Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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boceprevir 200mg capsule (Victrelis®) Treatment experienced patients SMC No. (722/11)

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 alfa and ribavirin, in adult patients with compensated liver disease who have failed previous therapy.

In the pivotal phase III randomised study, addition of boceprevir to current standard therapy in patients with HCV, who had failed previous therapy, increased the proportion of patients 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 alfa 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 have failed previous therapy 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 a day for 32 weeks, then peginterferon alfa and ribavirin for 12 weeks. Total treatment duration is 48 weeks.

In cirrhotic patients (Metavir score 4) and null responders to interferon the recommended treatment is peginterferon alfa and ribavirin for four weeks followed by boceprevir, peginterferon alfa and ribavirin for 44 weeks. Total treatment duration of 48 weeks.

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

Product availability date

21 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 the treatment of HCV.

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

Evidence comes from one pivotal phase III multi-centre randomised double-blind placebo-controlled study comparing peginterferon alfa-2b plus ribavirin (standard of care) with standard of care plus boceprevir 800mg three times daily in two different treatment regimens, in 403 adult patients with chronic HCV genotype 1 who had demonstrated interferon responsiveness (minimum duration of therapy, 12 weeks), but had failed to achieve a sustained virologic response (SVR). Previous null responders were excluded; only patients who had a poor response to interferon or had relapsed after treatment were included.

Following a four week lead-in period when all patients received peginterferon alfa-2b (1.5 micrograms per kg subcutaneously once weekly) plus ribavirin (600mg-1400mg orally daily in two divided doses, depending on body weight), patients remained on this treatment but in addition were randomised in a 1:2:2 ratio to:

- Group 1: (n=80) boceprevir-matched placebo for 44 weeks.

- Group 2: (n=162) a response-guided therapy (RGT) regimen of boceprevir, peginterferon alfa and ribavirin, for 32 weeks; further therapy was then determined by the 12 week stopping rule. Patients with an undetectable HCV RNA level at weeks 8 and 12 completed therapy at week 36, whereas patients with a detectable HCV RNA level at week 8 (but an undetectable level at week 12) received peginterferon alfa and ribavirin with placebo substituted for boceprevir for an additional 12 weeks.
- Group 3: (n=161) boceprevir, peginterferon alfa and ribavirin for 44 weeks.

Patients were randomised and stratified according to previous response to therapy (poor-response or relapse), and HCV subgenotype (1a or 1b). The length of the study was 72 weeks, including a treatment period of 36 or 48 weeks and a follow up period of 24 or 36 weeks. Any patient with detectable HCV RNA at week 12 was considered a treatment failure and treatment stopped. Patients who were hepatitis B and/or human immunodeficiency virus (HIV) positive were excluded from the study.

The primary outcome was the achievement of an 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.

In the FAS, rates of SVR were significantly higher among patients receiving boceprevir, peginterferon alfa and ribavirin than among those treated with peginterferon alfa and ribavirin alone, with overall rates of SVR of 21% (17/80), 59% (95/162), and 66% (107/161) in groups 1, 2, and 3, respectively ($p<0.001$). The absolute difference between group 2 and group 1 was 37%, (95% confidence interval [CI], 26 to 49) and between group 3 and group 1 45% (95% CI, 33 to 57).

The secondary analyses demonstrated that SVR rates were significantly higher in both boceprevir groups compared with peginterferon and ribavirin alone, in patients with prior relapse (69% and 75% versus 29% respectively) and prior poor-response (40% and 52% versus 7% respectively). Of the 102 patients with a poor response after the 4-week lead-in period, a SVR was achieved by no patients in the peginterferon plus ribavarin group (0/12) and 33% (15/46) and 34% (15/44) in the boceprevir groups. In 291 patients with a good response at week 4, the rates of SVR were 25% (17/67), 73% (80/110), and 79% (90/114) in group 1, 2 and 3, respectively.

A subgroup analysis of the baseline characteristics 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

During the pivotal study, an adverse event was reported by 96%, 99% and 100% of patients in groups 1, 2 and 3 respectively. There were more serious adverse events, discontinuations and dose modifications in the boceprevir groups. Serious adverse events were reported in 5%, 10% and 14%; discontinuation due to adverse effects occurred in 2%, 8% and 12%; and dose modifications due to adverse events occurred in 14%, 29% and 33% in groups 1, 2 and 3 respectively.

Significantly more patients experienced grade 3 neutropenia in the boceprevir groups (19% and 20% versus 9%), but the difference in grade 4 neutropenia was not significant (6% and 7% versus 4%).

