Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

boceprevir 200mg capsule (Victrelis®) Treatment naïve patients SMC No. (723/11)

Merck Sharpe and Dohme Ltd

09 September 2011

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

boceprevir (Victrelis®) is accepted for use within NHS Scotland.

Indication under review: Treatment of chronic hepatitis C (HCV) genotype 1 infection, in combination with peginterferon and ribavirin, in adult patients with compensated liver disease who are previously untreated.

In the pivotal, phase III randomised study, addition of boceprevir to current standard therapy in patients with HCV who were previously untreated increased the proportion of patients with HCV who achieved a sustained virologic response.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of chronic hepatitis C (HCV) genotype 1 infection, in combination with peginterferon and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

Dosing Information

In patients without cirrhosis who are previously untreated: the recommended treatment is peginterferon alfa and ribavirin (dose as per individual product licences) for four weeks, followed by peginterferon alfa, ribavirin and boceprevir 800 mg three times daily for:

- 24 weeks. Total treatment duration is 28 weeks for patients with undetectable HCV-RNA at treatment week 8 and 24
- 32 weeks, then peginterferon alfa and ribavirin for 12 weeks. Total treatment duration of 48 weeks in patients with detectable HCV-RNA at week 8 and undetectable at week 24.

Patients with cirrhosis (Metavir fibrosis score 4): Peginterferon alfa and ribavirin (doses as per product licences) for 4 weeks then add boceprevir 800mg three times daily for 44 weeks. Total treatment duration of 48 weeks.

If any patient has detectable disease at week 12 or week 24 then discontinue three-medicine regimen.

Product availability date

21st July 2011

Summary of evidence on comparative efficacy

Boceprevir is a structurally novel protease inhibitor that binds reversibly to the HCV non-structural 3 protease active site serine to inhibit viral replication in the HCV-infected host cell. It is the first drug in this therapeutic class to be licensed for treatment of HCV.

This submission considers the use of boceprevir in patients who are previously untreated. Separate SMC advice relates to the use of boceprevir in patients who have previously failed therapy.

Evidence comes from two pivotal randomised phase III studies of similar design in previously untreated and experienced patients, 18 years or over with chronic HCV genotype 1 disease. The primary outcome in both studies was the achievement of a sustained virological response (SVR), defined as undetectable plasma HCV RNA at follow up week 24, measured in the Full Analysis Set (FAS) which included all patients who received at least one dose of study medication. The study in previously untreated patients was designed as a superiority study to establish the difference in the rate of SVR with different boceprevir regimens compared with standard therapy alone.

The pivotal phase III study (SPRINT2) in 938 non-black and 159 black previously untreated patients compared standard of care (peginterferon alfa-2b plus ribavirin) with standard of care

plus boceprevir 800mg three times daily in two different treatment durations. Following a four week lead-in period when all patients received peginterferon alfa-2b (1.5micrograms per kg subcutaneously once weekly) plus ribavirin (600-1400mg orally daily depending on body weight), patients remained on this treatment but in addition were randomised to:

Group 1 (n=363) - placebo for 44 weeks (total treatment duration = 48 weeks)
Group 2 (n=368) - Boceprevir Response Guided Therapy (RGT) consisting of boceprevir for 24 weeks. Then at treatment week 28 patients were further assigned to one of two groups based on their HVC RNA results at and after treatment week 8:

- 28 week regimen: Patients who had undetectable HCV-RNA at treatment week 8 and at all assays through to treatment week 24 (early responders), received no further treatment (total treatment duration = 28 weeks).
- 48 week regimen: Patients with detectable HCV-RNA at treatment week 8 or at any assay through to treatment week 24 (late responders,) continued therapy but with boceprevir treatment substituted with placebo for an additional 20 weeks (total treatment duration = 48 weeks). The switch from boceprevir to placebo occurred in a blinded fashion.

Group 3 (n=366) - Boceprevir treatment for 44 weeks (total treatment duration = 48 weeks)

Randomisation was stratified for baseline viral load (high [>400,000 IU/mL] versus low [≤ 400,000 IU/mL]) and HCV genotype (1a versus 1b). Patients co-infected with human immunodeficiency virus (HIV) or hepatitis B virus were excluded. Patients with detectable HCV-RNA at treatment week 24 were discontinued from treatment.

