National Institute for Health and Clinical Excellence

# Telaprevir for the treatment of genotype 1 chronic hepatitis C

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**NICE technology appraisal guidance 252**

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# 1 Guidance

1.1 Telaprevir 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 with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin has failed, including people whose condition has relapsed, has partially responded or did not respond.

# 2 The technology

2.1 Telaprevir (Incivo, Janssen) is a peptidomimetic inhibitor of the hepatitis C virus (HCV) protease NS3/4A. Activity of this protease is essential for viral replication and may be partially responsible for the ability of HCV to evade clearance by the immune system. Telaprevir has a UK marketing authorisation 'in combination with peginterferon alfa and ribavirin for the treatment of genotype-1 chronic HCV in adult patients with compensated liver disease (including cirrhosis) who are treatment naive, or who have been previously treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders'. It is administered orally as a 750 mg dose (two 375 mg tablets) every 8 hours for 12 weeks.

2.2 The summary of product characteristics lists the following adverse reactions for telaprevir: anaemia, rash, thrombocytopenia, lymphopenia, pruritus, diarrhoea and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Telaprevir has a list price of £1866.50 for a 1-week, 42-tablet pack (excluding VAT; 'Monthly Index of Medical Specialities' [MIMS] January 2012). This equates to £22,398 for a 12-week course of therapy. 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 telaprevir and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer conducted a systematic review and identified six randomised control trials that investigated the effect of telaprevir in adults with genotype 1 chronic HCV. Of these, the three PROVE studies were excluded because they evaluated unlicensed dosing schedules, and did not incorporate response-guided therapy or a management plan for adverse reactions. The 110 trial was excluded because it was still ongoing with interim results at 12 weeks only and reported no results for sustained virological response. Therefore, the review of clinical effectiveness included two studies: the ADVANCE trial, which included patients who were treatment naive (previously untreated), and the REALIZE trial, which included patients who had been previously treated with peginterferon alfa and ribavirin but whose disease did not respond (null responder subgroup) or had a partial response to previous therapy (partial responder subgroup) or whose disease had relapsed after an initial response (prior relapser subgroup). Both trials were international, multicentre, randomised, double-blind, placebo-controlled, phase III manufacturer-supported trials comparing telaprevir plus peginterferon alfa-2a and ribavirin (PEG2a/R) with PEG2a/R alone.

3.2 The ADVANCE trial assigned 1095 patients to one of three groups:

- telaprevir plus PEG2a/R for 12 weeks followed by 'response-guided therapy' which incorporated 'stopping rules' (n = 365)
- telaprevir plus PEG2a/R for 8 weeks followed by 4 weeks of placebo plus PEG2a/R and then followed by PEG2a/R for 12 or 36 weeks (n = 365). The manufacturer's submission excluded the results of this arm from the main evidence section because this dosing regimen was unlicensed in the UK.

- placebo plus PEG2a/R for 12 weeks, followed by PEG2a/R alone for 36 additional weeks (control group, n = 365).

  The ADVANCE trial incorporated response-guided therapy, with the decision to stop treatment based on the unblinded independent reviewer. This decision was then communicated back to those providing treatment, whereby patients in the telaprevir arm who met the criteria for an extended rapid virological response (defined as undetectable HCV ribonucleic acid [RNA] at weeks 4 and 12) received 12 additional weeks of treatment with PEG2a/R alone, for a total treatment period of 24 weeks. Patients who had detectable HCV RNA either at week 4 or at week 12 received 36 additional weeks of treatment with PEG2a/R, for a total treatment period of 48 weeks. The trial used stopping rules: patients randomised to telaprevir who had HCV RNA levels greater than 1000 IU per ml at week 4 stopped telaprevir, but continued with PEG2a/R. All patients whose HCV RNA levels had not decreased to at least one-hundredth of baseline values at week 12 stopped all treatment. Patients also stopped treatment if HCV RNA was detected at any time between weeks 24 and 40.

3.3 The REALIZE trial randomised 663 patients to one of three interventions:

- telaprevir plus PEG2a/R for 12 weeks, followed by placebo plus PEG2a/R for 4 weeks, and then PEG2a/R alone for 32 weeks (n = 266)
- placebo plus PEG2a/R for 4 weeks, followed by telaprevir plus PEG2a/R for 12 weeks, and then PEG2a/R alone for 32 weeks (lead-in group; n = 264) (the results of the lead-in group were excluded from the main evidence section because this dosage regimen was unlicensed in the UK)
- placebo plus PEG2a/R for 16 weeks, followed by PEG2a/R alone for 32 weeks (control group; n = 133).

  People receiving telaprevir who had HCV RNA levels greater than 100 IU per ml at week 4, 6 and 8 stopped telaprevir but continued PEG2a/R. All study treatment was stopped if a patient's HCV RNA levels had not decreased to at least one-hundredth of baseline levels at week 12 or if HCV RNA was detected at either week 24 or 36.

3.4 The primary outcome measure for both trials was the proportion of patients with sustained virological response, defined as undetectable HCV RNA at the

end of treatment and 24 weeks after the last planned dose of study treatment (without any confirmed detectable HCV RNA between those visits). Secondary outcome measures for both trials included:

- extended rapid virological response (defined as undetectable HCV RNA at 4 and 12 weeks after the start of treatment)
- virological failure, including:
  - virological failure during treatment (detectable HCV RNA at weeks 4, 12, 24, 28, 36 or at the end of treatment for patients completing therapy)
  - relapse (defined as undetectable HCV RNA at end of treatment, but detectable HCV RNA during 24 weeks of follow-up)
  - detectable HCV RNA at the end of treatment for patients who did not complete the planned duration of therapy, and patients missing data for sustained virological response, either because of discontinuing the study during the 24-week follow-up period or missing the 24-week follow-up assessment
- adherence
- discontinuation rates
- health-related quality of life
- fatigue.

3.5 Results from the ADVANCE trial indicated that the percentage of patients with a sustained virological response was significantly higher in the telaprevir plus PEG2a/R arm compared with the placebo plus PEG2a/R arm (75% and 44% respectively, absolute difference 31%; 95% CI 24 to 38%, $p < 0.0001$). The percentage of patients with an extended rapid virological response was significantly higher in the telaprevir plus PEG2a/R arm compared with the PEG2a/R only arm (58% and 8% respectively, absolute difference 50%; 95% CI 45 to 56%, $p < 0.0001$). Of the patients in the telaprevir plus PEG2a/R group who had an extended rapid virological response, 89% went on to have a sustained virological response. The relapse rate among patients who had

undetectable HCV RNA levels at the end of treatment was lower in the telaprevir plus PEG2a/R arm compared with the placebo plus PEG2a/R arm (9% and 28% respectively).