There was a significantly higher incidence of anaemia in the groups receiving boceprevir (43% and 46% versus 20%); however, discontinuation because of anaemia was infrequent. Epoetin and blood transfusions were administered to manage anaemia: epoetin was given to 41% and 46% of boceprevir patients in groups 2 and 3 and a blood transfusion was received by 2% and 9% of patients in these groups. In the peginterferon alfa plus ribavirin group 21% of patients received epoetin and no patients required a blood transfusion. Sixteen patients who received blood transfusions also received epoetin.

The most common adverse events observed in all treatment groups were flu-like symptoms that are typically reported in association with peginterferon alfa and ribavirin. Dysgeusia, rash, and dry skin were reported more commonly in the boceprevir groups than in the control group.

Summary of clinical effectiveness issues

The Scottish Government's Hepatitis C Action Plan for Scotland estimated in 2006 that approximately 50,000 people in Scotland were infected with HCV so it is an important health issue.

In the pivotal study, the addition of boceprevir to standard therapy significantly increased the proportion of patients achieving an SVR by between 37% and 45% depending on the boceprevir regimen administered. This study included only patients with genotype 1 but these are the patients who are most difficult to treat. An increase in patients achieving a SVR should decrease the incidence of onward transmission and risk of developing complications from HCV.

The marketing authorisation granted by the European Medicines Agency (EMA) for all non-cirrhotic patients is based on one of the RGT regimens in group 2: the regimen used in patients who had a detectable HCV RNA level at week 8 (but an undetectable level at week 12) and who received a lead in period of peginterferon alfa and ribavirin for 4 weeks, then boceprevir, peginterferon alfa and ribavirin for 32 weeks then peginterferon alfa and ribavirin for an additional 12 weeks. The response guided therapy in group 2, which reduced the treatment length from 48 weeks to 36 weeks in early responders, has not been approved by the EMA.

Two additional groups have been included in the marketing authorisation: previous null responders and cirrhotic patients. Efficacy data in previous null responders is lacking as these patients were excluded from the pivotal study, however these have been included in the licence based on the responses seen in partial responders in the study. A subgroup analysis of cirrhotic patients versus non-cirrhotic patients in the pivotal study identified a higher SVR in cirrhotic patients in group 3 (77%) compared with group 2 (35%). Despite the study not being powered to detect a difference between these groups, the higher SVR rates in group 3 led to EMA granting a marketing authorisation for use in cirrhotic patients. Therefore the extended treatment length of boceprevir of 44 weeks, in combination with peginterferon alfa and ribavirin treatment for a total of 48 weeks, is the licensed treatment schedule for these groups.

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. 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 is highlighted.

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 may result in an increased 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 patients with HCV genotype 1 infection who have failed previous therapy. The results were estimated separately for non-cirrhotic patients with baseline fibrosis scores F0 - F3 (based on the Metavir scoring system), cirrhotic patients (fibrosis score F4) and previous null responders in order to reflect the different dosing regimens. Non-cirrhotic patients stopped triple therapy after 32 weeks treatment and continued on peginterferon alfa and ribavirin alone for an additional 12 weeks whereas cirrhotic patients and null responders received triple therapy for 44 weeks. 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 patients who had failed previous therapy. The transition probabilities for the Markov model phase were taken from various literature sources.

The utility values used in the model were taken from 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 such 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	£14,787	1.923	£7,690
Cirrhotic patients (F4)	£7,460	5.46	£1,368
Null responders	£18,515	2.3	£8,042

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 £8,778, £2,437 and £9,273 for the F0-F3, F4 and null responder 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 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 £12,838, £11,670, and £931 for the F0-F3, F4 and null responder groups respectively. Analysis combining both the transition probabilities and utilities from NICE indicated that the ICERs only rose to £15,668 £1,683 and £14,479 for the three 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. 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 both 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 Groups 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 Guideline 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 and ribavirin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
***boceprevir**	**800mg three times daily for 32 to 44 weeks**	**22,400 to 30,800**

Doses are for general comparison and do not imply therapeutic equivalence.
*In addition to peginterferon alfa 1.5micrograms per kg subcutaneously weekly plus ribavirin 1000mg daily for 48 weeks costing £9595. Costs from eVadis on 11 July 2011. Doses based on body weight of 70kg.

Additional information: budget impact

The submitting company provided a range of budget impact scenarios for F0-F3 patients, cirrhotic patients, null 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 market share was estimated to increase 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	39	525	39	782
Assuming 5% patients are F4	2	26	2	39
Assuming 15% patients are F4	6	79	6	117
Null responders	9	116	9	172

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	£883k	£11.7m	£883k	£17.5m
Assuming 5% of patients are F4	£61k	£809k	£61k	£1.2m
Assuming 15% of patients are F4	£182k	£2.4m	£182k	£3.6m
Null responders	£268k	£3.6m	£268k	£5.3m

References

The reference shaded in grey is additional to data supplied with the submission.

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.