Scottish Medicines Consortium

Resubmission

adefovir dipivoxil tablets 10mg (Hepsera®) No. (54/03)
Gilead Sciences Ltd

4 March 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full resubmission

Adefovir dipivoxil (Hepsera®) is accepted for restricted use within NHS Scotland for the treatment of chronic hepatitis B in adults with either compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis, or decompensated liver disease. Its use is restricted to patients who demonstrate lamivudine resistance.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Adefovir dipivoxil 10 mg tablets (Hepsera®)

Licensed indication under review

For the treatment of chronic hepatitis B in adults who have either:

- compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis or
- decompensated liver disease.

Dosing information under review

Adefovir dipivoxil 10mg once daily with or without food. The optimum duration of treatment is unknown.

UK launch date

April 2003

Comparator medications

Lamivudine (Zeffix, GSK)
Interferon alfa (Various, Roche, Schering Plough)

Cost per treatment period and relevant comparators

Annual* Basic NHS Costs

Adefovir dipivoxil 10mg daily	**£3822**
Lamivudine 100mg daily	£1092
Interferon alfa 5-10MIU subcutaneously 3 x weekly	£4209-8418

* The optimum duration of treatment of chronic hepatitis B is currently unknown and, for each treatment option, depends on clinical factors like HBeAg seroconversion.

Summary of evidence on comparative efficacy

Primary endpoints

Two pivotal studies of adefovir dipivoxil in chronic hepatitis B were conducted in patients without lamivudine-resistant infection: one in HBeAg-positive patients, the other in HBeAg-negative (presumed precore mutant) patients. Both are randomised, double-blind studies comparing adefovir dipivoxil 10mg daily with placebo. Full results are published to 48 weeks. The primary endpoint of both studies was histological improvement, defined as a reduction from baseline of two or more in the Knodell necro-inflammatory score, with no concurrent

worsening of the Knodell fibrosis score. Results are presented for patients with baseline and 48 weeks biopsies. In the HBeAg-positive patients, histological improvement was reported in 89 of 168 (53%) of the adefovir dipivoxil group compared with 41 of 161 (25%) of the placebo group, amounting to a treatment difference of 28% [95% CI: 17%-38%], p<0.001. In the HBeAg-negative patients, histological improvement was reported in 77 of 121 (64%) of the adefovir dipivoxil group, compared with 19 of 57 (33%) of the placebo group, amounting to a treatment difference of 30% [95%CI: 15%-45%], p<0.001. The Summary of Product Characteristics notes that histological improvement was seen regardless of baseline demographics and hepatitis B characteristics, including prior interferon-alfa therapy, though greater histological improvement was seen in patients with high baseline ALT levels ($\geq$ 2 x ULN), Knodell Histology Activity Index (HAI) scores $\geq$ 10 and low HBV DNA (< 7.6 $\log_{10}$ copies/ml).

There is ongoing follow-up to both those studies. In an open-label extension to the first study all patients received adefovir 10 mg daily, while in the second trial patients receiving placebo in the first stage were switched to adefovir, and those receiving adefovir were re-randomised to adefovir or placebo.

In other studies, primary end-points were based on circulating levels of Hepatitis B Virus DNA (HBV DNA) levels either as the change from baseline or as the proportion of patients achieving levels below a specified threshold. Reductions in viral load are summarised in Appendix 1, including some results from the trial extensions described above.

In a phase II randomised double blind trial, treatment naïve patients were assigned to lamivudine 100 mg daily as monotherapy or in combination with adefovir 10 mg daily and results are available for 52 weeks treatment. The primary end-point was change from baseline in HBV DNA at 16 weeks adjusted for time spent in the study, and the response was identical for mono- and combination therapy. Unadjusted reductions at week 52 were larger for combination therapy (Appendix1).

In two double-blind randomised controlled trials which recruited patients with lamivudine resistance and compensated liver disease, adefovir, alone or in combination with lamivudine, was significantly more effective in reducing viral load than lamivudine alone. In one trial the response to adefovir monotherapy was numerically greater than for lamivudine plus adefovir.

Secondary endpoints, sub-group analysis and uncontrolled trials

In the two pivotal studies, adefovir dipivoxil 10mg daily demonstrated significant improvement compared with placebo in secondary endpoints involving markers of histological, virological, biochemical and serological response. Patients treated with adefovir dipivoxil had more regression and less progression of fibrosis and necro-inflammation compared with placebo. More adefovir dipivoxil treated patients had normalised ALT compared with placebo (48% versus 16% in the HBeAg-positive patients and 72% versus 29% in the HBeAg-negative patients, p<0.001, both studies). Significantly more HBeAg-positive patients treated with adefovir dipivoxil than placebo underwent HBeAg seroconversion (12% versus 6%, respectively, p=0.049) and HBeAg loss (24% versus 11%, respectively, p<0.001).