The primary endpoint of SVR was achieved in significantly more patients treated with boceprevir than placebo: 63% (233/368) of patients in the boceprevir RGT group and 66% (242/366) in the boceprevir 44 week treatment group, compared to 38% (137/363) in the placebo group. This represents an improvement of 26% ($p < 0.0001$) for boceprevir RGT and 28% ($p < 0.0001$) for the boceprevir 48-week treatment group, compared to the placebo group.

The dosing regimen for previously untreated patients with cirrhosis is based on a subgroup analysis of the study in previously treated patients with cirrhosis. The pivotal phase lll study (RESPOND2) in previously treated patients who had failed to achieve a SVR on prior treatment with peginterferon alfa and ribavirin but demonstrated interferon responsiveness, compared the following treatment groups:

Group 1 (n=80) - placebo for 44 weeks (total treatment duration = 48 weeks).
Group 2 (n=162) - boceprevir RGT consisting of boceprevir for 32 weeks; according to the week 12 stopping rule, patients with an undetectable HCV RNA level at weeks 8 and 12 completed therapy at week 36, whereas those with a detectable HCV RNA level at week 8 (but an undetectable level at week 12) received peginterferon alfa and ribavirin with placebo for an additional 12 weeks.
Group 3 (n=161) - Boceprevir treatment for 44 weeks (total treatment duration = 48 weeks) and follow up for 24 weeks post treatment.

Rates of SVR in RESPOND2 were significantly higher among patients receiving boceprevir than placebo, with overall rates of SVR of 21% (17/80), 59% (95/162), and 66% (107/161) in groups 1, 2, and 3, respectively ($p<0.001$).

A subgroup analysis of the RESPOND2 study demonstrated SVR rates in the 49 patients with cirrhosis of nil (0/10), 35% (6/17) and 77% (17/22) in groups 1, 2 and 3 respectively.

Summary of evidence on comparative safety

In the pivotal study, more than 98% of patients reported an adverse event with serious adverse events reported in 9%, 11% and 12% of patients in groups 1, 2, and 3 respectively. The proportions of patients reporting serious adverse events, life threatening adverse events, and study drug discontinuation due to adverse events were similar across all groups. The proportion of patients with dose modification due to adverse events was higher in the boceprevir plus peginterferon plus ribavirin groups compared with the peginterferon plus ribavirin control groups in both treatment-naïve and previous treatment failure subjects.

Fatigue, headache and nausea were the most common adverse events in all treatment groups. Dysgeusia occurred more frequently in boceprevir-treated patients. Anaemia was more common with boceprevir, with 74% of patients experiencing grade 1 or 2 anaemia compared with 53% of peginterferon plus ribavarin patients, with 21% and 13% respectively requiring dose reductions. Treatment was discontinued due to anaemia in 13 patients in the boceprevir groups compared with four patients in the peginterferon plus ribavarin group. Epoetin was administered in 43% of boceprevir patients and 24% of peginterferon plus ribavarin patients.

Summary of clinical effectiveness issues

The Scottish Government's Phase II Hepatitis C Action Plan was published in 2008. This plan aimed to improve testing, treatment, care and support services for those infected with HCV, with a major emphasis on increasing the number of patients treated.

In the pivotal phase lll study boceprevir, in combination with peginterferon plus ribavirin, in previously untreated patients significantly increased the proportion of patients achieving a SVR compared with peginterferon plus ribavirin treatment only.

On the recommendation from the European Medicines Agency (EMA), the recommended duration of treatment for patients who are previously untreated and late responders has been derived from evidence provided in the phase lll study for patients who had been previously treated and were late responders. The dosing regimen for previously untreated patients with cirrhosis is based on a subgroup analysis of the study in previously treated patients with cirrhosis. These dosing regimens have been extrapolated from studies in different patient populations so the efficacy in this patient population is not fully evaluated. This was a conservative measure in view of the limitations of the data.

In January 2011 the European Medicines Agency issued draft guidelines for the clinical evaluation of medicinal products for the treatment of chronic hepatitis C. The current standard of care is a combination of peginterferon and ribavirin for 48 weeks pending approval of directly acting antivirals. They discuss the importance of new treatments for use in special populations including patients with decompensated liver disease, pre and post transplant, HCV and HIV co-infection, intolerance to pegylated interferon and/or ribavirin and patients with prior directly acting antiviral exposure.

Patients co-infected with Hepatitis B and/or HIV were excluded from the pivotal study and this may affect the generalisability of the results to the Scottish population. Clinical studies are

ongoing in these patient populations. Patients who were active substance abusers were also excluded and therefore the safety in these patients is not known.

