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Telaprevir for the treatment of genotype 1 chronic hepatitis C

Produced by Southampton Health Technology Assessments Centre

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Jeremy Jones (Principal Research Fellow) critically appraised the health economic systematic review and the economic evaluation, drafted the report and project managed the review; Debbie Hartwell (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report; Louise Baxter (Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; Petra Harris (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report.

Key to colour highlighting used in report

Commercial in confidence (CIC) information in blue
Academic in confidence (AIC) information in yellow.

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LIST OF ABBREVIATIONS

AE	Adverse event(s)
BMI	Body mass index
CC	Compensated cirrhosis
CEA	Cost effectiveness analysis
CHC	Chronic hepatitis C
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
DC	Decompensated cirrhosis
DSA	Deterministic sensitivity analysis
EMA	European Medicines Agency
ERG	Evidence Review Group
eRVR	Extended rapid virological response
EQ-5D	EuroQol five dimension
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCHS	Hospital and Community Health Services
HCV	Hepatitis C virus
HCV RNA	Hepatitis C virus ribonucleic acid
HIV	Human immunodeficiency virus
HPA	Health Protection Agency
HRQoL	Health Related Quality of Life
ICER	Incremental cost effectiveness ratio
IL-28B	Interleukin-28B
ITT	Intention to treat
LT	Liver transplant
LY	Life year(s)
MS	Manufacturer's submission
MTC	Mixed treatment comparison
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OR	Odds ratio
PBO	Placebo
PCR	Polymerase chain reaction
PR	Peginterferon alfa and ribavirin
PR48	Peginterferon alfa and ribavirin for 48 weeks
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised controlled trial
RR	Relative risk
RVR	Rapid virological response
SE	Standard Error
SG	Standard gamble
SmPC	Summary of Product Characteristics
SVR	Sustained virologic response

T	Telaprevir
T12	Telaprevir treatment for 12 weeks
TTO	Time trade-off

SUMMARY

Scope of the manufacturer submission

The manufacturer's submission (MS) reflects the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE). This was to consider telaprevir (T) in combination with peginterferon alfa and ribavirin (PR) for the treatment of genotype 1 chronic hepatitis C (CHC).

Summary of submitted clinical effectiveness evidence

The clinical effectiveness evidence in the MS comes from two phase III randomised controlled trials (RCTs):

- one trial (ADVANCE[1]) evaluates 12 weeks of telaprevir in combination with PR plus PR alone for an additional 12 or 36 weeks (i.e. total treatment duration of 24 or 48 weeks) in treatment-naïve patients (T12/PR);
- one trial (REALIZE[2]) evaluates 12 weeks of telaprevir in combination with PR followed by 4 weeks of placebo and PR plus 32 weeks of PR alone (i.e. total treatment duration of 48 weeks) in previously treated patients (T12/PR48).

Both trials compare the telaprevir arm to 48 weeks of placebo plus PR (PBO/PR) treatment.

The primary outcome is sustained virologic response (SVR). In treatment-naïve patients, the proportion of patients achieving an SVR increased significantly from 44% in those receiving PR alone (PBO/PR) to 75% with the addition of telaprevir (T12/PR) ($p<0.0001$; difference 31% [95% CI 24-38%]). A similar effect was seen in previously treated patients with a significant increase in SVR rate from 17% with PBO/PR to 64% with the addition of telaprevir (T12/PR48) ($p<0.001$; difference 47% [95% CI 37-57]). The beneficial effect of T/PR combination treatment was observed across the prior response patient subgroups with significantly higher SVR rates in T12/PR48 patients compared to PBO/PR48 for prior relapsers (83% vs 24%), prior partial responders (59% vs 15%) and prior null responders (29% vs 5%) ($p<0.001$ T12/PR48 vs PBO/PR for all subgroups). It should be noted that the numbers in these subgroups were small.

Secondary outcomes included extended rapid viral response (eRVR) rates and relapse rates. In treatment-naïve patients, rates of eRVR were higher in those receiving the T12/PR combination therapy compared to those receiving the current standard of care. The same was true for each

of the prior response subgroups of treatment-experienced patients. In addition, relapse rates were lower in both treatment-naïve and treatment-experienced patients receiving the T12/PR combination compared to PBO/PR alone. However, it should be noted that many of these differences in eRVR and relapse rates were not supported by statistical comparisons and groups for the previously treated patients were small.