3.6 The ADVANCE trial evaluated health-related quality of life using the EQ-5D questionnaire at day 1 (baseline) and at weeks 4, 12, 24, 36, 48 and 72. Patients in both treatment arms entered the trial with a baseline EQ-5D score of 0.89, which decreased during the initial 12-week treatment phase to between 0.72 and 0.76 in the telaprevir group and to between 0.77 and 0.79 in the control group. During the remainder of the treatment phase when patients received PEG2a/R alone, health-related quality of life remained below 0.80, finally recovering to around or above baseline when PEG2a/R was stopped. Most patients in the telaprevir group received 24 weeks of PEG2a/R, and their health-related quality of life improved earlier than for patients in the control group who all received up to 48 weeks of PEG2a/R. Both the telaprevir and control group had a mean fatigue severity scale score of 3.0 at baseline, which worsened to 4.8 and 4.4 respectively by week 12. Area under the curve analysis indicated that patients randomised to telaprevir experienced statistically significantly lower levels of fatigue compared with patients in the control group ($p = 0.002$).

3.7 Results from the REALIZE trial indicated that the percentage of patients who had a sustained virological response was significantly higher in the telaprevir plus PEG2a/R arm compared with the placebo plus PEG2a/R arm (64% and 17% respectively, absolute difference 47%; 95% CI 37% to 57%, $p < 0.001$). Patients randomised to telaprevir plus PEG2a/R also maintained significantly higher sustained virological response rates compared with patients randomised to placebo plus PEG2a/R for each of the patient subgroups defined according to prior response: 83% compared with 24% among prior relapsers; 59% compared with 15% among partial responders; and 29% compared with 5% among null responders ($p < 0.001$). The percentage of patients with an extended rapid virological response was significantly higher in the telaprevir plus PEG2a/R arm compared with the placebo plus PEG2a/R arm for each of the subgroups defined according to prior response: 66% compared with 3% among prior relapsers; 61% compared with 0% among partial responders; and 22% compared with 3% among null responders.

Although there was no response guided therapy in the REALIZE trial, the manufacturer's submission stated that in the real-world clinical setting, patients who do not have cirrhosis, and patients who had a prior relapse and an extended rapid virological response were eligible for a 24-week rather than a 48-week total duration of response-guided PEG2a/R. Consequently, based on the results, around two-thirds of telaprevir-treated patients who had prior relapse would have been eligible to halve the duration of their PEG2a/R therapy. The relapse rate was reduced from 65% in the control arm to 7% in the telaprevir arm in the prior relapser subgroup and from 60% to 27% in the null responder subgroup. The relapse rate in the telaprevir arm for the partial responder subgroup was 21%. None of the prior partial responders in the control arm relapsed.

3.8 The REALIZE trial evaluated health-related quality of life using the EQ-5D questionnaire at day 1 (baseline), at week 4, 12, 24, 48, 72 and at the time of early discontinuation. Patients in the telaprevir and control arms entered the trial with utility values of 0.89 and 0.90 respectively, which decreased during the initial 12-week treatment phase to between 0.72 and 0.76 in the telaprevir group and to between 0.76 and 0.81 in the control group. During the remainder of the treatment (PEG2a/R only) utility values remained below 0.80, recovering to approximately baseline levels at week 72 after PEG2a/R therapy had been stopped at week 48. Fatigue severity scale scores for patients in both treatment arms worsened during the 48-week treatment period. Scores for all patients returned to approximately baseline levels at week 72, following discontinuation of PEG2a/R therapy at week 48.

3.9 The manufacturer's submission presented data on sustained virological response according to IL-28B subtype for both previously untreated and previously treated patient populations. For both populations, this information was taken from conference proceedings that showed that the telaprevir plus PEG2a/R group had an improved sustained virological response compared with the PEG2a/R group, regardless of IL-28B subtype. No statistical tests for interaction were provided. The manufacturer's submission stated that the results for both populations need to be interpreted with caution because the analysis was post hoc; the IL-28B data were not available for all patients,

having been captured after the trials had started, and therefore participants were not stratified or randomised according to genetic subtype.

3.10 The manufacturer presented data from the ADVANCE and the REALIZE trials on sustained virological response by degree of hepatic fibrosis, that is, no or minimal fibrosis, portal fibrosis, bridging fibrosis and cirrhosis. Results from both trials indicated that the telaprevir plus PEG2a/R group had an improved sustained virological response compared with the PEG2a/R group, regardless of the degree of fibrosis. No tests of statistical significance were reported.

3.11 The most common adverse reactions (any grade) in the previously untreated population were fatigue, headache, insomnia and influenza-like symptoms. These occurred in a similar proportion of patients in each of the treatment arms. The other common adverse reactions (pruritus, nausea, anaemia, rash, diarrhoea and pyrexia) occurred more frequently in the telaprevir arm. No tests of statistical significance were reported. The most common adverse reactions (any grade) for the previously treated population were fatigue, pruritus, headache, rash, nausea, influenza-like symptoms, anaemia, insomnia, diarrhoea, pyrexia, cough and asthenia. With the exception of pyrexia and asthenia, these symptoms tended to occur more frequently in the telaprevir arm. No tests of statistical significance were reported.

3.12 In a systematic review the manufacturer identified six cost-effectiveness studies of the treatment of chronic HCV, which reported results for patients with genotype 1 HCV, but no studies were identified that compared telaprevir with alternative treatments.

3.13 The manufacturer submitted two de novo economic analyses that assessed the cost effectiveness of telaprevir plus PEG2a/R for the treatment of genotype 1 chronic HCV in adults, one each for patients who were previously untreated and patients who were previously treated. The two models were identical in structure and the manufacturer stated that the modelled population was in line with the UK marketing authorisation and the trial populations. The analysis was conducted from an NHS and personal and social services perspective and a lifetime horizon was used, with a cycle length of 1 year, applying a half cycle correction.

