telbivudine, 600mg film-coated tablets (Sebivo®) No. (438/08)
Novartis Pharmaceuticals UK Limited

11 January 2008

The Scottish Medicines Consortium 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 submission

telbivudine (Sebivo®) is accepted for use within NHS Scotland for the treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active inflammation and/or fibrosis.

For a number of therapeutic endpoints telbivudine proved to be equivalent or superior to a comparator nucleoside reverse transcriptase inhibitor.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Telbivudine is indicated for the treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active inflammation and/or fibrosis.

Dosing information

600mg (one tablet) once daily, taken orally, with or without food.

Product availability date

26th June 2007

Summary of evidence on comparative efficacy

Telbivudine is a synthetic thymidine nucleoside analogue of guanosine, with selective activity against hepatitis B virus (HBV) DNA polymerase (reverse transcriptase). Incorporation of the phosphorylated drug into viral DNA causes DNA chain termination, resulting in inhibition of HBV replication. The ultimate goal of treatment of HBV is to suppress HBV replication and to induce remission in liver disease before cirrhosis and hepatocellular carcinoma develop.

The efficacy of telbivudine was compared with that of lamivudine in a phase III, randomised, double-blind, multicentre trial over 104 weeks. Patients (n=1367) were adults aged 16 to 70, who had documented chronic hepatitis B (CHB), compensated liver disease and no prior nucleoside/nucleotide therapy (and no use of immunomodulators for at least one year previously). The population was mixed in terms of HBeAg-positive or HBeAg-negative status and had HBV DNA levels ≥ 6 $\log_{10}$ copies/ml. Patients were randomised 1:1 to receive either telbivudine 600mg once daily orally or lamivudine 100mg once daily orally, with stratification according to patients' status for HBeAg (positive or negative) and alanine aminotransferase (ALT) (< 2.5 x upper limit of normal (ULN) or ≥ 2.5 x ULN). The primary endpoint was therapeutic response, defined as a composite of serum HBV DNA < 5 $\log_{10}$ copies/ml with either HBeAg loss or ALT normalisation. Key secondary endpoints included histological response, antiviral efficacy (the level of HBV DNA suppression and the proportion of patients with undetectable HBV), ALT changes and, in the HBeAg-positive group, HBeAg loss, seroconversion (development of anti-HBeAg antibody) and virologic response (HBV DNA < 5 $\log_{10}$ copies/ml and HBeAg loss). The proportion of patients experiencing virologic breakthrough was also reported as a secondary outcome. Analysis was reported in the intention to treat (ITT) population (or modified ITT population for the histological response). The non-inferiority margin was set at -15% for the difference in therapeutic response rate between treatments, and superiority was tested for.

At 104 weeks, a therapeutic response was seen in a higher proportion of telbivudine treated patients, superiority to lamivudine being established in both the HBeAg-positive (63% (n=290/458) vs 48% (n=223/463) respectively) and HBeAg-negative patients (77% (n=172/222) vs 66% (n=148/224) respectively). The difference between telbivudine and lamivudine was 15% (95% confidence intervals [CI]: 8.6% to 22%) and 11% (95% CI: 2.9% to 20%) respectively. The secondary endpoint of histologic response was only measured at 52 weeks, when a statistically significantly larger proportion of HBeAg-positive patients (65% vs 56% for telbivudine and lamivudine respectively) achieved a response. For the HBeAg-negative population, there was no statistically significant difference in histologic response (67% vs 66% respectively). At 104 weeks, in the HBeAg-positive and negative groups, HBV DNA reduction was statistically significantly greater with telbivudine than with lamivudine

(HBeAg-positive group 5.7 vs 4.4 log_{10} copies/ml HBeAG-negative group 5.0 vs 4.2 log_{10} copies/ml). Both groups showed superiority of telbivudine over lamivudine in the proportion of patients achieving undetectable HBV DNA.