The addition of telaprevir to PR therapy led to an increase in the incidence of several adverse events compared to patients who received the current standard of care. Rash and anaemia were considered to be the most clinically important adverse events related to telaprevir therapy.

Summary of submitted cost effectiveness evidence

The MS includes:

i) a review of published cost-effectiveness analyses of anti-viral treatment for adults with CHC;

ii) a *de novo* economic evaluation to estimate the cost-effectiveness of telaprevir in combination with peginterferon alfa and ribavirin (T12/PR), compared with the standard combination of peginterferon alfa and ribavirin (PR), for the treatment of genotype 1 CHC in treatment-naïve adults and in adults for whom previous anti-viral therapy has failed.

A systematic search of the literature was undertaken by the manufacturer to identify previous economic evaluations of anti-viral therapy in adults with CHC, published since 2009. Six papers met the inclusion criteria. The search was not specific to studies which included telaprevir-containing regimens, and did not identify any studies that compared telaprevir to its alternatives.

The economic evaluation uses a Markov model to estimate the cost-effectiveness of T12/PR compared with PR in adults with genotype 1 CHC. Separate base case analyses are reported for treatment-naïve patients and for those who had previously been treated. The model adopted a lifetime horizon, with an annual cycle length. At baseline patients are distributed across age and severity of compensated liver disease, based on the relevant trial populations, with the primary treatment outcome (sustained virologic response (SVR) or non-SVR) assigned at the end of the first year of the model.

The modelling approach and structure adopted appear reasonable, and are based on previous models in this disease area. The distribution of patients across age and stage of compensated liver disease in the models is based on the overall populations recruited to the trials included in the clinical effectiveness section. Health related quality of life has been adapted from previous appraisals for NICE, with on-treatment disutility derived from the included RCTs. Resource use and costs have been adapted from previous appraisals in PR for NICE.

Results are presented for lifetime costs, quality adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for both treatment-naïve and treatment-experienced patients. For the base case an incremental cost per QALY gained of £13,553 is reported for treatment-naïve patients and £8,688 for treatment-experienced patients. Results are also presented for the subgroup analyses by IL-28B subtype for both patient populations and by prior treatment response for treatment-experienced patients.

The manufacturer's deterministic sensitivity analysis (DSA) reported both one-way analyses and scenario analyses. These indicated that the greatest variation in ICER for treatment-naïve patients is associated with the health state utility for mild CHC, variation in treatment duration (in the T12/PR-treated cohort) and SVR. The MS reports that the ICER remained below £18,000 per QALY gained in all instances for this population. The greatest variation in ICER for treatment-experienced patients is associated with the costs and utility values applied to the cirrhosis (compensated or decompensated) health states, treatment duration (in the T12/PR-treated cohort) and SVR. The MS reports that the ICER remained below £13,000 per QALY gained in all instances for this population.

The probabilistic sensitivity analysis (PSA) results state that for treatment-naïve patients, there is an 85.3% probability of T12/PR therapy being cost-effective, compared with PR alone, at a threshold willingness to pay of £20,000 per QALY gained, and 98.0% probability at a threshold of £30,000 per QALY gained. The equivalent values for treatment-experienced patients are 94.0% and 97.4%.

Commentary on the robustness of submitted evidence

Strengths

- The MS contains systematic searches for both the clinical and cost effectiveness studies of telaprevir. It is unlikely that any studies eligible for inclusion were missed.
- The systematic review meets the Centre for Reviews and Dissemination (CRD) criteria for methodological quality.
- The economic model presented in the MS is appropriate for the disease area and is based on models developed in previous economic evaluations. The model has the same structure and used parameter inputs similar to those adopted for previous NICE appraisals.
- The cost-effectiveness analysis meets the requirements of the NICE reference case.

Weaknesses and Areas of uncertainty

- The MS contains large amounts of unpublished data from the clinical study reports.
- Presentation of many of the outcomes are merely comparisons of percentage values without any effect size (ORs or RRs), confidence intervals or statistical significance tests (p values), making interpretation difficult.
- Patient numbers in many of the subgroup analyses are relatively small, are likely not powered, and should be interpreted with caution.
- The IL-28B subgroup analyses for both trials were post-hoc analyses with small patient numbers and were not adequately powered for statistical comparison. Randomisation was also broken within the subgroups. Results have to be treated with caution, as acknowledged by the manufacturer.
- The previously published economic evaluations identified in the systematic review are not discussed. Selective results are presented in a table.
- Peginterferon alfa-2a is used in the model, since this comparator was used in the trial. There is limited data on telaprevir in combination with peginterferon alfa-2b and ribavirin, and it is therefore unclear whether the conclusions are generalisable to peginterferon alfa-2b.
- Stopping rules employed in the model do not reflect those in the SmPC for telaprevir. As a result the treatment durations derived from the trials may not be generalisable to usual practice.