3.14 The manufacturer developed a Markov model based on other published health economic models of chronic HCV. The model simulates the natural history of chronic hepatitis C infection and extrapolates a patient's lifetime risk of developing advanced liver disease. At baseline, the simulated cohort of patients reflects the age of the patients in the ADVANCE and REALIZE trial populations, and the severity of their compensated liver disease. The primary treatment outcome, sustained virological response, is assigned at the end of the first year of the model. The model has seven health states. Patients enter the model in the health states defined by 'mild HCV', 'moderate HCV' or 'compensated cirrhosis' and can receive treatment with either telaprevir plus PEG2a/R or with PEG2a/R alone. The model assumes that patients who have a sustained virological response following treatment have cleared the virus, except for patients with compensated cirrhosis who remain in the 'cirrhotic post sustained virological response' health state or progress to the 'hepatocellular carcinoma' health state. If treatment does not lead to virological response, patients remain in their original health state for a period of time or progress to the more advanced stages of liver disease, including decompensated cirrhosis, hepatocellular carcinoma, liver transplantation or post liver transplant. The manufacturer incorporated the stopping rules used in the ADVANCE and REALIZE trials in the economic model. The manufacturer's submission stated that there were minor differences between the trial stopping rules and those in the summary of product characteristics, but this was not expected to have an important effect on the economic analyses presented in the submission.

3.15 The manufacturer applied age-specific general population mortality rates to the health states 'mild HCV', 'moderate HCV' and 'compensated cirrhosis'. The model assumes that patients with decompensated cirrhosis, patients with hepatocellular carcinoma or patients who have had a liver transplant have an increased mortality rate relative to other health states and to the general population. The ADVANCE and REALIZE trials provided the data on a given treatment's effectiveness on sustained virological response for the models. Transition probabilities between health states were derived from a range of sources. Most of the transition probabilities applied to later disease, which the manufacturer took from a previous NICE technology appraisal, Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (NICE technology appraisal guidance 200). The exception to this is the probability of liver

transplant for patients with hepatocellular carcinoma, which the manufacturer based on UK transplant statistics. The transition probabilities from mild to moderate HCV and from moderate HCV to compensated cirrhosis were taken from a published economic evaluation (Grishchenko et al. 2009). The manufacturer used age-specific transition probabilities, stating that this was because disease progression depends on a patient's age.

3.16 The manufacturer's model incorporated utility values from Hartwell et al. (2011), which were derived from the UK Mild Hepatitis C Trial, for consistency with previous economic analyses. These estimates were lower than the utility estimates derived using similar methods in the ADVANCE and REALIZE trials. However, Hartwell et al. provided the only estimates broken down by stages of early disease and for sustained virological response by stage prior to treatment, and the manufacturer considered these values to be more valid than those from the ADVANCE and REALIZE trials. The manufacturer did not explicitly assign disutilities to specific adverse events and only included the costs of managing adverse reactions. Instead, to capture the effect on health outcomes of adverse reactions, the manufacturer applied decrements observed in the ADVANCE and REALIZE trials to the baseline utility values provided by Hartwell et al.

3.17 The manufacturer's model included costs that reflected the UK NHS perspective, comprising treatment-related costs (drug acquisition and patient monitoring), health state costs and costs associated with adverse reactions. Drug costs were based on the list price, and duration of treatment was based on the mean duration of treatment in the ADVANCE and REALIZE trials. Costs for peginterferon alfa-2a were included in the model. Costs associated with the health states 'mild HCV', 'moderate HCV' and 'compensated cirrhosis' included costs during the first year of treatment as well as ongoing costs common across all health states. The costs of monitoring and investigations during the first year were taken from the published study by Shepherd et al. (2007) and adjusted for inflation to 2010 costs. The manufacturer assumed that patients receiving either treatment incurred these costs at the same time in the treatment year. The manufacturer assumed that patients in the 'mild HCV' or 'moderate HCV' health state with a sustained virological response would be monitored for 1 year and patients in the 'compensated cirrhosis' health state

with a sustained virological response would also need life-long monitoring consisting of 6-monthly ultrasound scans and monitoring of serum alfa-fetoprotein. Because the monitoring costs varied according to the duration of treatment, the manufacturer weighted them according to the mean treatment duration in the trials. The manufacturer estimated the ongoing costs associated with each health state predominantly from Hartwell et al. with two exceptions: it took the costs associated with hepatocellular carcinoma, decompensated cirrhosis and liver transplant health states that occurred after a sustained virological response health state from Grishchenko et al. (2009), and the estimates for costs incurred after liver transplant from Wright et al. (2006). The manufacturer applied the same costs in the modelling of both previously untreated and previously treated patients. Following clinical advice regarding the appropriate grades of adverse reactions to incorporate into the modelling, the manufacturer modelled adverse reactions including grade 3 pruritus, nausea, diarrhoea and anaemia, and rash (all grades). Rates of grade 3 pruritus and diarrhoea in the previously untreated model and grade 3 nausea and diarrhoea in the previously treated model were the same for both treatment groups. All other adverse reactions were more common in patients receiving telaprevir plus PEG2a/R than in patients receiving PEG2a/R alone.

3.18 For the previously untreated population, the manufacturer's model estimated that telaprevir plus PEG2a/R provides an incremental health gain of 0.84 quality-adjusted life years (QALYs) compared with PEG2a/R alone, at an incremental cost of £11,430, resulting in an incremental cost-effectiveness ratio (ICER) of £13,553 per QALY gained. For the previously treated population, the manufacturer's model estimated that telaprevir plus PEG2a/R provides an incremental health gain of 1.17 QALYs compared with PEG2a/R alone, at an incremental cost of £10,195, resulting in an ICER of £8688 per QALY gained.

3.19 The manufacturer conducted deterministic sensitivity analyses for a range of parameters. The ICERs for previously untreated patients were most sensitive to the values for utility for the health state of mild HCV and moderate HCV where patients did not achieve an sustained virological response, to the duration of treatment for patients receiving telaprevir plus PEG2a/R, and to the rate of sustained virological response for moderate HCV patients. The ICERs

ranged from £10,542 to £17,739 per QALY gained. These ICERs remained below £18,000 per QALY gained in all instances.

3.20 The ICERs for previously treated patients were most sensitive to the costs and utility values applied to the health states reflecting cirrhosis (compensated or decompensated), to treatment duration in patients receiving telaprevir plus PEG2a/R, and to the rate of sustained virological response for moderate HCV prior relapse patients on PEG2a/R alone. The ICERs ranged from £6024 to £12,162 per QALY gained.

3.21 The manufacturer conducted a probabilistic sensitivity analysis. For previously untreated patients, at £20,000 and £30,000 per QALY gained, the probability that telaprevir plus PEG2a/R was a cost-effective option compared with PEG2a/R alone was 85.3% and 98.0% respectively. For the previously treated population, the probability that telaprevir plus PEG2a/R was a cost-effective option compared with PEG2a/R alone was 94% and 97.4% at £20,000 and £30,000 per QALY gained respectively.

