

Boceprevir for the treatment of genotype 1 chronic hepatitis C

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1 Guidance

1.1 Boceprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease:

- who are previously untreated **or**
- in whom previous treatment has failed.

2 The technology

- 2.1 Boceprevir (Victrelis, Merck Sharp & Dohme) is a NS3/4A serine protease inhibitor that is administered orally (800 mg three times daily with food). NS3/4A serine protease is essential for viral replication and may be partially responsible for the ability of the hepatitis C virus (HCV) to evade clearance by the host immune system. Boceprevir has a UK marketing authorisation 'for the treatment of chronic hepatitis C 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'. The recommended duration of treatment with boceprevir depends on a person's previous treatment exposure, presence or absence of cirrhosis and their response to treatment with boceprevir (as indicated by the viral load). For full details of the different treatment regimens, see the summary of product characteristics.
- 2.2 The summary of product characteristics lists the following adverse reactions for boceprevir as the most frequently reported: fatigue, anaemia, nausea, headache and dysgeusia. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 Boceprevir is priced at £2800 for a 28-day, 336-tablet pack (excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] January 2012) and costs £30,800 for a 44-week course. The recommended duration of treatment with boceprevir may be shorter (24 weeks or 32 weeks) depending on patient and disease characteristics. The marketing authorisation states that boceprevir should be given in combination with peginterferon alfa and ribavirin, which has an estimated additional cost of around £11,000 (see [Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C](#) [NICE technology appraisal guidance 200] for details). For full details of the different recommended dosing regimens, see the summary of product characteristics. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of boceprevir and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).

Clinical effectiveness

- 3.1 The manufacturer identified five randomised controlled trials that investigated the effect of boceprevir in adults with genotype 1 chronic hepatitis C and presented three of these in full in its submission. Results from an ongoing non-randomised phase II study (PROVIDE) were also presented.
- 3.2 One placebo-controlled phase III trial (SPRINT-2) evaluated the addition of boceprevir to peginterferon alfa-2b and ribavirin (PEG2b/R) therapy in treatment-naive patients (that is, patients who had not been previously treated). The study drugs were peginterferon alfa-2b (1.5 micrograms/kg subcutaneously once weekly), ribavirin (divided daily oral dose 600–1400 mg according to body weight) and boceprevir (800 mg orally three times daily) or placebo. The trial enrolled two patient cohorts, black and non-black patients. Patients were randomised to one of three treatment arms:
- In the control arm, patients (n = 363) received 4 weeks of PEG2b/R lead-in then 44 weeks of placebo plus PEG2b/R and 24 weeks of further follow-up.
 - In the response-guided boceprevir plus PEG2b/R arm, patients (n = 368) received 4 weeks of PEG2b/R lead-in then 24 weeks of boceprevir plus PEG2b/R. At treatment week 28, these patients were assigned to one of two groups based on their HCV RNA results from treatment week 8 to treatment week 24.
 - Patients who had an early response (undetectable HCV RNA at and after treatment week 8) received no further treatment and entered follow-up for 44 weeks.
 - Patients who had a late response (detectable HCV RNA at or after treatment week 8 but undetectable at week 24) continued therapy with placebo plus PEG2b/R for an additional 20 weeks then were followed up for 24 weeks post-treatment.

- In the third treatment arm, patients (n = 366) received 4 weeks of PEG2b/R lead-in then 44 weeks of boceprevir plus PEG2b/R and 24 weeks of further follow-up.
- 3.3 Two other phase III trials (RESPOND-2 and P05685) investigated the effect of adding boceprevir to peginterferon alfa and ribavirin in previously treated patients who had not experienced a sustained virological response following treatment with peginterferon alfa plus ribavirin but who had demonstrated interferon responsiveness. Patients whose disease had not responded to previous therapy ('null responders' who had less than a 2 log₁₀ decline in HCV RNA at treatment week 12) were excluded from the studies.
- 3.4 Using dosages as described for SPRINT-2, RESPOND-2 compared boceprevir plus PEG2b/R with PEG2b/R alone:
- In the control PEG2b/R arm, patients (n = 80) received 4 weeks of PEG2b/R lead-in then 44 weeks of placebo plus PEG2b/R and further follow-up for 24 weeks.
 - In the response-guided boceprevir plus PEG2b/R arm, patients (n = 162) received 4 weeks of PEG2b/R lead-in then 32 weeks of boceprevir plus PEG2b/R. At treatment week 36, patients in this treatment arm were assigned to one of two groups based on their HCV RNA results at and after treatment weeks 8 and 12.
 - Patients who had an early response (undetectable HCV RNA at and after treatment week 8) received no further treatment, and entered follow-up for 36 weeks.
 - Patients who had a late response (detectable HCV RNA at treatment week 8 but not week 12) continued therapy with placebo plus PEG2b/R for an additional 12 weeks then entered follow-up for 24 weeks.
 - In the third treatment arm, patients (n = 161) received 4 weeks of PEG2b/R lead-in then 44 weeks of boceprevir plus PEG2b/R and 24 weeks of further follow-up.
- 3.5 P05685 investigated the addition of boceprevir to peginterferon alfa-2a and ribavirin (PEG2a/R). Study drugs were peginterferon alfa-2a (180 micrograms subcutaneously once weekly), ribavirin (divided daily oral dose 1000–1200 mg according to body weight) and boceprevir (800 mg, orally three times daily) or placebo. In the control arm, patients (n = 67) received 4 weeks of lead-in with

PEG2a/R then 44 weeks of placebo plus PEG2a/R and 24 weeks of follow-up. In the experimental arm, patients (n = 134) received 4 weeks of lead-in treatment with PEG2a/R then 44 weeks of boceprevir plus PEG2a/R and 24 weeks of further follow-up.

- 3.6 PROVIDE is an ongoing single-arm, multicentre phase II follow-up study evaluating boceprevir plus PEG2b/R (dosages as described for SPRINT-2) in 168 patients who had been previously randomised to the control arm of one of the phase II/III boceprevir studies and had not achieved a sustained virological response. An interim subanalysis of the PROVIDE trial provided by the manufacturer included 48 patients who were originally treated in either the SPRINT-2 or RESPOND-2 trials and whose condition had not responded to previous therapy with PEG2b/R ('null responders' who had less than a 2 log₁₀ HCV RNA decline from baseline by treatment week 12). All patients in this subanalysis received a 4-week PEG2b/R lead-in then boceprevir plus PEG2b/R for up to 44 weeks' and 24 weeks' follow-up.
- 3.7 All arms in the phase III clinical trials and the phase II PROVIDE study included a 4-week lead-in period of PEG2b/R or PEG2a/R to decrease the potential for resistance, to allow assessment of adherence and tolerance, and for the drugs to reach steady state. During this period, a patient's responsiveness to interferon was also assessed. The trials employed stopping rules where patients discontinued therapy at a pre-specified time point if HCV RNA was still detectable (treatment week 24 in SPRINT-2 and treatment week 12 in RESPOND-2, P05685 and PROVIDE). SPRINT-2 and RESPOND-2 included response-guided therapy arms to allow patients who experienced an early response to shorten the treatment duration.
- 3.8 The primary outcome for all four trials was sustained virological response (defined as undetectable HCV RNA at 24 weeks after completing therapy). In the phase III trials, the primary endpoint was reported for the 'full analysis set' population (defined as patients who had received at least one dose of any study drug). A key secondary outcome for the phase III trials was sustained virological response in the 'modified intention-to-treat' population (defined as patients who had received at least one dose of boceprevir or placebo). Other secondary outcomes included proportion of patients with early virological

response (defined as undetectable HCV RNA by treatment week 12) and the proportion of patients with undetectable HCV RNA at follow-up week 12. None of the trials collected health-related quality-of-life data. Patient characteristics were generally similar across treatment arms. Results are reported in this document for the 'full analysis set' population except where specified.