A large number of capsules (four capsules three times a day) must be taken every day with food, in addition to the current treatment regimen of weekly subcutaneous injections of peginterferon alpha and up to seven capsules a day of ribavirin. This could potentially affect patient adherence with therapy.

The increased incidence of anaemia with boceprevir may increase the need for epoetin and/or transfusions, increasing the overall cost of treatment. Epoetin is currently not licensed for use in patients with anaemia developed in response to treatment for HCV.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing boceprevir in combination with peginterferon alfa and ribavirin with peginterferon alfa and ribavirin alone, in previously untreated patients with HCV genotype 1 infection. The results were estimated separately for non-cirrhotic patients with baseline fibrosis scores F0 - F3 (based on the Metavir scoring system) and for cirrhotic patients (fibrosis score F4) in order to reflect the different dosing regimens. For non-cirrhotic patients, early responders stopped treatment after 24 weeks whereas late responders continued for an additional 20 weeks. Cirrhotic patients received 44 weeks of triple therapy. Patients with detectable disease at week 12 or week 24 discontinued treatment.

A Markov model was used over a lifetime horizon. The structure of the model was in two parts: the first part had a decision-tree structure which modelled the outcomes for patients during the treatment and follow-up phases, and the second part was a Markov model which predicted the natural epidemiology of the disease for patients who had not achieved SVR. The source of the clinical evidence for the treatment phase of the model came from the pivotal study in treatment - naive patients. The transition probabilities for the Markov model phase were taken from various literature sources.

The utility values used in the model were taken the NICE technology appraisal of antiviral therapy where quality of life was measured in patients with HCV using EQ-5D. The assumption was made that the treatment-related utilities, which were based on patients receiving peginterferon alfa and ribavirin, could be applied to patients receiving boceprevir in combination with peginterferon alfa and ribavirin. However, a utility decrement was included to capture the quality of life loss due to anaemia which was the main additional adverse event associated with boceprevir treatment. Another key difference in comparison with the NICE model was patients who achieved SVR were assigned the same utility value regardless of baseline disease severity.

Resource use relating to the costs of initial tests and monitoring associated with treatment were included. In addition, the costs associated with the different health states of SVR, chronic HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplant were included in the model. As the liver-related complications are expensive to treat, the boceprevir arm benefits from the increase in patients who responded to treatment and therefore do not incur the future costs and quality of life loss associated with these events. The resource

use estimates included in the submission for these events were taken from the NICE technology appraisal of HCV.

The submitting company estimated the following results:

Patient group	Incremental cost	Incremental quality adjusted life years (QALYs)	Cost per QALY
Patients with fibrosis scores F0 – F3	£8,712	0.991	£8,800
Cirrhotic patients (fibrosis score F4)	£17,949	1.531	£11,722

The key limitations of the analysis were:

- The NICE model applied different utility values to the SVR health state depending on the severity of disease at baseline, whereas the boceprevir model assumes all patients who achieve SVR have a utility value of 0.82 regardless of baseline severity. As there are more patients in the boceprevir arm who achieve SVR this could bias the analysis in favour of boceprevir as the quality of life of patients who achieve SVR from moderate or severe disease may have been overestimated. Analysis using the NICE values was however provided and this resulted in cost per QALY figures of £9,989 and £20,921 for the F0-F3 and F4 groups respectively.
- The transition probabilities move patients through the severities of fibrosis and from compensated cirrhosis to hepatocellular carcinoma at a higher rate than the data sources used in the NICE model. If the rates of progression are overestimated this could bias the analysis in favour of boceprevir as there are more patients in the standard care arm who move through the natural disease progression part of the model. Therefore, patients would progress to the more severe health states earlier in the model. In addition to providing a helpful supplementary case to support the use of the base case transition probabilities, the submitting company also subsequently provided additional analyses based on the transition probabilities from the NICE model. Use of these figures altered the cost per QALY figures to £14,595 and £11,557 for the F0-F3 and F4 groups respectively. Analysis combining both the transition probabilities and utilities from NICE indicated that the ICERs rose to £18,225 and £20,808 for the two subgroups respectively.

