferon alfa or peginterferon alfa-2a is poorly tolerated or contraindicated

<table>
<thead>
<tr>
<th>100% of adults with chronic hepatitis B (HBeAg-positive or -negative) who meet any of 2a–2c</th>
</tr>
</thead>
</table>

### 3. Adefovir dipivoxil is given before treatment with lamivudine

<table>
<thead>
<tr>
<th>0% of people with chronic hepatitis B for whom initial treatment options are being considered</th>
</tr>
</thead>
</table>

**B. The person has a contraindication to adefovir dipivoxil**

Clinicians will need to agree locally on the sources of evidence for 2a–c and how consideration of the options for treatment is documented for audit purposes.

'Interferon alfa' includes interferon alfa-2a or -2b.

'Successful' treatment is considered to be treatment that leads to HBeAG seroconversion (in the case of HBeAg-positive disease) or an adequate reduction in viral load (in the case of HBeAg-negative disease). Clinicians will need to agree locally on how success of treatment is assessed, and how relapse after initial treatment and tolerance to adverse effects are documented for audit purposes.

See the ‘Summary of product characteristics’ for details of contraindications.

**C. There is a clinical justification for treating with adefovir dipivoxil before lamivudine**

Clinicians will need to agree locally on clinical justifications for treating people with chronic hepatitis B with adefovir dipivoxil before lamivudine.
4. Adefovir dipivoxil is used either alone or in combination with lamivudine in either of the following circumstances:
   a. treatment with lamivudine has resulted in viral resistance or
   b. lamivudine resistance is likely to occur rapidly and development of lamivudine resistance is likely to have an adverse outcome

<table>
<thead>
<tr>
<th>Measure</th>
<th>Compliance (%)</th>
<th>Non-compliance</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir dipivoxil for the treatment of chronic hepatitis B (TA96)</td>
<td>100% of the people with chronic hepatitis B for whom adefovir dipivoxil is being prescribed</td>
<td>None</td>
<td>Clinicians will need to agree locally on how treatment with lamivudine resulting in viral resistance and adverse outcomes are documented for audit purposes. An example of lamivudine resistance being likely to occur rapidly is the presence of highly replicative hepatitis B disease. An example of an adverse outcome is a flare of the infection that is likely to precipitate decompensated liver disease.</td>
</tr>
</tbody>
</table>

5. Drug treatment with peginterferon alfa-2a and adefovir dipivoxil is initiated by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Compliance (%)</th>
<th>Non-compliance</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (TA96)</td>
<td>100% of people with chronic hepatitis B for whom peginterferon alfa-2a or adefovir dipivoxil is prescribed</td>
<td>None</td>
<td>Clinicians will need to agree locally on the definition of an appropriately qualified healthcare professional with expertise in the management of viral hepatitis, for audit purposes.</td>
</tr>
</tbody>
</table>

**Calculation of compliance**

Compliance (%) with each measure described in the table above is calculated as follows.
Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.
Changes after publication

March 2014: implementation section updated to clarify that adefovir dipivoxil and peginterferon alfa-2a are recommended as options for treating chronic hepatitis B. Additional minor maintenance update also carried out.

June 2013: Recommendations 1.2–1.4 replaced by recommendations 1.5.13–1.5.15 in Hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults (NICE clinical guideline 165).

March 2012: minor maintenance
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE multiple technology appraisal process.

It has been updated by NICE clinical guideline 165 (published June 2013) and incorporated into the NICE pathway on hepatitis B (chronic) in the antiviral treatment in adults with chronic hepatitis B path along with other related guidance and products.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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