3.22 The manufacturer also conducted several scenario analyses to explore the sensitivity of the results to key assumptions used in the model. These included incorporating a shorter treatment duration for PEG2a/R alone in previously untreated patients, incorporating response guided therapy for prior relapse patients in the telaprevir arm, using the definitions in the summary of product characteristics for sustained virological response (instead of the definitions from the trials), incorporating health-related quality of life data from the trials (instead of the literature), using erythropoietin (instead of not using erythropoietin) to manage anaemia, varying patient age (from that observed in the trials), and varying the time horizon (from 70 years) in the economic model. The ICERs for both populations remained below £20,000 per QALY gained, except when a 30-year time horizon was used for previously untreated patients, in which case the ICER increased to £20,689 per QALY gained. The manufacturer also provided a sensitivity analysis using a discount rate of 3.5% for costs as per the NICE reference case, but using a discount rate of 1.5% for benefits. This resulted in ICERs of £8516 and £5806 per QALY gained for the previously untreated and previously treated patients respectively.

3.23 The ICERs by IL-28B subtype ranged, depending on the subtype (CC, CT or TT), between £5056 and £16,585 per QALY gained for previously untreated patients, and between £7516 and £19,037 per QALY gained for previously treated patients. The ICERs by prior treatment response for previously treated patients were £4514, £12,554 and £23,981 per QALY gained for the prior relapser, partial responder and null responder subgroups respectively.

3.24 The ERG stated that the literature search conducted by the manufacturer was appropriate and the manufacturer had included trials that were relevant to the decision problem in its analysis. The ERG noted that the manufacturer's submission appropriately excluded one trial arm from each of the ADVANCE and REALIZE trials because of the use of dosage schedules unlicensed in the UK. However, the ERG noted some potential problems with respect to the quality of the trials:

- Trials excluded patients who were co-infected with hepatitis B or HIV or who used intravenous drugs, which could affect generalisability to UK patients.
- The use of a predefined randomisation list constructed through random permuted blocks in the REALIZE trial made it unclear if randomisation was carried out appropriately. It was not clear why patients were randomised in a 2:2:1 ratio, leading to smaller subgroups in one treatment arm in the subsequent prespecified analysis by prior treatment response.
- Although the manufacturer described the baseline characteristics and disease severity of patients in the treatment arms of the REALIZE trial as similar, it was unclear if any of the differences between them were statistically significant.
- In the ADVANCE trial, viral response monitoring of patients was conducted by an unblinded independent reviewer up to week 28, and HCV RNA results were available to the lead investigator, raising questions around the quality of blinding in the trial.
- Neither the manufacturer's submission nor the published papers relating to the trials outlined clearly how the analyses accounted for missing data. The ERG sought clarification from the manufacturer and did not consider some of the statistical methods described in the manufacturer's response, such as linear interpolation, to be best practice.

3.25 The ERG's main concern with the clinical evidence was the lack of transparency in the reporting of some of the data and the lack of statistical analysis to support the data. The ERG also noted that although the results for all relevant outcomes had been presented in the manufacturer's submission, odds ratios, absolute differences, 95% confidence intervals and p values to test for statistical significance were not reported for a number of outcomes. The ERG noted that the manufacturer had not defined the methods used to adjust for multiple comparisons in the ADVANCE trial or to analyse secondary outcomes either in the manufacturer's submission or in the trial publication. The ERG noted that no interim data were presented in the manufacturer's submission.

3.26 The ERG agreed with the manufacturer that the subgroup analyses based on IL-28B gene subtype in previously untreated patients should be treated with caution because these were post-hoc analyses with small patient numbers and randomisation had been broken within the IL-28B subgroups. No statistical comparisons were presented in the manufacturer's submission and the ERG was of the opinion that any analyses were likely to be inadequately powered. The ERG noted that, although other subgroup analyses had been reported in the manufacturer's submission, including sustained virological response according to definition of when sustained virological response had been measured, and sustained virological response according to disease severity, the manufacturer had presented no statistical analyses (for example, tests for heterogeneity) and the source of the data was not clear. Lastly, the ERG highlighted the small numbers in each of the null responder, partial responder and prior relapser subgroups in the REALIZE trial.

3.27 The ERG noted that a number of adverse reactions occur frequently with telaprevir, particularly anaemia and rash. The ERG noted that to address these issues, the manufacturer stated that clinicians would manage anaemia by reducing the dose of ribavirin and would have an adverse reaction management plan for rash. The clinical advisers to the ERG agreed that this would be acceptable practice.

3.28 The ERG was aware that the manufacturer did not provide clinical evidence about use of peginterferon alfa-2b. The ERG stated that clinical opinion

concurs with the manufacturer's opinion that there is likely to be no difference in efficacy between the two formulations of peginterferon alfa when used with telaprevir. The ERG concluded that, in general, the manufacturer's submission contained an unbiased estimate of treatment effect within the scope of the decision problem.

3.29 The ERG stated that, in general, the manufacturer's model structure, parameters and methods of analysis were appropriate and consistent with previous economic evaluations of antiviral treatment for chronic hepatitis C, including those supporting previous NICE appraisals. However, the ERG expressed some concern about the manufacturer's economic model. The ERG stated that costs for drugs were calculated assuming no wastage and were based on the mean duration of treatment in the phase III clinical trials. The ERG was aware that patients in the UK who attend clinics for regular monitoring during treatment are typically prescribed sufficient medication to last until the next follow-up visit, but may stop treatment before the drugs run out. Therefore, the mean treatment duration may not reflect the cost of drugs prescribed. In addition, the ERG noted that the administration of peginterferon alfa-2b is by body weight and was not considered explicitly in the manufacturer's submission. The ERG was also aware that the stopping rules incorporated in the manufacturer's model were different from those in the summary of product characteristics and stated that the impact of this on the cost-effectiveness results was unclear.

3.30 The ERG conducted additional exploratory analyses to address some of the issues identified in the manufacturer's economic model. The ERG varied the mean age and distribution of disease severity at treatment to bring them in line with previous NICE appraisals of antiviral therapy for chronic hepatitis C. The proportion of patients with cirrhosis modelled by the ERG was lower than in the manufacturer's base case (10% compared with 20% for previously untreated patients and 32% compared with 48% for previously treated patients). The mean ages were approximately 5 years lower in the ERG's analyses than in the manufacturer's base case. These changes reduced the ICER from £13,553 to £11,916 per QALY gained for previously untreated patients and from £8688 to £8086 per QALY gained for previously treated patients.

3.31 The ERG stated that in the manufacturer's model, patients with cirrhosis included patients with bridging fibrosis, and therefore more people in the baseline population appear to have more severe liver disease; this may have misrepresented the sustained virological response for cirrhotic patients in the model. The ERG recalculated the sustained virological responses for patients with bridging fibrosis, reclassified as moderate HCV as per the trial publications and the clinical evidence section of the manufacturer's submission. This change resulted in a slight reduction in the ICER from £13,553 to £13,368 per QALY gained for previously untreated patients and an increase in the ICER from £8688 to £9521 per QALY gained for previously treated patients.