Additional areas of uncertainty were:

- The time horizon of the analysis was 120 years. While a lifetime horizon is appropriate for this condition, a time horizon which covers 120 years is unrealistic. However, sensitivity analysis was subsequently provided which truncated the analysis at 50 years and the ICERs increased only marginally. This indicates that the majority of patients were predicted to have died long before the end of the model time horizon.
- The approved dosing regimens and patient groups modelled in the economic analysis differed from those defined in the trial. This introduces some uncertainty into the analysis.
- A number of different data sources were used to estimate the progression of patients through the various stages of HCV in the model and it is not clear if the patient populations are comparable.
- The analysis of cirrhotic patients was based on small patient numbers and includes the response rate of F3 and F4 patients.

- The submission was complex and lacked transparency in some areas. This was further complicated by the changes made to the model as a result of the differences between the study design and EMA approved dosing regimens.

The study results indicate a significant increase in response with boceprevir treatment which results in a larger proportion of patients achieving SVR and avoiding the long-term complications associated with HCV. As such, despite some limitations with the analysis, the economic case was considered demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Waverley Care
- The Hepatitis C Trust

Additional information: guidelines and protocols

The Scottish Government has published a Hepatitis C Action Plan for Scotland: Phase I was issued in 2006 and phase II in 2008. There are six strands of work that involve co-ordination of services, prevention, testing, treatment, care and support, education, training and awareness-raising and surveillance and monitoring.

Guidelines were published by the Scottish Intercollegiate Guidelines Network (SIGN) for the management of hepatitis C in December 2006. The treatment of choice for chronic hepatitis C is 48 weeks of combination treatment with peginterferon alfa and ribavirin. In patients who have not achieved a sustained virologic response with non-pegylated interferon with our without ribavirin, retreatment with peginterferon alfa and ribavirin is successful in some patients.

Additional information: comparators

Boceprevir is additional to the current standard treatment of peginterferon alfa plus ribavirin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
***Boceprevir**	**800mg three times daily for 24 weeks**	**16,800**
#Boceprevir	**800mg three times daily for 32 weeks**	**22,400**
#Boceprevir	**800mg three times daily for 44 weeks**	**30,800**

Doses are for general comparison and do not imply therapeutic equivalence. * In addition to pegylated interferon 1.5micrograms per kg subcutaneously weekly plus ribavarin 1000mg daily for 28 weeks costing £5,595. #In addition to pegylated interferon 1.5micrograms per kg subcutaneously weekly plus ribavarin 1000mg daily for 48 weeks costing £9,595. Costs from eVadis on 11 July 2011. Doses based on body weight of 70kg.

Additional information: budget impact

The submitting company provided budget impact scenarios for F0-F3 patients, cirrhotic patients, early and late responders, aggressive uptake and conservative uptake scenarios. In the conservative uptake scenarios, the manufacturer estimated an uptake rate of 5% in year 1 and 30% in year 5. In the aggressive uptake scenarios, the manufacturer estimated an uptake rate of 5% in year 1 rising to 50% in year 5. SMC clinical expert responses suggest that the aggressive uptake scenario may apply to uptake of the new class of protease inhibitors in hepatitis C infection.

Table 1: Estimated eligible patient numbers in conservative and aggressive uptake scenarios

Patient group	Conservative uptake		Aggressive uptake	
	Year 1	Year 5	Year 1	Year 5
F0 – F3 patients	127	651	127	1,085
Assuming 5% patients are F4	6	33	6	54
Assuming 15% patients are F4	19	98	19	163

Table 2: Estimated net budget impact in conservative and aggressive uptake scenarios

Patient group	Conservative uptake		Aggressive uptake	
	Year 1	Year 5	Year 1	Year 5
F0 – F3 patients: all patients are early responders	£2.1m	£10.9m	£2.1m	£18.2m
F0 – F3 patients: all patients are late responders	£2.8m	£14.6m	£2.8m	£24.3m
Assuming 5% of HCV patients are F4	£195k	£1m	£195k	£1.7m
Assuming 15% of HCV patients are F4	£584k	£3m	£584k	£5m

References

The undernoted reference was supplied with the submission. The reference shaded in grey is additional to the one supplied with the submission.

Poordad F, McCone J, Bacon B, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. SPRINT-2. N Engl J Med, 31st March 2011; 364(13): Pages 1195 - 1206.

Bacon BR et al; HCV RESPOND-2 investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. NEnglJMed 2011; 364(13): 1207–1217 and supplementary appendix www.nejm.org

This assessment is based on data submitted by the applicant company up to and including 12 August 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.