Treatment-naive patients

- 3.9 The manufacturer considered that because the SPRINT-2 trial results showed that boceprevir provided considerable benefit for both black and non-black cohorts, it was not appropriate to evaluate the two populations separately. For the combined cohort (both black and non-black cohorts) of treatment-naive patients, sustained virological response rates were statistically significantly higher in patients receiving boceprevir plus PEG2b/R response-guided therapy compared with PEG2b/R therapy alone (63.3% versus 37.7%, absolute difference from control 25.6%; 95% confidence interval [CI] 18.6 to 32.6, $p < 0.001$). Sustained virological response rates were also statistically significantly higher in the other group of patients who were all treated with 48 weeks of therapy either with boceprevir plus PEG2b/R or with PEG2b/R alone (66.1% versus 37.7%, absolute difference from control 28.4%; 95% CI 21.4 to 35.3, $p < 0.001$).
- 3.10 The manufacturer provided results from the SPRINT-2 trial for treatment-naive patients with compensated cirrhosis. These showed a numerically higher sustained virological response rate with PEG2b/R (46.2%) than with boceprevir plus PEG2b/R (31.3% in the response-guided boceprevir plus PEG2b/R arm and 41.7% in the boceprevir plus PEG2b/R arm) but the differences were not statistically significant. The manufacturer explained that the results are difficult to interpret because the number of patients with cirrhosis was low (53 patients in total) and the high percentage of patients taking PEG2b/R experiencing a sustained virological response was inconsistent with other studies.

Previously treated patients

- 3.11 The manufacturer's submission reported that significantly more previously treated patients receiving boceprevir plus peginterferon alfa and ribavirin (PEG2a/R or PEG2b/R) experienced a sustained virological response

compared with those taking peginterferon alfa and ribavirin alone in the RESPOND-2 and P05685 trials. In RESPOND-2, sustained virological response rates were 58.6% for response-guided boceprevir plus PEG2b (absolute difference from control 37.4; 95% CI 25.7 to 49.1, $p < 0.001$); 66.5% for boceprevir plus PEG2b/R for a total of 48 weeks (absolute difference from control 45.2; 95% CI 33.7 to 56.8, $p < 0.001$) and 21.3% for PEG2b/R for a total of 48 weeks. In P05685, sustained virological response rates were 64.2% for boceprevir plus PEG2a/R and 20.9% for PEG2a/R (absolute difference 43.3; 95% CI 30.6 to 56.0, $p < 0.001$).

- 3.12 The manufacturer's interim subanalysis of the PROVIDE study showed that patients whose disease had not responded to previous therapy with peginterferon alfa and ribavirin ('null responders' who had less than a $2 \log_{10}$ HCV RNA decline by treatment week 12 in the previous study) had a sustained virological response rate of 38% (16/42 patients) after treatment with boceprevir plus PEG2b/R. The manufacturer considered that the limited patient numbers precluded the identification of any baseline characteristics that might predict sustained virological response.
- 3.13 The manufacturer provided results from the RESPOND-2 and P05685 trials for previously treated patients with compensated cirrhosis. RESPOND-2 showed a higher sustained virological response rate for patients treated with boceprevir plus PEG2b/R than for patients treated with PEG2b/R therapy alone (35.3% for response-guided boceprevir plus PEG2b/R, $p = 0.057$; 77.3% for boceprevir plus PEG2b/R, $p < 0.0001$; 0% for PEG2b/R). In the P05685 trial, sustained virological response rates were numerically higher for patients treated with boceprevir plus PEG2a/R than with PEG2a/R alone (50.0% versus 11.1%, $p = 0.056$). The manufacturer explained that the results are difficult to interpret because of low patient numbers (a total of 82 patients with cirrhosis in the two trials).

Meta-analysis

- 3.14 The manufacturer conducted a meta-analysis of the RESPOND-2 and P05685 trials to investigate the sustained virological response rate in two small subgroups: patients with compensated cirrhosis and patients whose disease had not responded to previous therapy. Data from the boceprevir triple-therapy

and control dual-therapy treatment arms (48-week duration) were used. The manufacturer's meta-analysis showed higher sustained virological response rates in patients with compensated cirrhosis receiving boceprevir plus peginterferon alfa and ribavirin (63%; 95% CI 49 to 76%) than with peginterferon alfa and ribavirin alone (5%; 95% CI 1 to 24%). Although patients whose disease had not responded to previous treatment had been excluded from the phase III studies, the manufacturer used data from patients whose disease had responded poorly to interferon at treatment week 4 (less than 1 log₁₀ decrease in HCV RNA) to estimate sustained virological response rates for the previously treated population. The meta-analysis showed higher sustained virological response rates with boceprevir plus peginterferon alfa and ribavirin than with peginterferon alfa and ribavirin alone in patients whose disease had not previously responded to therapy (40%; 95% CI 28 to 54%, versus 0%).

Retrospective analysis of boceprevir efficacy data analysed according to the UK marketing authorisation

- 3.15 The UK marketing authorisation for boceprevir recommends treatment regimens that differ from those in the clinical trials. The manufacturer conducted a retrospective analysis using sustained virological response rates from the populations from SPRINT-2 (treatment-naive patients) and RESPOND-2 and P05685 (previously treated patients) to consider the efficacy of boceprevir in line with the dosing regimen in its marketing authorisation. Patients whose disease had not responded to previous therapy ('null responders' who had less than a 2 log₁₀ decline in HCV RNA at treatment week 12 of their previous regimen) were excluded from the phase III clinical trials so the sustained virological response rate for this group was estimated based on patients whose disease had a poor response to interferon (less than a 1 log₁₀ decrease in HCV RNA) at treatment week 4.
- 3.16 Using patient groups defined in the UK marketing authorisation according to METAVIR score (which scores the degree of fibrosis from no fibrosis [F0] to compensated cirrhosis [F4]), the manufacturer reported that sustained virological response rates were 96.8% with boceprevir plus PEG2b/R versus 37.2% with PEG2b/R in treatment-naive patients without cirrhosis whose disease had an early virological response (METAVIR score F0–3 with HCV

RNA undetectable at treatment weeks 8 and 24). Sustained virological response rates for treatment-naive patients without cirrhosis whose disease responded late (METAVIR score F0–3 with HCV RNA detectable at treatment week 8 and undetectable at treatment week 24) were 67.7% for those receiving boceprevir plus PEG2b/R compared with 37.2% for those receiving PEG2b/R. Sustained virological response rates were 41.7% with boceprevir plus PEG2b/R and 46.2% with PEG2b/R in treatment-naive patients with compensated cirrhosis (METAVIR score F4).