There were continued improvements in adefovir-treated patients during the extension phases of these trials. ALT normalisation was achieved in 81% of HbeAg positive patients treated continuously for 144 weeks. The proportion of HBeAg positive patients with seroconversion rose to 43%. Further improvements in viral load were also seen (Appendix 1).

In treatment naïve patients the proportion of patients achieving ALT normalisation at 52 weeks was higher with lamivudine alone than with lamivudine plus adefovir – 39/56 (70%) vs 25/52

(48%). Seroconversion data were not given, but the percentage losing HBeAg was 20% and 19% respectively.

In the randomised double blind trials involving patients with lamivudine-resistant infection, adefovir, alone or in combination with lamivudine, was more effective than lamivudine for secondary end-points including biochemical and serological responses. Further supportive studies in lamivudine resistant disease included patients with decompensated liver disease, patients pre- and post-liver transplantation and patients co-infected with HIV.

Resistance sub-studies, performed in the two pivotal studies and the study in post-liver transplant patients and the patients co-infected with HIV, have found the incidence of adefovir-associated resistance in HBV DNA polymerase with adefovir dipivoxil to be low, with a cumulative incidence of 3.9% over three years in a pooled analysis.

In the study involving treatment-naïve patients, resistance to lamivudine was evident in 10/49 (20%) of patients receiving lamivudine alone but only 1/49 (2%) in patients receiving lamivudine plus adefovir.

Summary of evidence on comparative safety

Renal tolerance is the primary safety concern with adefovir dipivoxil following the association of higher doses (to treat HIV) and nephrotoxicity. A dose of 30 mg daily in the early development programme for the treatment of chronic hepatitis B was discontinued because of concerns about potential nephrotoxicity. At the recommended dose of 10mg daily, renal adverse events consisted of mild to moderate elevations in serum creatinine in patients with compensated liver disease. With extended treatment in clinical trials, increases in serum creatinine >0.5 mg/dl from baseline were reported in two patients out of 492 (<1%) treated with 10 mg adefovir dipivoxil. Increases in serum creatinine, renal insufficiency and renal failure were more common in patients pre- and post transplantation, however those patients were likely to receive other potentially nephrotoxic therapy. The Summary of Product Characteristics advises of the potential risk, particularly for patients with underlying renal dysfunction or those receiving drugs which may affect renal function. For patients with normal renal function, serum creatinine should be measured every 3 months.

Summary of clinical effectiveness issues

Adefovir dipivoxil has demonstrated efficacy in terms of histological, virological, biochemical, serological or clinical response in the different types of patients outlined in the above studies. Efficacy was evident in all different subgroups of patients, including treatment naïve, those with lamivudine-resistant infections, as well as patients considered difficult to treat: HBeAg-negative, transplanted, co-existing HIV infection or decompensated liver disease. However in terms of use in practice a number of issues remain unanswered. These include the optimum duration of treatment, the risk of any delayed development of resistance and the appropriate use (substitution or combination) for patients with lamivudine-resistant infection. These factors will all affect the drug's clinical effectiveness in practice.

Summary of comparative health economic evidence

A Markov model using Monte Carlo simulation was provided examining the cost-effectiveness of various different treatment pathways in adult patients with both the wild type virus and those with the precore mutant strain. The most relevant treatment pathways examined the cost-effectiveness of using adefovir after lamivudine (LAM-AD) compared to a treatment strategy of lamivudine following by no active treatment (LAM-NT). The model also addressed the use of adefovir followed by lamivudine (AD-LAM) compared to lamivudine followed by adefovir (LAM-AD) i.e. first line use of adefovir. The model did not analyse the cost-effectiveness of adefovir and lamivudine used in combination or the cost-effectiveness of adefovir in patients co-infected with HIV. The model was complex involving eleven or twelve Markov states in each sub-model and followed patients over their lifetimes. Transition probabilities were derived mainly from literature sources and costs originated from expert opinion or published literature. One-way and probabilistic sensitivity analyses (PSA) were provided.