For ALT normalisation at week 104, there was a significantly better response in the telbivudine group in the HBeAg-positive group but, in the HBeAg-negative group, telbivudine was only numerically better than lamivudine. Similarity between the two drugs was demonstrated at week 104 in the endpoints specific for HBeAg-positive patients (numbers achieving HBeAg loss, HBeAg seroconversion and virologic response). With regard to virologic breakthrough at week 104, telbivudine showed superiority in both the HBeAg-positive and negative groups. Telbivudine also showed superiority over lamivudine with a lower proportion of treatment-emergent resistance cases, in both the HBeAg-positive and negative groups, at week 48.

A "combined response" re-analysis was requested by the licensing authorities as a recommended endpoint (comprising ALT normalisation, loss of HBeAg in HBeAg-positive patients or a decrease in HBV DNA to < 5 log10 copies/ml and histologic improvement). This showed that telbivudine retained superiority over lamivudine in HBeAg-positive patients and non-inferiority in HBeAg-negative patients.

Summary of evidence on comparative safety

Most patients in both treatment arms experienced at least one adverse event (AE) by week 104 (81% (n=551/680) on telbivudine and 77% (n=529/687) on lamivudine). There were no differences in reporting rates, regardless of allocation to study drug, between the HBeAg-positive and negative groups. The distribution of AEs was similar in the two arms with the exception of increased creatine kinase (CK) levels, which occurred more frequently in the telbivudine group (12% vs 7.4%). Discontinuation due to an adverse event occurred in 0.6% of telbivudine and 2.0% of lamivudine recipients.

Serious AEs (SAEs) were infrequent, occurring in 5.6% of all patients. Only 5 patients had SAEs that were considered to be possibly attributable to study drug (3 on telbivudine). No deaths due to SAEs were reported in either group.

There were rare cases of myopathy (0.3% of the telbivudine group) and myositis (0.3% in the telbivudine group and 0.1% in the lamivudine group). Symptoms suggestive of peripheral neuropathy were seen in 0.3% of the telbivudine group.

On-treatment ALT flares (a recognised complication of anti-viral therapy) occurred more frequently in the lamivudine arm (7.4%) than the telbivudine arm (4.1%). On treatment new-onset CK elevations occurred more often in telbivudine patients (66% grade 1/2; 13% grade 3/4) than in lamivudine patients (45% grade 1/2; 4.1% grade 3/4).

Summary of clinical effectiveness issues

Limitations of the trial include the fact that missing data were treated as "treatment failures" in the ITT analysis. This means that treatment failures were likely to be over-reported since data may have been missing for a number of other reasons.

The patient population in the study were mainly Asian, with the largest ethnic group being Chinese. Only 98 patients of 680 who received telbivudine were Caucasians (209/1367 overall). It was observed that the therapeutic response for both telbivudine and lamivudine was lower in Caucasian than Asian patients. This also translates into an uneven spread of

virus genotypes (which have a broad geographical link) and so there is an under-representation of genotype A, which is mainly found in Europe. There was an excess of males (76%) and of HBeAg-positive patients (67%), although these could be said to reflect the infected population.

The data for ethnic mix also differed from those in the trials used for the indirect comparison (with entecavir) in the submission, although the comparative trials had a more even spread of ethnic races. This also translates into an uneven spread of virus genotypes (which have a broad geographical link), although the clinical relevance of this is thought to be minimal. Another limitation identified in the indirect comparison is that, although a number of endpoints were common between all trials, the primary endpoints were different, and only the telbivudine trial used a composite endpoint.

There are limited data on resistance currently available.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing telbivudine to entecavir for the treatment of chronic hepatitis B in adult patients with compensated liver disease. The analysis was supported by an indirect comparison of the clinical efficacy of the two drugs. Assuming equivalent clinical efficacy, the economic evaluation was a simple price comparison of the annual cost of telbivudine 600mg (£3,788) and entecavir 0.5mg (£4,602). The manufacturer noted entecavir has demonstrated to SMC that it is cost-effective compared to current clinical practice (lamivudine). The manufacturer asserted that the submission demonstrated comparability between telbivudine and entecavir and therefore, by extension, that telbivudine is cost-effective compared to lamivudine.