- 3.17 The manufacturer stated that sustained virological response rates in previously treated patients without cirrhosis whose disease had an early virological response (METAVIR score F0–3 with HCV RNA undetectable at treatment weeks 8 and 24) were 90.6% with boceprevir plus PEG2b/R and 24.2% with PEG2b/R. For previously treated patients without cirrhosis whose disease responded late (METAVIR score F0–3 with HCV RNA detectable at treatment week 8 and undetectable at treatment week 24), the sustained virological response rate was 85.2% with boceprevir plus PEG2b/R and 24.2% with PEG2b/R alone. These figures were solely derived from RESPOND-2 trial data, because the groups were not applicable to the P05685 trial.
- 3.18 For previously treated patients with compensated cirrhosis (METAVIR score F4), the manufacturer estimated the sustained virological response rates were 77.3% and 50% with boceprevir plus peginterferon alfa and ribavirin and 0% and 11.1% with peginterferon alfa plus ribavirin, using RESPOND-2 and P05685 data respectively. In patients whose disease had not responded to previous therapy (estimated based on patients whose disease responded poorly to interferon at treatment week 4 of the trials [less than a 1 log₁₀ decrease in HCV RNA]), sustained virological response rates were 38.9% and 42.9% with boceprevir plus peginterferon alfa and ribavirin, and 0% with peginterferon alfa plus ribavirin alone, using RESPOND-2 and P05685 data respectively.

Adverse reactions

- 3.19 The manufacturer included a pooled safety analysis from three boceprevir clinical trials: SPRINT-2, RESPOND-2 and SPRINT-1 (an open-label, randomised phase II trial in treatment-naive patients). The manufacturer's

pooled safety analysis showed that there were no adverse reactions specifically associated with boceprevir. Mortality and treatment discontinuation caused by adverse reactions were broadly similar with boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone. However, a higher percentage of patients receiving boceprevir plus peginterferon alfa and ribavirin compared with those receiving peginterferon alfa and ribavirin alone experienced anaemia (49% versus 29%, relative risk 1.7; 95% CI 1.5 to 1.9), neutropenia (23% versus 18%; relative risk 1.3; 95% CI 1.0 to 1.6) and altered sensation of taste (37% versus 15%; relative risk 2.4; 95% CI 1.9 to 3.0).

- 3.20 Patients in the trials who developed anaemia were treated using dose reduction (predominantly of ribavirin), erythropoietin and transfusions. Dose reduction was more likely for patients receiving boceprevir plus peginterferon alfa and ribavirin than peginterferon alfa and ribavirin alone (39% versus 24%). Erythropoietin alone was used in 37% of patients receiving peginterferon alfa and ribavirin alone and 33% of patients receiving boceprevir plus peginterferon alfa and ribavirin. A combination of erythropoietin treatment and ribavirin dose reduction was used in 32% of patients receiving peginterferon alfa and ribavirin alone and 46% of patients receiving boceprevir plus peginterferon alfa and ribavirin. The manufacturer noted that erythropoietin does not have a UK marketing authorisation for the treatment of anaemia related to HCV therapy and estimated that its use varies from around 0–50% of cases in clinical practice (being highest in specialist HCV centres). A post-hoc analysis by the manufacturer indicated that the likelihood of a patient experiencing a sustained virological response was not affected by the method used to manage anaemia. The manufacturer noted that this finding was consistent with results from another study (IDEAL), which found that ribavirin dose reduction was not associated with lower sustained virological response rates in patients who developed anaemia during treatment with peginterferon alfa and ribavirin.

Cost effectiveness

- 3.21 The manufacturer submitted a de novo economic analysis that assessed the cost effectiveness of boceprevir plus peginterferon alfa and ribavirin for the treatment of genotype 1 chronic hepatitis C in adults who were previously

untreated or who had experienced treatment failure. The manufacturer stated that the modelled population was aligned with the UK marketing authorisation and the patient population expected to receive boceprevir (in terms of age, gender, ethnicity and degree of fibrosis) in UK clinical practice. The analysis was conducted from an NHS and personal and social services perspective and a lifetime horizon was used.

- 3.22 The manufacturer developed a Markov model to estimate the expected costs and benefits associated with the treatment strategies applied in the clinical trials (SPRINT-2, RESPOND-2, and P05685) relative to the boceprevir UK marketing authorisation. The structure of the model is based on other published health economic models of chronic HCV, including [NICE technology appraisal guidance 200](#). Data from the clinical trials were used to inform model inputs for treatment effects and adverse reactions. The model simulates treatment and the subsequent natural history of chronic HCV, depending on whether the patient experiences a sustained virological response. Patients enter the model with chronic hepatitis C and begin drug therapy. The first 72 weeks (48 weeks' treatment and 24 weeks' follow-up) are modelled using a weekly cycle then the remaining cycles each last 1 year. At each cycle, a patient can discontinue or continue treatment. Patients who discontinue treatment or have detectable HCV RNA during treatment or follow-up return to the chronic HCV health states.
- 3.23 The model has a total of 16 health states according to disease stage and treatment response. The severity of chronic HCV infection is described by the degree of fibrosis using the METAVIR scoring system (from no fibrosis [F0] to compensated cirrhosis [F4]). The model assumes that a patient may develop more advanced liver disease or remain in their current health state, and that patients who experience a sustained virological response will not progress to more severe health states during or after therapy. Reversion to less severe health states is not permitted in the model if treatment is successful. The sustained virological response health state is stratified by the patient's original fibrosis stage to allow for differences in risk and outcomes. Patients with decompensated cirrhosis, hepatocellular carcinoma or a liver transplant are assumed to have an increased mortality compared with the general population in the model. All other patients in the model, including those with compensated

cirrhosis, are assumed to have the same mortality risk as the general population.

- 3.24 The duration spent in each health state, the likelihood of developing serious disease-related complications and the probability of requiring a liver transplant are determined by the progression rates from Thein et al. (2008). These progression rates were chosen by the manufacturer because they were available for each stage and by fibrosis level (unlike progression rates used in previous NICE technology appraisals for HCV). The natural progression of the disease was modelled using disease-specific transition probabilities between health states. Some of the sources used by the manufacturer had been used in previous NICE technology appraisals for HCV.
- 3.25 Different scenarios were modelled by the manufacturer according to patients' fibrosis scores and whether they had been previously treated or not with peginterferon alpha and ribavirin. Using the treatment regimens in the UK marketing authorisation for boceprevir, treatment with boceprevir plus peginterferon alfa and ribavirin was compared with peginterferon alfa and ribavirin in:
- treatment-naive patients without cirrhosis (METAVIR score F0–F3)
 - treatment-naive patients with compensated cirrhosis (METAVIR score F4)
 - treatment-naive patients eligible for response-guided treatment with peginterferon alfa and ribavirin (low viral load when starting treatment and no detectable virus at both weeks 4 and 24)
 - previously treated patients without cirrhosis (METAVIR score F0–F3)
 - previously treated patients with compensated cirrhosis (METAVIR score F4)
 - previously treated patients whose disease had not responded to prior treatment.
- 3.26 The manufacturer applied utility values from [NICE technology appraisal guidance 200](#) in its analysis. Treatment-related utility values were applied to reflect the initial decrease in health state that patients experience while taking peginterferon alfa and ribavirin (0.66 for mild HCV [METAVIR F0–1], 0.55 for

moderate HCV [F2–3] and 0.44 for severe HCV [F4]). The same values were applied for patients receiving peginterferon alfa and ribavirin treatment and for those who did not experience further adverse reactions when boceprevir was added to peginterferon alfa and ribavirin. A utility decrement of 12.2% was applied for treatment-related anaemia with boceprevir plus peginterferon alfa and ribavirin. Utility values for sustained virological response differed according to the degree of fibrosis at baseline (0.82 for mild HCV [F0–1], 0.72 for moderate HCV [F2–3] and 0.60 for severe HCV [F4]). For patients who did not experience a sustained virological response, different utility values were applied: 0.77 for mild HCV [F0–1], 0.66 for moderate HCV [F2–3], 0.55 for severe HCV [F4] and 0.45 for decompensated cirrhosis, hepatocellular carcinoma and first year after liver transplant (which rose to 0.67 subsequently).