3.32 The ERG stated that although the manufacturer's submission applied age-specific transition probabilities for early disease, the source publication (Grishchenko et al. 2009) states that these transition probabilities should be dependent on patients' age at treatment and then remain constant with treatment despite the patients ageing. The ERG updated the manufacturer's model for previously untreated patients with the appropriate age at treatment and this resulted in an increase in the ICER from £13,553 to £15,903 per QALY gained for the previously untreated population. The ERG stated that the ICER obtained by applying baseline characteristics from previous appraisals and by using age at treatment for transition probabilities for early disease increased the manufacturer's base-case ICER from £13,533 to £18,360 per QALY gained for previously untreated patients and from £8688 to £10,369 per QALY gained for previously treated patients. Combining this with recalculation to consider patients with bridging fibrosis as having moderate HCV rather than cirrhosis increased the manufacturer's base-case ICER from £13,533 to £18,091 per QALY gained for previously untreated patients and from £8688 to £10,388 per QALY gained for previously treated patients.

3.33 The ERG re-ran the probabilistic sensitivity analysis with the variables omitted in the manufacturer's probabilistic sensitivity analysis, and stated that this had little impact on the mean cost and outcomes, or the confidence intervals. However, re-running the probabilistic sensitivity analysis with the omitted variables and the changes discussed in sections 3.31 and 3.32 resulted in probabilities of 59.1% and 88.5% that telaprevir plus PEG2a/R was a cost-

effective option compared with PEG2a/R alone for previously untreated patients at £20,000 and £30,000 per QALY gained respectively. The probabilities that telaprevir plus PEG2a/R was a cost-effective option over PEG2a/R alone for previously treated patients were 92.2% and 97.4% at £20,000 and £30,000 per QALY gained respectively.

3.34 The ERG stated that its additional analyses, presented to address limitations within the manufacturer's economic model, did not have a substantial impact on the ICERs.

3.35 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/TA252

# 4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of telaprevir, having considered evidence on the nature of genotype 1 chronic hepatitis C and the value placed on the benefits of telaprevir 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 considered the nature of the condition, and noted evidence submitted and presented by the patient experts and clinical specialists on the clinical symptoms associated with chronic hepatitis C. 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 Committee heard that the symptoms of genotype 1 chronic hepatitis C, particularly when the condition reaches the fibrosis and cirrhosis stage, have a significant daily impact on the patient and their carers. The Committee also heard that there is a stigma attached to having this condition, because of a link between chronic hepatitis C and intravenous drug use. The patient experts also stated that the side effects of currently available treatments can have a significant impact on daily life. However, they stressed that patients are willing to accept these negative aspects of therapy for the possibility of experiencing a sustained virological response, but because treatment can be difficult to tolerate and takes many months, any successful treatments that could shorten the full 48-week course would be much preferred. The Committee acknowledged the significant public health impact that a sustained virological response can have in reducing transmission of the hepatitis C virus to uninfected people.

4.3 The Committee discussed the clinical treatment pathway for genotype 1 chronic hepatitis C in the UK. For those patients diagnosed with chronic hepatitis C who receive treatment, the Committee 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 previously untreated and previously treated patients with chronic hepatitis C. The Committee heard that considerable commitment and discipline is needed to adhere to protease

inhibitors, which some patients are unable to do. However, the Committee also heard that many patients who seek medical advice and receive treatment become very knowledgeable about their condition, are actively involved in its management and therefore adhere to the current twice daily treatment regimen with ribavirin. The patient experts stated that patients should start treatment only when they are ready, because they need to prepare for the commitment needed and know how the treatment is going to affect them. The clinical specialists stated that specialist nurses keep in contact with patients on a weekly basis to help ensure adherence to treatment. The Committee heard that although patients need to take telaprevir three times daily in addition to the current twice daily regimen, patients are not deterred by this, and those whose condition has not responded to treatment are extremely committed to treating their condition. The Committee heard from the clinical specialists that most current treatment is provided by specialist units. Although there are now a number of community-based centres, these remain attached to a secondary care unit. The patient experts informed the Committee that they preferred to be treated by a specialist who is experienced in managing chronic hepatitis C.

4.4 The Committee discussed the clinical effectiveness of telaprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone in previously untreated patients. It noted that the telaprevir-containing regimen statistically significantly increased sustained virological response rates for 'standard' treatment (48 weeks) and response-guided regimens. The Committee observed that telaprevir did not appear to be less effective in patients with cirrhosis than in patients with lower degrees of fibrosis, although it had not been presented with any statistical tests of these data. The Committee noted that the stopping rules differed between the clinical trial and the summary of product characteristics, but heard from the manufacturer that the difference would affect probably only 1–2% of patients. The Committee concluded that telaprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in previously untreated patients.

4.5 The Committee discussed the clinical trial data for telaprevir in patients who had been previously treated. It noted that telaprevir statistically significantly increased sustained virological response rates for 'standard' treatment

(48 weeks) and that the higher rates of sustained virological response were also seen in the patient subgroups (patients whose condition had relapsed, partially responded or not previously responded). The Committee noted that no test for interaction had been carried out to check for heterogeneity between the subgroups. It observed that there was no difference in the proportion of patients with cirrhosis who had a sustained virological response to telaprevir compared with the overall trial population. The Committee concluded that telaprevir 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 relapsed, partially responded or not previously responded to treatment.

4.6 The Committee discussed the clinical effectiveness of telaprevir for patients of different IL-28B genotype, which has been shown to affect response to treatment with peginterferon alfa and ribavirin. The Committee noted that for all IL-28B genotypes (CC, CT and TT) higher sustained virological response rates were obtained in the telaprevir arms of the trials. However the Committee noted the manufacturer's and ERG's concerns that these subgroup analyses were carried out post hoc on a small proportion of patients, and therefore the estimates were potentially uncertain. The Committee also noted that no statistical test of interaction with the treatment effect between the subgroups had been conducted. The Committee heard from the clinical specialists that in UK clinical practice IL-28B testing is not carried out routinely. Based on the lack of testing in current clinical practice, and on the lack of evidence for a statistically significant difference of the effectiveness of telaprevir according to IL-28B genotype, the Committee concluded that it was not appropriate to develop separate recommendations for the different IL-28B genotypes.

