Gilead - Submission

Adefovir dipivoxil (Hepsera®) for the treatment of chronic hepatitis B

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EXECUTIVE SUMMARY

More than 30 trials have demonstrated that adefovir dipivoxil (Hepsera®) is an effective and well-tolerated treatment for chronic hepatitis B (CHB) with a substantially lower risk of drug resistance than lamivudine. Economic analysis shows that both first and second-line adefovir are cost-effective compared with lamivudine followed by no treatment.

Background

Hepatitis B is a blood-borne viral infection that can cause both acute and chronic hepatitis. CHB comprises a persistent infection with the hepatitis B virus (HBV) that often causes liver damage leading to liver failure, hepatocellular cancer (HCC) and death.

The World Health Organisation estimates that around 360 million people suffer from CHB worldwide. Although the prevalence in the UK is much lower than many other countries, there are approximately 156,000 people in England and Wales with CHB. Around 6800 new chronic cases arise each year from infection within England and Wales and migration of HBV carriers into the country. Based on an audit of patients at a London clinic, around 63% of people with CHB are male and 31% are infected with the precore mutant strain of HBV that cannot express the hepatitis B "e" antigen (HBeAg) and is associated with faster disease progression. Modelling work demonstrates that the average 38-year-old with CHB will die at age 64, while those without CHB can expect to live until they are 76.

Treatment options for CHB include interferon-α, lamivudine and adefovir dipivoxil. Interferon-α is often poorly tolerated and is suitable for only selected patients. Drug resistance to lamivudine is extremely common: around 67-75% of patients develop lamivudine resistance after four years of continuous treatment. Before the introduction of adefovir in April 2003, treatment options for lamivudine-resistant patients were extremely limited.

Adefovir dipivoxil (Hepsera®) is a nucleotide analogue that selectively blocks HBV replication, which, in turn, prevents liver damage and slows or even reverses disease progression. Resistance to adefovir is relatively rare: 7% of patients develop resistance after three years of therapy[1], compared with 53-56% of patients receiving lamivudine. This makes adefovir ideal for patients requiring long-term treatment and those with severe disease in whom drug resistance may precipitate hepatic decompensation. Adefovir is also extremely effective against lamivudine-resistant HBV, making it a safe and effective second-line option, in addition to being an appropriate first-line agent for many patients.

Clinical effectiveness

A systematic review of the literature was conducted to identify trials evaluating adefovir and/or lamivudine. Interferon-α was not considered as a comparator, since it is given to a subset of patients early in the disease and is therefore not a direct competitor to adefovir. Five randomised controlled trials (RCTs) and 28 non-randomised trials evaluating adefovir were identified, which followed more than 5000 patients with CHB for up to four years. Monitoring will continue in long-term efficacy/safety studies lasting five years. Lamivudine has been evaluated in 12 RCTs and numerous non-randomised studies.

[1] The information highlighted within this summary should be considered confidential until 17th April 2005.

These trials demonstrate that both adefovir and lamivudine are effective treatments for CHB, decreasing viral load, improving liver histology and normalising liver enzymes such as alanine transaminase (ALT). One year of treatment with adefovir enables 35-100% of patients to normalise ALT levels – 2.5-3.0-fold more than with placebo. In addition, 8-21% of patients expressing HBeAg develop antibodies to this antigen after one year of therapy – more than twice as many as with placebo. Trials have shown that adefovir is highly effective in a wide range of patients, regardless of disease severity, sensitivity to lamivudine, HBV genotype or HBeAg status.

Although lamivudine and adefovir initially have similar efficacy, drug resistance develops substantially more rapidly with lamivudine: after three years of therapy, 53-56% of lamivudine-treated patients will have become resistant, compared with 7% of those receiving adefovir. Drug resistance can lead to exacerbation of liver disease and, occasionally, hepatic decompensation and death. Before the introduction of adefovir, the only option for these patients was continuation of lamivudine therapy with limited effectiveness. Eleven clinical trials in lamivudine-resistant patients have demonstrated that adefovir is highly effective against lamivudine-resistant viral strains, reducing HBV DNA and ALT levels and minimising the risk of disease progression. Over time, drug resistance will reduce or even reverse the clinical benefits of lamivudine therapy, while adefovir can be continued for longer periods and provide effective treatment for lamivudine-resistant patients, thereby improving survival and quality of life.

Extensive clinical trial and post-marketing surveillance data have demonstrated that both adefovir and lamivudine are well-tolerated, with safety profiles similar to that of placebo. Although higher doses of adefovir were associated with reversible nephrotoxicity, less than 1% of patients with compensated disease develop any signs of renal impairment when receiving long-term treatment with 10 mg adefovir.