3.27 The manufacturer's drug costs were based on the list price in MIMS (July 2011). Blended prices for (a) peginterferon alfa-2a and peginterferon alfa-2b, and (b) both branded ribavirins were calculated based on an average body weight of 79 kg and the current market share of each product. The resulting daily prices were £18.74 for peginterferon alfa and £11.98 for ribavirin, and the daily price for boceprevir was £100. Costs for monitoring patients being treated with peginterferon alfa and ribavirin were taken from protocols developed for [Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C](#) (NICE technology appraisal guidance 106) and inflated to 2009/10 values. Total costs at week 48 for monitoring during treatment were £1095.99 for peginterferon alfa and ribavirin, increasing to £1279.89 when boceprevir was added because of a further mandatory HCV viral load test. Health-state costs for sustained virological response, chronic HCV, compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma, liver transplant and post liver transplant were taken from [NICE technology guidance 200](#). Costs for erythropoietin (epoetin alfa) to treat anaemia were taken from the costing statement for [Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia](#) (NICE technology appraisal guidance 142) and inflated to 2009/10 values of £199.14 weekly (assumed to be given for 18 weeks).

- 3.28 The manufacturer presented base-case analyses for boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin in treatment-naive and previously treated patients. The manufacturer's results show that adding boceprevir to peginterferon alfa and ribavirin increased the cost of treatment but was associated with more quality-adjusted life years (QALYs) than treatment with peginterferon and ribavirin alone.
- 3.29 In treatment-naive patients, the base-case incremental cost-effectiveness ratios (ICERs) for boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone were £11,601 per QALY gained (incremental costs £10,570; incremental QALYs 0.91) for the whole population (METAVIR score F0–4), £10,565 per QALY gained for patients without cirrhosis (METAVIR score F0–3) and £8880 per QALY gained for patients who received response-guided therapy. The base-case ICER was £246,958 per QALY gained for treatment-naive patients with compensated cirrhosis (METAVIR score F4).
- 3.30 In previously treated patients, the base-case ICERs for boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone were £2909 per QALY gained (incremental costs £5478; incremental QALYs 2.00) for the whole population (METAVIR score F0–4), £3327 per QALY gained for patients without cirrhosis (METAVIR score F0–3), £817 per QALY gained for patients with compensated cirrhosis (METAVIR score F4) and £4817 per QALY gained for patients whose disease had not responded to previous therapy ('null responders').
- 3.31 The manufacturer undertook a probabilistic sensitivity analysis to explore uncertainty and found this supported the results of the deterministic analyses. Compared with peginterferon alfa and ribavirin alone, the probability of boceprevir plus peginterferon alfa and ribavirin being cost effective at £20,000 per QALY gained was 92.5% across all treatment-naive patients (that is, irrespective of initial METAVIR score). For patients without cirrhosis (METAVIR score F0–3), the probability was 94.8%. For patients with compensated cirrhosis (METAVIR score F4), the probability was only 19.1%. The manufacturer noted that the stage F4 results were generated using clinical data from a small subset within the trial population. When using response-

guided treatment, the probability of cost effectiveness for treatment with boceprevir was 97.7%. The probability of boceprevir plus peginterferon alfa and ribavirin being cost effective at £30,000 per QALY gained was greater than 99% for all treatment-naive populations studied except for patients with compensated cirrhosis (METAVIR score F4; 26.4%).

- 3.32 For previously treated patients, the manufacturer found that the probability of boceprevir plus peginterferon alfa and ribavirin being cost effective compared with peginterferon alfa and ribavirin was 100% for patients without compensated cirrhosis (METAVIR score F0–3) at £20,000 per QALY gained and 100% for patients with compensated cirrhosis (METAVIR score F4) at £30,000 per QALY gained. The probability of boceprevir plus peginterferon alfa and ribavirin being cost effective in patients who had not responded to previous treatment ('null responders') was 99.9% at £20,000 per QALY gained.
- 3.33 The manufacturer tested the robustness of the model using deterministic sensitivity analyses. Structural sensitivity analyses showed that the ICERs had some sensitivity to changes in discount rate. The manufacturer reported the ICERs were most sensitive to changes in response to treatment (that is, varying the sustained virological response rate \pm 25%). In all sensitivity analyses, the manufacturer's ICERs remained below £20,000 per QALY gained for all groups of treatment-naive and previously treated patients except treatment-naive patients with compensated cirrhosis. The manufacturer's analyses generally showed a similar pattern for treatment-naive and previously treated patients.
- 3.34 To explore uncertainty around the cost-effectiveness estimates for patients whose disease had not responded to previous therapy ('null responders'), the manufacturer incorporated data from the ongoing PROVIDE study into its economic model. Using the sustained virological response rate from this study (38.1%), treatment with boceprevir plus peginterferon alfa and ribavirin yielded an ICER of £5390 per QALY gained for this population, which is similar to the results estimated by the manufacturer (ICER £4817 per QALY gained) when the sustained virological response rate of 40% from the meta-analysis of RESPOND-2 and P05685 was used.

Evidence Review Group comments

- 3.35 The ERG considered that the manufacturer had included trials that were relevant to the decision problem in its analysis. No additional relevant trials were identified and the ERG found the manufacturer's systematic review to be of good quality. The ERG stated that the manufacturer's submission contained a largely unbiased estimate of the treatment effect in relation to the decision problem, but noted four areas of weakness or uncertainty:
- There was considerable uncertainty associated with the post-hoc analysis of patients with compensated cirrhosis because of the low numbers involved.
 - Patients whose disease had not responded to previous therapy ('null responders') were excluded from the phase III trials so data for this group of patients were only available from the manufacturer's interim analysis of 42 patients from the ongoing phase II PROVIDE study, leading to considerable uncertainty.
 - The manufacturer's retrospective subgroup analysis of sustained virological response rates in patients from the clinical trials who received boceprevir in line with the dosing regimen specified in the UK marketing authorisation had low patient numbers and should be viewed with caution.
 - The high incidence of treatment-related adverse reactions in the clinical trials that was observed for patients receiving boceprevir plus peginterferon alfa and ribavirin in the clinical trials did not concur with the manufacturer's conclusion that 'boceprevir was generally well tolerated when used in combination with peginterferon alfa and ribavirin' (page 109 of the manufacturer's submission).
- 3.36 The ERG stated that the manufacturer's methods of economic evaluation and the model produced were acceptable. However, the ERG felt that the patient population in the clinical trials was unlikely to reflect the population treated in secondary care in the UK because the trials included a lower proportion of patients with compensated cirrhosis. It noted that the group of patients with compensated cirrhosis in the clinical trials was not adequately powered to provide reliable efficacy estimates.
- 3.37 The ERG noted concerns about the reliability of subgroup analyses in the manufacturer's submission that grouped initial fibrosis levels in line with the

marketing authorisation (F0–3 and F4). The ERG found that the methods for deriving efficacy estimates were not clearly described in the manufacturer's submission, and noted that the probabilities of achieving a sustained virological response for patients receiving boceprevir plus peginterferon alfa and ribavirin were derived from the clinical trials by initial level of fibrosis, whereas the probabilities for patients receiving peginterferon alfa and ribavirin were derived from the manufacturer's meta-analysis.