The key issue is whether entecavir and telbivudine have equivalent clinical effectiveness. The ethnic mix and spread of virus genotypes does differ between the studies of telbivudine and entecavir, though the clinical relevance of this is probably small. In addition, the primary endpoints of the studies of the two drugs were different, though a number of endpoints are common to the two drugs and do appear to show clinical equivalence. Resistance at one year is similar for each of the drugs – data beyond one year are not comparable because of differences in the study design.

Overall, the assumption of clinical equivalence between telbivudine and entecavir is accepted. This supports the conclusion that telbivudine is cost-effective compared to entecavir and lamivudine.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

NICE issued a technology appraisal (TA96) in February 2006, entitled "Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B". The guidance states that peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative).

The European Association for the Study of the Liver (EASL) guidelines were developed in September 2002. These recommend that interferon alfa may be used as first choice in HBeAg-positive and HBeAg-negative patients with moderate or severe chronic hepatitis without cirrhosis

Additional information: previous SMC advice

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 8th September 2006 that entecavir is accepted for the treatment of chronic hepatitis B infection in adults with compensated liver disease and evidence of viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active inflammation and or fibrosis. Clinical studies have shown that entecavir is more effective than lamivudine in nucleoside-naïve HBeAg-positive and -negative patients and in lamivudine refractory patients.

After review of a full submission, the SMC issued advice on 11 July 2005 that pegylated interferon alfa 2a (Pegasys) is accepted for use within NHS Scotland for the treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis. Compared with conventional interferon alfa 2a, it offers comparable efficacy and the convenience of once-weekly rather than three-times weekly subcutaneous administration. It has been shown to be cost-effective when compared to a number of comparator medicines in a range of patient groups.

Following a resubmission, the SMC issued advice on 4th March 2005 that 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.

Additional information: comparators

Other drugs licensed for this indication are interferon-alfa, peginterferon-alfa, lamivudine, adefovir dipivoxil and entecavir.

Cost of relevant comparators

There is uncertainty about the optimal duration of treatment of chronic hepatitis B, it being closely related to clinical progress and disease markers. Some drugs (namely interferon-alfa and peginterferon-alfa) are more likely to be used for shorter periods. Here, costs for interferon-alfa have been calculated for 4 – 6 months; costs for peginterferon-alfa are for 48 weeks (as specified in their respective Summaries of Product Characteristics). For the nucleoside/nucleotide analogues (oral) treatments, costs are for one year.

Drug	Dose regimen	Cost per year (£)
telbivudine	**600mg once daily, orally**	**3774**
entecavir	500micrograms once daily, orally	4586
adefovir dipivoxil	10mg once daily, orally	3822
lamivudine	100mg once daily, orally	1015

Drug	Dose regimen	Cost per course (£)
peginterferon-alfa	180 micrograms once weekly, subcutaneously	6339
interferon-alfa	2.5-5MIU/m^2 three times a week, subcutaneously	1175 – 3525

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 31st October 2007.

Additional information: budget impact

The manufacturer estimated an annual gross budget impact of £8k in year one, rising to £102k after five years. The manufacturer estimated there would be net savings to the NHS of £2k in year one, rising to £22k by year five compared to existing treatments. This assumes that 2 patients will be treated with telbivudine in year one, rising to a total of 27 patients by year five.

The analysis may underestimate the potential market share and additional cost should telbivudine gain market share from the most commonly used first-line treatment.

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 06 December 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted reference was supplied with the submission.

European Medicines Agency (EMEA). European public assessment report (EPAR) for Sebivo. http://www.emea.eu.int