The results indicated that the LAM-AD strategy versus the LAM-NT strategy was associated with an incremental cost per QALY of £23000. The AD-LAM versus LAM-AD strategy gave an incremental cost per QALY of £63000. One way sensitivity analysis indicated that the results showed some variability when utility values, discount rates, resistance rates of adefovir and some of the assumed transition probabilities were altered. PSA indicated that we could be 60% confident that the cost per QALY for LAM-AD versus LAM-NT is less than £30000 per QALY.

The model was necessarily complex in order to cover the relevant disease states of CHB, however it was often difficult to follow and lacked transparency. On the basis of the cost effectiveness information presented, the model would not support the use of adefovir as a first line treatment or its use in combination with lamivudine or in patients co-infected with HIV.

Budget impact

The budget impact figures presented by the company were possibly not representative of current use of lamivudine in Scotland in that they assumed many more patients on lamivudine than we currently have. A revised estimate was submitted looking at the costs of introducing adefovir as second line treatment for the existing patient population thought to be on lamivudine in Scotland. The company estimated that the additional cost of using adefovir after patients developed lamivudine resistance was £0, £225, £46700, £76000 and £97000 in the first five years respectively. It should be noted however that these figures assumed a relatively high cost for patients who currently develop lamivudine resistance and then cease treatment. The figures aim to reflect the costs associated with resource use such as consultations and blood tests and also the costs of treating CHB complications such as cirrhosis.

Additional information

At its meeting in July 2003, after consideration of a full submission, the Scottish Medicines Consortium recommended that adefovir was not recommended for use within NHS Scotland.

This is superseded by the current advice. Based on the evidence submitted at that time, it was summarised as follows:

"Adefovir dipivoxil may offer an alternative, convenient oral therapy for the treatment of chronic hepatitis B. However, there are limited data to assess the efficacy of adefovir dipivoxil relative to other treatments in treatment-naïve patients. Moreover there are limited data on sustained response rates and the optimum duration of therapy remains to be determined. The cost-effectiveness of adefovir dipivoxil in managing chronic hepatitis B has not been addressed by the company in this submission. The current information suggests that it is almost three times more costly than its principal competitor without evidence of commensurate benefit."

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 8 February 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

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Those shaded grey are additional to those supplied with the submission.

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Appendix 1: 1 Median change in viral load (HBV DNA) in adefovir dipivoxil studies

Type of study and patient population	Treatment groups	Treatment duration	Median change in HBV DNA (log_{10} copies/ml)
Pivotal study: randomised, placebo-controlled, double-blind. HBeAg-positive patients with compensated liver disease	Adefovir (n=171)	48 weeks	-3.5
	Placebo (n=167)	48 weeks	-0.6
	Adefovir (n=84)	144 weeks	*
Pivotal study: randomised, placebo-controlled, double-blind. HBeAg-negative patients with compensated liver disease	Adefovir (n=123)	48 weeks	-3.9
	Placebo (n=61)	48 weeks	-1.4
	Adefovir (n=79)	96 weeks	-3.5
	Adefovir (n= 67)	144 weeks	-3.6
Randomised, double-blind, lamivudine monotherapy vs lamivudine adefovir. Treatment naïve patients, most with HBeAg +ve disease	Lamivudine (n=57)	52 weeks	-4.8
	Adefovir plus lamivudine (n=55)	52 weeks	-5.4
Supportive: randomised, active-controlled, double-blind. HBeAg-positive patients with lamivudine- resistant infection and compensated liver disease	Adefovir (n=19)	48 weeks	-4.0
	Lamivudine (n=19)	48 weeks	0.0
	Adefovir plus lamivudine (n=20)	48 weeks	-3.6
Supportive: randomised, double-blind. Patients with lamivudine-resistant infection and compensated liver disease (Group A)	Adefovir plus lamivudine (n=46)	52 weeks	-4.6
	Lamivudine (n=48)	52 weeks	0.3
Open label HBeAg-positive or negative patients, with lamivudine-resistant infection, compensated/decompensated liver disease, pre- or post-liver transplant	Post-transplant (n=196)	48 weeks	-4.3
	Pre-transplant (n=128)	48 weeks	-4.1
Open label: adefovir added to existing lamivudine in HBeAg-positive and negative patients with lamivudine-resistant infection and decompensated liver disease, pre- or post-liver transplant (Group B)	Adefovir (n=40)	-	-4.6
Open label pilot study: adefovir added to existing lamivudine in patients with lamivudine-resistant infection and co-infected with HIV	Adefovir (n=35)	48 weeks	-4.7

* Median change not given, but the percentage of patients achieving HBV DNA <1000 copies/ml increased from 28% at 48 weeks to 56% with continuous adefovir for 144 weeks