- 3.38 The ERG stated that a rationale for using transition probabilities between fibrosis severity states that were different from those in [NICE technology appraisal guidance 200](#) was provided by the manufacturer, but noted that no information on selection, relevance, and quality assessment was given. Although there were some sizeable differences compared with the earlier technology appraisal, the ERG felt the transition probabilities used by the manufacturer were appropriate because they were from a more recent source and in a more relevant format (that is, they used the METAVIR scoring system).
- 3.39 The ERG noted that the manufacturer's health-related quality of life estimates and patient outcome estimates were consistent with previous NICE technology appraisals. The ERG felt that all relevant costs had been considered by the manufacturer. The ERG noted that the manufacturer adopted the same approach as in [NICE technology appraisal guidance 200](#) for treatment-related and health-state resource use and felt the associated assumptions were generally reasonable. However, the ERG noted that the manufacturer's model assumes that 25% of patients with anaemia will receive treatment with erythropoietin, which is higher than the rate seen in UK clinical practice (according to the ERG's clinical specialist). The ERG concluded that this could mean an increase in patients who cannot tolerate treatment beyond that seen in the clinical trials.
- 3.40 The ERG stated that the manufacturer's ICERs were generally robust to changes in parameters except for changes in response to treatment (that is, the probability of a sustained virological response). The ERG found that most ranges in the manufacturer's sensitivity analyses were assigned arbitrarily and

would have preferred these to be linked to the confidence intervals for the treatment effects in the clinical trials.

ERG exploratory analyses

- 3.41 The ERG varied the distribution of fibrosis severity at model entry so that it was similar to that used in [NICE technology appraisal guidance 200](#) (that is, with a greater proportion of patients with advanced fibrosis and cirrhosis at study entry). This had no marked effect on the ICERs for all treatment-naive patients (£11,552 per QALY gained compared with £11,601 per QALY gained in the manufacturer's base case for the whole population). In previously treated patients, the ICER decreased to £1300 per QALY gained (from the manufacturer's base case of £2909 per QALY gained).
- 3.42 The ERG noted that although the estimates for progression rates in the manufacturer's submission were derived from studies where patients largely had similar characteristics to the study used in [NICE technology appraisal guidance 200](#), they were not derived from UK data and may not adequately reflect disease progression rates in UK patients. Given the uncertainty surrounding these estimates, the ERG conducted an exploratory analysis using parameter values from NICE technology appraisal guidance 200 for progression rates between fibrosis states for mild to moderate HCV (that is, for F0–F1 and F1–F2). The ERG found that these changes significantly increased the ICERs to £26,645 per QALY gained for treatment-naive patients and £6902 per QALY gained for previously treated patients. However, the ERG indicated that the transition probabilities used by the manufacturer were appropriate because they were from a more recent source (see section 3.38).
- 3.43 The ERG noted the relatively low use of erythropoietin in routine clinical practice in the UK, which contrasts with how anaemia was treated in the clinical trials for boceprevir and how erythropoietin use was incorporated into the model. Because of these concerns, the ERG ran an additional analysis that explored the impact of having no anaemic patients receiving erythropoietin and simultaneously increasing the discontinuation rate for medical reasons (including anaemia). It confirmed that this had little impact on the ICER.

3.44 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TA253

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of boceprevir, having considered evidence on the nature of genotype 1 chronic hepatitis C and the value placed on the benefits of boceprevir by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed the clinical treatment pathway for genotype 1 chronic hepatitis C. The Committee heard that patients who have been diagnosed and seek medical advice about managing their condition generally take a high level of responsibility for its management. However, many patients remain undiagnosed or do not prioritise treatment. It also heard from clinical specialists that current UK practice broadly follows NICE guidance (NICE technology appraisal guidance 75, 106 and 200), which recommends treatment with peginterferon alfa plus ribavirin for both treatment-naive and previously treated patients with chronic hepatitis C. The clinical specialists confirmed that interferon can be difficult to tolerate for some patients, although its toxicity is acceptable overall. They also advised that some patients are deterred from undertaking a year-long course of treatment because they perceive efficacy rates to be low relative to the side effects they are likely to experience. The Committee heard from the patient experts and clinical specialists that many patients have also chosen to defer treatment until new agents become available. The Committee acknowledged the difficulties patients face when using currently available therapies and concluded that further treatment options are needed for the management of genotype 1 chronic hepatitis C.
- 4.3 The Committee heard from the patient experts that symptoms of genotype 1 chronic hepatitis C and the side effects of treatment can have a significant impact on daily life. The patient experts described how many people fear the consequences of long-term progression of the disease, as well as transmitting it to others. Fear of vertical transmission is a particular concern for women of child-bearing age. The patient experts also described the severe symptoms that can be associated with treatment with peginterferon alfa plus ribavirin including flu-like illness, debilitating fatigue and psychological issues. However,

the patient experts stressed that, although treatment can be difficult to tolerate and the treatment regimen is lengthy, patients are willing to accept these negative aspects of therapy for the possibility of experiencing a sustained virological response. The Committee recognised the demands that living with genotype 1 chronic hepatitis C places on patients and concluded that treatments which enable patients to achieve a sustained virological response (considered equivalent to a cure) and which consequently help to reduce HCV transmission are of significant importance.

- 4.4 The Committee examined the clinical trial evidence presented by the manufacturer on the efficacy and safety of boceprevir plus peginterferon alfa and ribavirin. It noted multiple differences between the clinical trial designs and the UK marketing authorisation for boceprevir, and had concerns over the uncertainty associated with the manufacturer's retrospective analyses that assessed the patient subgroups in the trials relative to how they are classified in the marketing authorisation. Overall, however, the Committee concluded that the trials provided adequate evidence for assessing boceprevir for the treatment of genotype 1 chronic hepatitis C and were generalisable to the UK setting.
- 4.5 The Committee discussed the baseline fibrosis levels of the populations in the clinical trials. The clinical specialists explained that the extent of fibrosis at baseline was generally lower in the trials than would be seen in UK clinical practice and, specifically, that patients with compensated cirrhosis were under-represented in the trials (in both the treatment-naive and the previously treated populations). The Committee heard from the ERG that the small number of patients with compensated cirrhosis in the clinical trials generated considerable uncertainty in the manufacturer's analyses according to fibrosis level, and therefore the Committee concluded that reliable results for this subgroup on its own could not be established.
- 4.6 The Committee discussed the clinical effectiveness of boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone in treatment-naive patients (all fibrosis levels combined). It considered that the boceprevir-containing regimen produced sustained virological response rates that were higher than peginterferon alfa and ribavirin alone for

the 'standard' (48 weeks' treatment) and response-guided regimens. The Committee concluded that boceprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in treatment-naive patients, irrespective of baseline fibrosis level.