4.7 The Committee discussed the clinical effectiveness of telaprevir for patients with different levels of fibrosis and noted that telaprevir increased sustained virological response rates in patients at all levels of fibrosis. The Committee heard from the clinical specialists that patients with compensated cirrhosis were under-represented in the trials (in both the previously untreated and the previously treated populations). The Committee noted that for the small subgroup of patients with cirrhosis whose condition had not previously responded to treatment, the rate of sustained virological response appeared

lower than for the other subgroups in both arms of the trial. The Committee heard from the clinical specialists that they would expect telaprevir to be less effective in this group of patients. The Committee noted the ERG's concerns that no statistical analyses were provided by the manufacturer and therefore it was unable to determine whether there was a difference between the groups. The Committee concluded that based on the sparse evidence, it would not be appropriate to develop separate recommendations for patients with different levels of fibrosis.

4.8 The Committee noted that there were more adverse reactions in the telaprevir arms than in the control arms in both trials. The Committee heard from the clinical specialists that most adverse reactions from treatment could be managed medically. It heard that a serious adverse reaction was anaemia and that in clinical practice, as in the trials, the dose of ribavirin would be reduced. The clinical specialists explained that if anaemia persists, they would occasionally give erythropoietin to patients to maintain the dosage of ribavirin for treatment efficacy and to avoid resistance. The Committee concluded that increased rates of adverse reactions with telaprevir can be managed within current standard care.

4.9 The Committee considered the manufacturer's economic model, the assumptions underlying the values of the parameters, and the critique and exploratory analyses conducted by the ERG. The Committee noted that the manufacturer's model was similar to that used in NICE technology appraisal guidance 200 and was based on the clinical association between the intermediate outcome of virological response and the outcomes of liver disease, including decompensated cirrhosis, hepatocellular carcinoma, liver transplantation or post liver transplant. The Committee considered that the model closely adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of telaprevir. The Committee also discussed the generalisability of the population with compensated cirrhosis in the manufacturer's model to UK patients. It was aware that the higher proportion of patients with cirrhosis in the UK population could decrease the ICER because these patients were at higher risk of poor outcomes, but that it was also possible that the ICER could increase because of the observation that patients with cirrhosis tend to respond less well. It heard

from clinical specialists that people with compensated cirrhosis have a higher mortality rate than the general population and noted that this was not accounted for in the manufacturer's model (see section 4.14). Despite these shortcomings, the Committee concluded that the model was fit for purpose.

4.10 The Committee discussed the costs used in the model. The Committee examined whether drug wastage, unlike in the model, would occur in routine practice in the NHS (for example, in patients awaiting HCV RNA test results to establish virological response, which might ultimately lead to them stopping the drugs). The Committee heard that it could take up to 2 weeks to establish virological response in some places, but that with the arrival of the protease inhibitors the clinical specialists anticipated that laboratories could turn tests around within 5 days. The clinical specialists suggested that in that time some patients may receive an additional dose of peginterferon alfa; the manufacturer indicated that this could cost £200. The Committee noted that the costs of peginterferon alfa-2a had been included in the model and discussed the issue of whether peginterferon alfa-2b could be considered equivalent to peginterferon alfa-2a, noting that peginterferon alfa-2b was more expensive and, being given according to body weight, would probably be used at higher doses than peginterferon alfa-2a. The Committee heard from the clinical specialists that most patients received peginterferon alfa-2a, but that peginterferon alfa-2b could be considered equivalent (see section 4.14). The Committee concluded that overall, the costs in the model were appropriate.

4.11 The Committee considered the utility values used in the manufacturer's model. It noted that the decrements estimated from the trials that the manufacturer applied to the baseline utility values to reflect adverse reactions may have underestimated the true utility value. The Committee was aware that in the one-way sensitivity analysis presented by the manufacturer, a variation in health state utilities led to a small increase in the ICERs. The Committee also noted that the ERG re-ran the probabilistic sensitivity analysis conducted by the manufacturer after including health state utilities for mild and moderate disease as well as compensated cirrhosis that had been excluded because of an error. The ERG also included some other variables omitted by the manufacturer. The Committee concluded that this had little impact on the ICER.

4.12 The Committee considered the manufacturer's base-case results and noted that the deterministic ICERs for previously untreated and previously treated patients were £14,000 and £9,000 per QALY gained respectively. However, the Committee noted that the ICERs appeared to be robust in the manufacturer's sensitivity analyses, with all deterministic and probabilistic ICERs below £21,000 per QALY gained. The Committee noted the ERG's comments and exploratory deterministic and probabilistic analyses and accepted that the most plausible ICERs were £18,000 and £10,000 per QALY gained for the previously untreated and previously treated patients respectively.

4.13 The Committee noted a number of health-related benefits, which, if taken into account, would decrease the ICERs:

- The model did not account for the benefit to public health from reducing transmission of HCV as a result of successful treatment.
- Achieving a sustained viral response would reduce the stigma associated with having HCV.

4.14 The Committee also noted a number of factors, which, if taken into account, would increase the ICERs:

- The increased mortality rate of patients with compensated cirrhosis. However, this could be approximated by the analysis with a shorter time horizon of 30 years, which increased the ICERs to £21,000 and £12,000 per QALY gained for the previously untreated and previously treated patients respectively.
- Although there was uncertainty around the utility values, sensitivity analysis indicated that variation in these values was unlikely to increase the ICER above £20,000 per QALY gained.
- The occasional use of erythropoietin in patients with severe anaemia.
- The use of peginterferon alfa-2b instead of peginterferon alfa-2a.
- The issue of re-infection.

- The potential for decreased adherence in routine clinical practice compared with the trial setting.

On balance, the Committee agreed that the ICERs would be unlikely to increase to a point where telaprevir would not be considered cost effective. The Committee concluded that telaprevir in combination with peginterferon alfa and ribavirin represents a cost-effective use of NHS resources and should be 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.

4.15 The Committee discussed assessing the cost effectiveness of different treatment strategies. Aware that treatment with telaprevir was more cost effective in previously treated patients, the Committee discussed comparing telaprevir plus peginterferon alfa and ribavirin treatment, in previously untreated patients whose chronic hepatitis C had not achieved a sustained virological response after 12 weeks of treatment, with peginterferon alfa and ribavirin alone. The Committee noted however that such a comparison of the cost effectiveness of sequential strategies had not been specified in the scope for this appraisal and therefore concluded that it would not be appropriate to request these analyses from the manufacturer. The Committee also heard from patient experts that a strategy of treating only those whose treatment with peginterferon alfa and ribavirin alone had previously failed would not be welcomed by patients.

4.16 The Committee considered what impact excluding from trials patients co-infected with HIV and intravenous drug users had on the generalisability of the results to the UK population. The Committee heard from the clinical specialists that treatment for these patient groups is considered on an individual basis because of concerns about safety, and clinicians would offer telaprevir to intravenous drug users or people co-infected with HIV, taking into account the precautions in the summary of product characteristics. 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.