Cost-effectiveness

Previous economic evaluations have shown that lamivudine is dominant over interferon-α (ie less expensive and more effective) and cost-effective relative to no treatment. A Markov model was constructed to model disease progression in CHB, taking into account the precore mutant strain and resistance to lamivudine and adefovir. This was used to compare four treatment strategies: no treatment, lamivudine followed by no treatment after resistance develops, lamivudine followed by adefovir after resistance develops and adefovir followed by lamivudine.

This analysis demonstrates that at a cost-effectiveness threshold of £30,000 per quality-adjusted life-year (QALY) gained, both first and second-line use of adefovir are cost-effective. Adefovir followed by lamivudine costs £11,400/QALY compared with lamivudine followed by no treatment, while lamivudine followed by adefovir costs £9200/QALY compared with lamivudine followed by no treatment. At this threshold, we can be more than 90% confident that lamivudine followed by adefovir costs less than £30,000/QALY relative to lamivudine followed by no treatment and this strategy remained cost-effective in extensive one/two-way sensitivity analyses. In contrast, the common practice of continuing lamivudine monotherapy in lamivudine-resistant patients costs £13,300/QALY gained compared with stopping therapy when resistance develops, which means that it is more cost-effective to switch to adefovir.

First-line adefovir was also cost-effective relative to second-line adefovir, with an incremental cost-effectiveness ratio of £29,400. However, this finding was extremely sensitive to changes in assumptions, including the rate at which costs and benefits were discounted, although there is a strong clinical argument for first-line use of adefovir in a subgroup of patients for whom early development of drug resistance has a catastrophic effect on prognosis. Patients infected with the HBeAg-negative

precore mutant strain of HBV need long-term therapy with a low risk of resistance as they cannot undergo HBeAg seroconversion, while the development of drug resistance in cirrhotic patients can lead to hepatic decompensation and death. Liver failure and mortality associated with viral breakthrough were conservatively excluded from the model, which means that the benefits of adefovir over lamivudine are underestimated.

Wider NHS implications

Although first-line adefovir is cost-effective relative to lamivudine followed by no treatment and would be particularly beneficial for patients with severe disease in whom drug resistance could precipitate liver failure, it is difficult to quantify the number of patients in this category and the clinical benefits they would experience. We therefore calculated the budget implications of widespread use of lamivudine followed by adefovir.

Of the 156,000 people in England and Wales chronically infected with HBV, around 26% are diagnosed and around 31,800 would be suitable for therapy with lamivudine followed by adefovir after drug resistance develops. In practice, however, only around 10-15% of suitable patients are likely to receive treatment, equating to around 4000 patients in England and Wales. Treating 12.5% of suitable patients with lamivudine followed by adefovir if/when their condition requires treatment would cost the NHS an additional £14.4 million over the next five years, compared with current practice in which 45% of patients receive lamivudine followed by no treatment and the remainder receive no treatment. This equates to an average of £2.9 million per year. The incremental cost in the first year after NICE guidance is likely to be around £1.6 million, rising to £4.7 million in Year 5.

However over the lifetime of this cohort, this strategy will gain 9000 QALYs, prevent 236 patients progressing to liver failure and enable 124 additional patients to resolve the infection even if only 12.5% of suitable patients are treated. In addition to these direct health benefits, treatment will make many patients less infectious, thereby reducing the number of new cases of acute and chronic hepatitis B. Treating 12.5% of patients with this strategy will also avoid 11 liver transplants over the lifetime of current patients. Each transplant avoided will enable another patient to receive a lifesaving operation and save the NHS at least £37,000, even excluding the cost of long-term follow-up and assessing patients for transplantation.

In addition to the three therapies currently available for the treatment of CHB, several new antiviral medications, such as tenofovir and entecavir, are under development and may be licensed for CHB in the next five years. The introduction of these additional therapies will expand the potential for combination therapy and provide effective treatment options for patients who have developed resistance to both lamivudine and adefovir. These new developments mean that long-term projections of health benefits and healthcare costs may be subject to change.

At present, there are large disparities in the management of CHB across England and Wales in terms of the frequency and intensity of monitoring, the proportion of patients receiving treatment and the management of patients who develop drug resistance. Current provision of adefovir shows particularly pronounced variation across the country, although it is the only treatment available for patients with lamivudine-resistant CHB who are not indicated for interferon-α. Clear evidence-based guidance is likely to reduce such variation, making treatment of CHB more equitable and more efficient.

Conclusions

In conclusion, this report demonstrates that adefovir dipivoxil is a well-tolerated treatment for CHB that is effective in a wide range of patient groups and has a far lower risk of drug resistance than the current market leader, lamivudine. The economic evaluation demonstrates that both first and second-line adefovir cost less than £30,000 per QALY gained. Although second line adefovir is more cost-effective than first-line, there is also a strong clinical argument in favour of first-line use in a subset of patients with severe disease in whom drug resistance may precipitate hepatic decompensation and potentially death.