- 4.7 The Committee reviewed the clinical trial data comparing boceprevir plus peginterferon alfa and ribavirin with peginterferon alfa and ribavirin alone in patients who had been previously treated. It considered that the boceprevir-containing regimen produced sustained virological response rates that were greater than peginterferon alfa and ribavirin alone for the 'standard' (48 weeks' treatment) and response-guided regimens. The Committee noted that patients whose disease had not responded to previous therapy ('null responders') were excluded from the phase III trials. However, it accepted the 'null responders' group estimated using phase III trial data in the manufacturer's submission (see [section 3.15](#)) in light of the phase II PROVIDE data that showed a similar proportion of patients whose condition had not responded to peginterferon alfa and ribavirin in the control arm of an earlier boceprevir clinical trial subsequently responded to a boceprevir-containing regimen. The Committee concluded that boceprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in previously treated patients, including those whose condition had not previously responded to treatment, and irrespective of baseline fibrosis level.
- 4.8 The Committee considered the likely long-term effects of boceprevir and whether a sustained virological response achieved by patients with a METAVIR (fibrosis) score of F0-3 could prevent them from developing cirrhosis in the future. It heard from the clinical specialists that a patient without cirrhosis (METAVIR score F0-3) who experienced a sustained virological response following treatment would be very unlikely to develop compensated cirrhosis (F4) or further complications. The Committee also acknowledged the significant public health impact that achieving a sustained virological response can have in terms of reducing transmission of HCV to uninfected people. The Committee concluded that a sustained virological response in a patient who did not have compensated cirrhosis could be broadly considered to be

equivalent to a cure, and can also have significant positive effects at a population level by reducing HCV transmission rates.

- 4.9 The Committee considered the adverse reactions associated with treatment with boceprevir plus peginterferon alfa and ribavirin. It heard from the clinical specialists that most adverse reactions from treatment were medically manageable. The Committee was also cautioned by the clinical specialists and patient experts that adding boceprevir to peginterferon alfa and ribavirin may increase rates of anaemia. The Committee acknowledged that although erythropoietin was widely available to patients in the boceprevir clinical trials to treat anaemia, it is not routinely used in the UK and it does not have a UK marketing authorisation for the treatment of anaemia associated with treatment for chronic hepatitis C. Instead, ribavirin dose reduction is often carried out in routine practice to manage anaemia. After hearing further evidence from the clinical specialists, the Committee noted that evidence relating to the effect of anaemia treatment strategies on the likelihood of experiencing a sustained virological response is mixed, with some studies favouring erythropoietin use and others finding no difference between this and ribavirin dose reduction. The Committee concluded that the adverse reactions associated with boceprevir plus peginterferon alfa and ribavirin were generally tolerable and that there was currently no clear evidence to suggest that ribavirin dose reduction was not an acceptable strategy for managing anaemia following treatment with boceprevir.
- 4.10 The Committee discussed if it was possible to identify treatment-naive patients who would be most likely to benefit from adding boceprevir to peginterferon alfa and ribavirin treatment. The Committee heard from the clinical specialists that IL-28B polymorphism testing can identify patients whose disease is more likely to respond to treatment with peginterferon alfa. However, it noted the European Public Assessment Report for boceprevir states that the findings of an IL-28B retrospective analysis were uncertain and that results from a prospective study are not expected until 2014. The Committee concluded that there was insufficient evidence to determine the role of IL-28B polymorphism testing and it was not possible at this time to predict if there are any subgroups of treatment-naive patients who would derive particular benefit from boceprevir therapy.

- 4.11 The Committee considered the manufacturer's economic model, the assumptions on which the parameters were based, and the critique and exploratory analyses conducted by the ERG. The Committee noted the manufacturer's model was similar to that used in [NICE technology appraisal guidance 200](#). The Committee acknowledged that the model did not allow for the possibility of reduced HCV transmission that may result from the increased sustained virological response rate associated with boceprevir. The Committee concluded that the model closely adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of boceprevir.
- 4.12 The Committee discussed the baseline fibrosis levels of patients assumed in the manufacturer's model. It heard from the clinical specialists that the distribution used by the manufacturer may have underestimated the baseline severity overall and also the number of patients with compensated cirrhosis (F4 population) who would be seen in clinical practice. The Committee noted, however, that the ERG's exploratory analysis that used the baseline fibrosis distribution from [NICE technology appraisal guidance 200](#) showed that this had little effect on the ICERs for both the treatment-naïve and previously treated populations. The Committee concluded that although the baseline fibrosis distribution used by the manufacturer in the model did not accurately reflect the distribution of fibrosis levels of patients treated in UK clinical practice, this had minimal impact on the accuracy of the cost-effectiveness estimates for boceprevir.
- 4.13 The Committee discussed the generalisability of the population with compensated cirrhosis in the manufacturer's model to UK patients. It again heard from clinical specialists that there is an excess mortality for patients with compensated cirrhosis compared with the general population and noted that this was not accounted for in the manufacturer's model. It also heard from the clinical specialists that the proportion of patients with compensated cirrhosis would be higher in clinical practice than assumed in the manufacturer's model. In addition to the uncertainty surrounding the clinical trial data for patients with compensated cirrhosis (see section 4.5), the Committee considered that the incremental survival gain for treatment-naïve patients with compensated cirrhosis had been underestimated by the manufacturer (0.59 life years

gained), but the incremental survival gain for previously treated patients with compensated cirrhosis was likely to have been overestimated (11.43 life years gained). The Committee concluded that there was considerable uncertainty associated with the modelling of patients with compensated cirrhosis. Therefore, the Committee concluded it reasonable that the decisions on the use of boceprevir in the NHS should be informed by the modelling for the whole population regardless of initial fibrosis level (that is, METAVIR score F0–4) for both the treatment-naive and previously treated populations.

- 4.14 The Committee discussed the transition probabilities used in the manufacturer's model. It noted that these differed from those used in [NICE technology appraisal guidance 200](#). The Committee heard from the ERG that the transition probabilities used by the manufacturer could lead to an overestimation of treatment effect with boceprevir, but that the probabilities were more up-to-date than those used in the previous appraisal and were also already aligned with METAVIR score. The Committee concluded that the transition probabilities used by the manufacturer were acceptable.
- 4.15 The Committee discussed the utility values used in the manufacturer's model and noted that these did not account for age-related changes. The Committee heard from the ERG that this could cause an overestimation of boceprevir's treatment effect but it was unlikely to be substantial. The Committee concluded that the utility values used by the manufacturer were acceptable for use in this appraisal.
- 4.16 The Committee discussed the discount rate used in the manufacturer's model. It considered whether it was appropriate to use a lower discount rate for health benefits because treatment effects were both substantial in restoring health and sustained over a very long period (as described in the clarification to section 5.6.2 of the [Guide to the methods of technology appraisals](#) issued by the Board of NICE). It was noted that the manufacturer's sensitivity analyses showed that the ICERs were not particularly sensitive to discounting. The Committee concluded that the manufacturer's approach of discounting health benefits in accordance with the NICE reference case was appropriate.

- 4.17 The Committee considered whether boceprevir is an innovative technology. It agreed that it is clinically more effective than current therapy, which in itself would not represent a major development in the management of HCV. However, the Committee agreed that the potential for shortening the treatment time needed for a virological response is particularly important for patients and that therefore boceprevir could be considered a major development. The Committee accepted that boceprevir is a valuable new therapy for the treatment of genotype 1 chronic HCV and that its mechanism of action was novel. The Committee agreed that there were health benefits which had not been adequately captured in the QALY calculation (see section 4.11), but it was satisfied that these benefits had been included in its considerations.
- 4.18 The Committee considered the most plausible ICERs presented by the manufacturer and also by the ERG in their exploratory analyses. It noted that although the cost effectiveness of boceprevir was sensitive to changes in the assumed rate of sustained virological response, and that reducing the efficacy of boceprevir plus peginterferon alfa and ribavirin by 25% increased the ICERs compared with peginterferon alfa plus ribavirin alone, the ICERs for the treatment-naïve and previously treated populations remained below £20,000 per QALY gained. The Committee concluded that the base-case ICERs for boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone for the treatment-naïve population (£11,601 per QALY gained) and the previously treated population (£2909 per QALY gained) were robust to sensitivity analyses and demonstrated that boceprevir represents a cost-effective use of NHS resources for patients with genotype 1 chronic hepatitis C. The Committee therefore recommended boceprevir in combination with peginterferon alfa and ribavirin as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease who are previously untreated or in whom previous treatment has failed.
- 4.19 The Committee considered the use of boceprevir plus peginterferon alfa and ribavirin in patients with HCV infection who are co-infected with HIV. The Committee concluded that although these patients were not represented in the pivotal clinical trials, based on the current evidence available, there was no reason to make any different provision for these patients. It did, however, note

that there might be occasions where ribavirin may interact with medication for HIV, necessitating a review of the patient's optimal treatment strategy.