4.17 The Committee discussed whether this appraisal met the criteria for differential discounting of health benefits that can be applied in situations when treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years, as described in the clarification to section 5.6.2 of the Guide to the methods of technology appraisal issued by the Board of NICE). The manufacturer had provided a sensitivity analysis using discounts rates of 3.5% for costs and 1.5% for benefits, reducing the ICERs to £9,000 and £12,000 per QALY gained for previously untreated and previously treated patients respectively. The Committee heard from the clinical specialists that a patient who does not have cirrhosis and experiences a sustained virological response could be considered cured. However, those patients with cirrhosis who experience a sustained virological response would not have their health restored. Therefore the Committee concluded that telaprevir did not meet the criteria for differential discounting of health benefits, but that this had no impact on its recommendation for telaprevir.

4.18 The Committee considered whether telaprevir is an innovative technology. It agreed that it is clinically more effective than current therapy, but this in itself would not represent a major development in the management of chronic hepatitis C. The Committee agreed that the potential for shortening the treatment time needed for a virological response is particularly important for patients and that therefore telaprevir could be considered a major development. The Committee accepted that telaprevir is a valuable new therapy for the treatment of chronic hepatitis C. It agreed that there were health benefits not captured in the QALY calculation and had included these in its considerations (see section 4.13).

4.19 The Committee heard from the clinical specialists and the patient experts that treatment decisions for patients with chronic hepatitis C are made on an individual basis by clinicians and patients, taking into account the patient's specific circumstances. These could include concurrent illnesses that need medication, possible interactions between telaprevir and any other substances, and whether a patient is prepared to adhere to the treatment regimen and tolerate the adverse reactions. The Committee noted that the summary of product characteristics for telaprevir states the need for a physician experienced in the management of chronic hepatitis C to initiate and monitor

treatment, and heard from the clinical specialists that such physicians are experienced in taking individual circumstances into consideration when making treatment decisions in consultation with patients. The Committee concluded that it did not need to make any further recommendations about initiating and monitoring treatment because the requirement for a physician experienced in managing chronic hepatitis C was sufficiently covered within the summary of product characteristics.

4.20 The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations. The Committee discussed comments from consultees indicating that in practice the availability of treatment for people with chronic hepatitis C who use intravenous drugs, misuse alcohol and/or are co-infected with HIV was limited. The Committee agreed that this was an issue related to implementation and could not be addressed through technology appraisal recommendations. It concluded that there was no need to alter or add to its recommendations.

# Summary of Appraisal Committee's key conclusions

| TA252 | Appraisal title: Telaprevir for the treatment of genotype 1 chronic hepatitis C | Section |
|---|---|---|
| **Key conclusion** | | |

<table>
<tr><td colspan="2">Telaprevir 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:<ul><li>who are previously untreated or</li><li>in whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin has failed, including people whose condition has relapsed, has partially responded or did not respond.</li></ul>The Committee concluded that telaprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in previously untreated and previously treated patients.<br>The Committee concluded that telaprevir in combination with peginterferon alfa and ribavirin represents a cost-effective use of NHS resources and should be 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.</td><td>1.1<br>4.4<br>4.5<br>4.14</td></tr>
<tr><td colspan="3">Current practice</td></tr>
<tr><td>Clinical need of patients, including the availability of alternative treatments</td><td>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 Committee heard that the symptoms of genotype 1 chronic hepatitis C, particularly when the condition reaches the fibrosis and cirrhosis stage, have a significant daily impact on the patient and their carers. The Committee also heard that there is a stigma attached to having this condition.<br>UK practice broadly follows NICE guidance (NICE technology appraisal guidance 75, 106 and 200), which recommends treatment with peginterferon alfa plus ribavirin for both previously untreated and previously treated patients with chronic hepatitis C.</td><td>4.2<br>4.3</td></tr>
<tr><td colspan="3">The technology</td></tr>
</table>

| | | |
|---|---|---|
| Proposed benefits of the technology<br>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | The Committee considered whether telaprevir is an innovative technology. It agreed that it is clinically more effective than current therapy, but this in itself would not represent a major development in the management of chronic hepatitis C. The Committee agreed that the potential for shortening the treatment time needed for a virological response is particularly important for patients and that therefore telaprevir could be considered a major development. The Committee accepted that telaprevir is a valuable new therapy for the treatment of chronic hepatitis C. | 4.18 |
| What is the position of the treatment in the pathway of care for the condition? | Telaprevir has a UK marketing authorisation 'in combination with peginterferon alfa and ribavirin for the treatment of genotype-1 chronic HCV in adult patients with compensated liver disease (including cirrhosis) who are treatment naive, or who have been previously treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders'. | 2.1 |
| Adverse reactions | The Committee concluded that increased rates of adverse reactions with telaprevir can be managed within current standard care. | 4.8 |
| **Evidence for clinical effectiveness** | | |

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| Availability, nature and quality of evidence | The review of clinical effectiveness included two studies: the ADVANCE trial, which included patients who were treatment naive (previously untreated), and the REALIZE trial, which included patients who had been previously treated with peginterferon alfa and ribavirin but whose disease did not respond (null responder subgroup) or had a partial response to previous therapy (partial responder subgroup) or whose disease had relapsed after an initial response (prior relapser subgroup). Both trials were international, multicentre, randomised, double-blind, placebo-controlled, phase III manufacturer-supported trials comparing telaprevir plus peginterferon alfa-2a and ribavirin (PEG2a/R) with PEG2a/R alone.<br>Both trials evaluated health-related quality of life using the EQ-5D questionnaire. | 3.1<br>3.6<br>3.8 |
| Relevance to general clinical practice in the NHS | The Committee considered what impact excluding from trials patients co-infected with HIV and intravenous drug users had on the generalisability of the results to the UK population. It 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. | 4.16 |
| Uncertainties generated by the evidence | The Committee noted that the stopping rules differed between the clinical trial and the summary of product characteristics, but heard from the manufacturer that the difference would affect probably only 1–2% of patients.<br>The Committee noted that no test for interaction had been carried out to check for heterogeneity between the subgroups of patients whose condition had relapsed, partially responded or not previously responded | 4.4<br>4.5 |