- 4.20 The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations. The clinical specialists indicated that it is known that virological response to peginterferon alfa plus ribavirin is relatively poor in black patients. The Committee considered that the SPRINT-2 trial, which was stratified for black and non-black patients, showed that boceprevir could provide considerable benefit to all patients and that this did not present an equality issue. The Committee discussed whether the availability of treatment for people with chronic hepatitis C in clinical practice was limited for people who use intravenous drugs, misuse alcohol and/or are co-infected with HIV. The Committee agreed that this was an issue related to implementation and could not be addressed through technology appraisal guidance. The Committee therefore concluded that its decision on the use of boceprevir would not have a particular impact on any of the groups whose interests are protected by the equalities legislation and that there was no need to alter or add to its recommendations.

Summary of Appraisal Committee's key conclusions

TA253	Appraisal title: Boceprevir for the treatment of genotype 1 chronic hepatitis C	Section
Key conclusion		

<p>Boceprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease:</p> <ul style="list-style-type: none"> • who are previously untreated or • in whom previous treatment has failed. <p>The Committee concluded that boceprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in treatment-naive patients and previously treated patients, irrespective of baseline fibrosis level.</p> <p>The Committee concluded that the base-case ICERs for boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone for the treatment-naive population (£11,601 per QALY gained) and the previously treated population (£2909 per QALY gained) were robust to sensitivity analyses and were all below £20,000 per QALY gained, demonstrating that boceprevir represents a cost-effective use of NHS resources for patients with genotype 1 chronic hepatitis C.</p>		1.1, 4.6, 4.18
Current practice		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard that standard treatment for genotype 1 chronic hepatitis C in the UK is peginterferon alfa plus ribavirin for both treatment-naive and previously treated patients. It heard that although its toxicity is acceptable overall, interferon can be difficult to take for some patients. Patients may be deterred from undertaking a year-long course of treatment because they perceive efficacy rates to be low relative to the likely side effects. Patients also fear the consequences of long-term disease progression, as well as transmitting it to others. The Committee heard from the patient experts and clinical specialists that many people have chosen to defer treatment until new agents become available. The Committee acknowledged the difficulties patients face when using currently available therapies and concluded that further treatment options are needed for the management of genotype 1 chronic hepatitis C.</p>	4.2, 4.3
The technology		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>Boceprevir is a NS3/4A serine protease inhibitor. NS3/4A serine protease is essential for viral replication and may be partially responsible for the ability of the hepatitis C virus to evade clearance by the host immune system.</p> <p>The Committee concluded that a sustained virological response in a patient with genotype 1 chronic hepatitis C who did not have compensated cirrhosis could be broadly considered to be equivalent to a cure, and could have significant positive effects at a population level by reducing viral transmission rates.</p> <p>The Committee accepted that boceprevir is a valuable new therapy for the treatment of chronic HCV and that its mechanism of action was novel.</p>	<p>2.1, 4.8, 4.17</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The Committee recommended boceprevir in combination with peginterferon alfa and ribavirin as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease who are previously untreated or in whom previous treatment has failed.</p>	<p>1.1, 4.18</p>
<p>Adverse effects</p>	<p>The summary of product characteristics lists fatigue, anaemia, nausea, headache and dysgeusia as the most frequently reported adverse reactions for boceprevir. The Committee heard from clinical specialists that most adverse reactions associated with treatment with boceprevir plus peginterferon alfa and ribavirin were medically manageable but that adding boceprevir to peginterferon alfa and ribavirin may increase rates of anaemia. The Committee concluded that the adverse reactions associated with boceprevir plus peginterferon alfa and ribavirin were generally tolerable.</p>	<p>2.2, 4.9</p>
<p>Evidence for clinical effectiveness</p>		

<p>Availability, nature and quality of evidence</p>	<p>The Committee examined the clinical trial evidence presented by the manufacturer on the efficacy and safety of boceprevir plus peginterferon alfa and ribavirin in adults with genotype 1 chronic hepatitis C. This comprised five randomised controlled trials (three presented in full) and an ongoing non-randomised phase II study. The ERG considered these to be relevant to the decision problem and that the manufacturer's systematic review was good quality; however some areas of weakness or uncertainty were noted. The Committee concluded that the clinical trials with boceprevir provided evidence that was adequate for assessment.</p>	<p>3.1, 3.35, 4.4</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee found that the clinical trials with boceprevir were generalisable to the UK setting.</p> <p>The Committee considered how anaemia associated with treatment for chronic hepatitis C would be managed in routine clinical practice. Although erythropoietin was widely available to patients in the boceprevir clinical trials, the Committee noted that it is not routinely used in the UK and does not have a UK marketing authorisation for the treatment of anaemia associated with treatment for chronic hepatitis C. Instead, ribavirin dose reduction is often carried out in routine practice to manage anaemia. The Committee concluded that there was currently no clear evidence to suggest that ribavirin dose reduction was not an acceptable strategy for managing anaemia following treatment with boceprevir.</p>	<p>4.4, 4.9</p>

<p>Uncertainties generated by the evidence</p>	<p>The Committee noted multiple differences between the clinical trial designs and the UK marketing authorisation for boceprevir, and had concerns over the uncertainty associated with the manufacturer's retrospective analyses that assessed the patient subgroups in the trials relative to how they are classified in the marketing authorisation. Overall, however, the Committee concluded that the trials provided adequate evidence for assessing boceprevir for the treatment of genotype 1 chronic hepatitis C.</p> <p>The Committee heard from clinical specialists that the extent of fibrosis at baseline was generally lower in the trials than would be seen in UK clinical practice and, specifically, that patients with compensated cirrhosis were under-represented in the trials (in both the treatment-naive and the previously treated populations). The Committee heard from the ERG that the small number of patients with compensated cirrhosis in the clinical trials generated considerable uncertainty in the manufacturer's analyses according to fibrosis level, and therefore concluded that reliable results for this subgroup on its own could not be established.</p>	<p>4.4, 4.5</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The Committee heard from the clinical specialists that IL-28B polymorphism testing can identify patients whose disease is more likely to respond to treatment with peginterferon alfa, but noted the European Public Assessment Report for boceprevir states that the findings of an IL-28B retrospective analysis were uncertain. The Committee concluded that it was not possible at this time to predict if there are any subgroups of treatment-naive patients who would derive particular benefit from boceprevir therapy.</p> <p>The Committee considered the use of boceprevir plus peginterferon alfa and ribavirin in patients with HCV infection who are co-infected with HIV. Although these patients were not represented in the pivotal clinical trials, based on the current evidence available, the Committee concluded that there was no reason to make any different provision for these patients.</p>	<p>4.10, 4.19</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee concluded that boceprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in treatment-naive patients and previously treated patients, irrespective of baseline fibrosis level.</p>	<p>4.6, 4.7</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The Committee considered the manufacturer's economic model and its associated assumptions, and the critique and exploratory analyses conducted by the ERG, and noted the manufacturer's model was similar to that used in NICE technology appraisal guidance 200. The Committee concluded that the model closely adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of boceprevir.</p>	<p>4.11</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee concluded that although the baseline fibrosis distribution used in the manufacturer's model did not reflect that seen in UK clinical practice, the ERG's exploratory analysis showed that this had minimal impact on the accuracy of the cost-effectiveness estimates for boceprevir.</p> <p>The Committee concluded that there was considerable uncertainty associated with the modelling of patients with compensated cirrhosis and therefore based its decision-making on the modelling for the whole population (METAVIR score F0–4) for both the treatment-naive and previously treated populations.</p> <p>The Committee noted that the transition probabilities used in the manufacturer's model differed from those used in NICE technology appraisal guidance 200, which could lead to an overestimation of boceprevir's treatment effect. However, the Committee heard from the ERG that the manufacturer's probabilities were more up-to-date and aligned with the METAVIR score, and consequently concluded that they were acceptable.</p> <p>The Committee noted that the utility values used in the manufacturer's model did not account for age-related changes, but concluded that they were acceptable for use in this appraisal because it was unlikely that any overestimation of boceprevir's treatment effect would be substantial.</p>	<p>4.12, 4.13, 4.14, 4.15</p>
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<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee concluded that treatments which enable patients to achieve a sustained virological response, consequently helping to reduce HCV transmission, are of significant importance.</p> <p>The Committee agreed that there were health benefits not adequately captured in the QALY calculation but that it had included these benefits in its considerations.</p>	<p>4.3, 4.17</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No specific groups were identified in which boceprevir was particularly cost effective.</p>	<p>4.10</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The effects of boceprevir were primarily driven by the assumed rate of sustained virological response.</p>	<p>3.33, 4.18</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee considered the most plausible ICERs presented by the manufacturer and the ERG. The Committee concluded its decision-making on the modelling should be based on the whole population (METAVIR score F0–4) for both the treatment-naive and previously treated populations because there was considerable uncertainty associated with the modelling of patients with compensated cirrhosis.</p> <p>The Committee concluded that the base-case ICERs for boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone for the treatment-naive population (£11,601 per QALY gained) and the previously treated population (£2909 per QALY gained) were robust to sensitivity analyses and were all below £20,000 per QALY gained, demonstrating that boceprevir represents a cost-effective use of NHS resources for patients with genotype 1 chronic hepatitis C.</p>	<p>4.13, 4.18</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>Not applicable to this appraisal.</p>	
<p>End-of-life considerations</p>	<p>Not applicable to this appraisal.</p>	
<p>Equalities considerations and social value judgements</p>	<p>Although it is known that virological response to peginterferon alfa plus ribavirin is relatively poor in black patients, the Committee concluded that boceprevir could provide considerable benefit to all patients and that this did not present an equality issue.</p> <p>The Committee discussed whether the availability of treatment for people with chronic hepatitis C in clinical practice was limited for people who use intravenous drugs, misuse alcohol and/or are co-infected with HIV. The Committee agreed that this was an issue related to implementation and could not be addressed through technology appraisal guidance.</p>	<p>4.20</p>

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TA253).

- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Audit support for monitoring local practice.

6 Recommendations for further research

- 6.1 The Committee acknowledges ongoing studies of boceprevir and of the role of IL-28B polymorphism in identifying patients who are likely to be sensitive to treatment with peginterferon alfa and ribavirin. The Committee recommends that data from these studies should be considered in any review of this guidance.

7 Related NICE guidance

Published

- [Telaprevir for the treatment of genotype 1 chronic hepatitis C](#). NICE technology appraisal guidance 252 (2012).
- [Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C \(part review of NICE technology appraisal guidance 75 and 106\)](#). NICE technology appraisal guidance 200 (2010).
- [Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C](#). NICE technology appraisal guidance 106 (2006).
- [Interferon alfa \(pegylated and non-pegylated\) and ribavirin for the treatment of chronic hepatitis C](#). NICE technology appraisal guidance 75 (2004).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Hepatitis B and C: ways to promote and offer testing. NICE public health guidance. Publication expected December 2012

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review in April 2015. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
April 2012

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Peter Clark (Chair)

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Professor Jonathan Michaels (Vice Chair)

Professor of Clinical Decision Science, University of Sheffield

Professor Darren Ashcroft

Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Matthew Bradley

Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell

Honorary Consultant Physician, Llandough Hospital

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Dr Martin Duerden

Assistant Medical Director, Betsi Cadwaladr University Health Board

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Gillian Ells

Prescribing Advisor, NHS Sussex Downs and Weald

Dr Jon Fear

Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

Paula Ghaneh

Senior Lecturer and Honorary Consultant, University of Liverpool

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor John Hutton

Professor of Health Economics, University of York

Professor Peter Jones

Emeritus Professor of Statistics, Keele University

Dr Steven Julious

Senior Lecturer in Medical Statistics, University of Sheffield

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Rachel Lewis

Advanced Nurse Practitioner, Manchester Business School

Professor Paul Little

Professor of Primary Care Research, University of Southampton

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge

GP and Consultant in Medicines Management, NHS Lothian

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Murray D Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie

Lay Member

Dr Lok Yap

Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust

B Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

- Professor Geoffrey Dusheiko, Professor of Medicine, Royal Free Hospital, University College London Medical School

C NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Linda Landells

Technical Lead

Fiona Rinaldi

Technical Adviser

Kate Moore

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre:

- Mendes D, White K, Cooper K et al. Boceprevir for the treatment of genotype 1 chronic hepatitis C, October 2011

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on boceprevir by providing a written statement to the Committee. Organisations listed in I, II and III have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor

- Merck Sharp & Dohme

II Professional/specialist and patient/carer groups:

- British Liver Trust
- Hepatitis C Trust
- Association of Clinical Biochemistry – Microbiology Group
- British Association for the Study of the Liver
- British Society of Gastroenterology
- Health Protection Agency
- Royal College
- Royal of Pathologists
- Royal of Physicians
- United Kingdom Clinical Pharmacy Association

III Other consultees:

- Department of Health
- Welsh Government
- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Janssen
- Roche Products
- Merck Sharp & Dohme
- Foundation for Liver Research
- Southampton Health Technology Assessment Centre (SHTAC), University of Southampton
- National Institute for Health Research Health Technology Assessment Programme
- National Clinical Guidelines Centre

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Janssen
- Roche Products
- Merck Sharp & Dohme

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- Foundation for Liver Research
 - Southampton Health Technology Assessment Centre (SHTAC), University of Southampton
 - National Institute for Health Research Health Technology Assessment Programme
 - National Clinical Guidelines Centre

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on boceprevir by providing oral evidence to the Committee.

- Dr Phillip Harrison, Senior Lecturer and Consultant Hepatologist, King's College Hospital, nominated by the British Association for the Study of the Liver – clinical specialist
- Dr Michael Jacobs, Consultant in Infectious Diseases, Royal Free Hampstead NHS Trust, nominated by the Royal College of Physicians – clinical specialist
- Richard Hall, Support Group Manager, British Liver Trust, nominated by the British Liver Trust – patient expert
- Raquel José, nominated by The Hepatitis C Trust – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Merck Sharp & Dohme

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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