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| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | Based on the lack of testing in current clinical practice, and on the lack of evidence for a statistically significant difference of the effectiveness of telaprevir according to IL-28B genotype, the Committee concluded that it was not appropriate to develop separate recommendations for the different IL-28B genotypes.<br>The Committee concluded that based on the sparse evidence, it would not be appropriate to develop separate recommendations for patients with different levels of fibrosis. | 4.6<br>4.7 |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The Committee concluded that telaprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in previously untreated and previously treated patients. | 4.4, 4.5 |
| **Evidence for cost effectiveness** | | |
| Availability and nature of evidence | The manufacturer developed a Markov model based on other published health economic models of chronic HCV, one each for patients who were previously untreated and patients who were previously treated. The Committee noted that the manufacturer's model was similar to that used in NICE technology appraisal guidance 200 and considered that the model closely adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of telaprevir. | 3.13, 3.14, 4.9 |

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| Uncertainties around and plausibility of assumptions and inputs in the economic model | The Committee noted a number of health-related benefits, which, if taken into account, would decrease the ICERs:<br>• The model did not account for the benefit to public health from reducing transmission of HCV as a result of successful treatment.<br>• Achieving a sustained viral response would reduce the stigma associated with having HCV.<br>The Committee also noted a number of factors, which, if taken into account, would increase the ICERs:<br>• The increased mortality rate of patients with compensated cirrhosis. However, this could be approximated by the analysis with a shorter time horizon of 30 years, which increased the ICERs to £21,000 and £12,000 per QALY gained for the previously untreated and previously treated patients respectively.<br>• Although there was uncertainty around the utility values, sensitivity analysis indicated that variation in these values was unlikely to increase the ICER above £20,000 per QALY gained.<br>• The occasional use of erythropoietin in patients with severe anaemia.<br>• The use of peginterferon alfa-2b instead of peginterferon alfa-2a.<br>• The issue of re-infection.<br>• The potential for decreased adherence in routine clinical practice compared with the trial setting.<br>On balance, the Committee agreed that the ICERs would be unlikely to increase to a point where telaprevir would not be considered cost effective. | 4.13<br>4.14 |

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| Incorporation of health-related quality-of-life benefits and utility values<br>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? | The model did not account for the benefit to public health from reducing transmission of HCV as a result of successful treatment, or that achieving a sustained viral response would reduce the stigma associated with having HCV.<br>The Committee agreed that there were health benefits not captured in the QALY calculation and that it had included these in its considerations. | 4.13, 4.18 |
| Are there specific groups of people for whom the technology is particularly cost effective? | No. The Committee concluded that telaprevir in combination with peginterferon alfa and ribavirin represents a cost-effective use of NHS resources and should be 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. | 4.14 |
| What are the key drivers of cost effectiveness? | The Committee noted that the ICERs appeared to be robust in the manufacturer's sensitivity analyses, with all deterministic and probabilistic ICERs below £21,000 per QALY gained. | 4.12 |

| | | |
|---|---|---|
| Most likely cost-effectiveness estimate (given as an ICER) | The Committee concluded that the most plausible ICERs were £18,000 and £10,000 per QALY gained for the previously untreated and previously treated patients respectively. | 4.12 |
| **Additional factors taken into account** | | |
| Patient access schemes (PPRS) | Not applicable to this appraisal. | - |
| End-of-life considerations | Not applicable to this appraisal. | - |
| Equalities considerations and social value judgements | Comments from consultees indicated that the availability of treatment for chronic hepatitis C patients in 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 recommendations. It concluded that there was no need to alter or add to its recommendations. | 4.20 |

# 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/TA252).

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

# 6 Related NICE guidance

### Published

- Boceprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 253 (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.

# 7 Proposed date for review of guidance

7.1 The guidance on this technology will be considered for review by the Guidance Executive 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 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.

**Dr Amanda Adler (Chair)**
Consultant Physician, Addenbrooke's Hospital

**Professor Ken Stein (Vice Chair)**
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

**Dr Ray Armstrong**
Consultant Rheumatologist, Southampton General Hospital

**Dr Jeff Aronson**
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

**Dr Peter Barry**
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

**Professor John Cairns**
Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

**Dr Mark Chakravarty**
External Relations Director - Pharmaceuticals & Personal Health, Oral Care Europe

**Mark Chapman**
Health Economics and Market Access Manager, Medtronic UK

**Eleanor Grey**
Lay member

**Dr Neil Iosson**
General Practitioner

**Terence Lewis**
Lay Member

**Dr Rubin Minhas**
General Practitioner and Clinical Director, BMJ Evidence Centre

**Dr Peter Norrie**
Principal Lecturer in Nursing, DeMontfort University

**Professor Stephen Palmer**
Professor of Health Economics, Centre for Health Economics, University of York

**Dr John Pounsford**
Consultant Physician, Frenchay Hospital, Bristol

**Alun Roebuck**
Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

**Navin Sewak**
Primary Care Pharmacist, NHS Hammersmith and Fulham

**Roderick Smith**
Finance Director, West Kent Primary Care Trust

**Cliff Snelling**
Lay Member

**Marta Soares**
Research Fellow, Centre for Health Economics, University of York

**Professor Andrew Stevens**
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

**Professor Rod Taylor**
Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

**Tom Wilson**
Director of Contracting & Performance, NHS Tameside & Glossop

**Dr Nerys Woolacott**
Senior Research Fellow, Centre for Health Economics, University of York

# B 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.

**Raisa Sidhu**
Technical Lead

**Joanna Richardson**
Technical Adviser

**Jeremy Powell**
Project Manager

# Appendix B: Sources of evidence considered by the Committee

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

- Baxter L, Harris P, Hartwell D et al. Telaprevir for the treatment of genotype 1 chronic hepatitis C, December 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 telaprevir 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:

- Janssen

II Professional/specialist and patient/carer groups:

- Association of Clinical Biochemists - Microbiology Section
- British Association for the Study of the Liver Nurses Forum
- British HIV Association
- British Infection Society (British Infection Association)
- British Liver Nurses Forum
- British Liver Trust
- British Society of Gastroenterology
- British Transplantation Society
- Haemophilia Society
- Hepatitis C Trust

- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

III Other consultees:

- Department of Health
- NHS Norfolk
- Welsh Government

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

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

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 telaprevir by providing oral evidence to the Committee.

- Dr Steve Ryder, Consultant Hepatologist – Nottingham University Hospitals NHS Trust, nominated by the British Society of Gastroenterology – clinical specialist
- Dr Jacquelyn Smithson, Consultant Hepatologist – Hull And East Yorkshire Hospitals NHS Trust, nominated by the Royal College of Physicians – clinical specialist
- Raquel Jose, International Relations Director – World Hepatitis Alliance, nominated by the Hepatitis C Trust – patient expert

- Andrew Langford, Chief Executive – British Liver Trust, nominated by the British Liver 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.

- Janssen

# 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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