- The health-related quality of life (HRQoL) reported in the trials did not correspond to those of previously published studies, and were not applied in the model. The estimates from the trials were used to calculate on-treatment disutility. Methods for handling missing data in the calculation of on-treatment disutility are unclear.
- Consultant time during active treatment with T12/PR is not accounted for in resource use and cost calculation, despite the clinical advisory board advising that this would be necessary.
- The possibility of drug wastage is not accounted for in the MS.
- No evidence is presented of internal validation checks of the model, or calibration of the model against independent data. No checks of model results have been presented comparing these against previous studies of PR.
- There is no discussion or rationale provided in the MS for the choice of variables included or excluded from the sensitivity analyses.
- Arbitrary ranges have been employed for a number of variables in the one-way DSA without accompanying rationale, in some cases where appropriate variations are available.
- All variables in the DSA and PSA are treated as independent: in some cases it may have been appropriate to consider where variables should be treated as correlated.

Summary of additional work undertaken by the ERG

Eight additional analyses were undertaken by the ERG. The mean age and distribution of disease severity were adjusted for consistency with previous NICE appraisals, SVRs were applied based on a definition of cirrhosis consistent with the original trial publications, disease severity was applied based on a definition of cirrhosis consistent with the original trial publications and early transition probabilities were applied that were consistent with the definition in the source publication. The manufacturer's PSA was also re-run, including omitted variables and applying each of baseline characteristics consistent with previous NICE appraisals, age of treatment transition probabilities and SVRs as above. In treatment naïve patients, changes to both age at treatment and transition probabilities and baseline population as in previous appraisals resulted in the highest ICER OF £18, 360. In treatment experienced patients adjusting the age at treatment, transition probabilities and baseline population to be consistent with previous NICE appraisals and the SVR calculated with bridging fibrosis resulted in the highest ICER of £10,388.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Janssen on the clinical effectiveness and cost effectiveness of telaprevir, in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic Hepatitis C (CHC). It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 8 November 2011. A response from the manufacturer via NICE was received by the ERG on 29 November 2011. It should be noted that much clinical data presented in the MS was sourced from unpublished clinical study reports. These were large documents (300+ pages), provided by the manufacturer following the request for clarification. The ERG referred to them only to verify statistical comparisons reported in the MS.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The MS provides a clear and accurate overview of CHC.

2.2 Critique of manufacturer's overview of current service provision

The MS provides an accurate overview of current service provision.

2.3 Critique of manufacturer's definition of decision problem

Population

The population described in the decision problem is appropriate for the NHS.

Intervention

Telaprevir was granted marketing authorisation by the EMA on 20th September 2011. The description of the intervention in the decision problem is in agreement with the SmPC for telaprevir[3] and is appropriate for the NHS. The standard dose of telaprevir is 750 mg orally three

times daily with food. Telaprevir should only be prescribed in combination with peginterferon alfa and ribavirin and should not be re-initiated if it is discontinued (either due to adverse events or insufficient virology response).

Comparators

The comparator in the MS decision problem is combination therapy consisting of peginterferon alfa and ribavirin (PR). This is the current standard of care for CHC in the UK.

Outcomes

The outcomes included in the MS are appropriate and clinically meaningful to patients.

Economic analysis

The economic evaluation in the MS decision problem appears to be appropriate, being a cost utility analysis from the NHS and Personal Social Services (PSS) perspective.

Other relevant factors

The MS considers evidence on duration of treatment as indicated in the SmPC for telaprevir,[3] where non-cirrhotic, treatment-naïve patients who achieve an extended rapid viral response (eRVR, defined as undetectable HCV RNA at week 4 and week 12 of treatment) may be considered for a total of 24 weeks (rather than 48 weeks) treatment with peginterferon alfa and ribavirin.

Evidence is presented for subgroups based on IL-28B subtype (for treatment-naïve and treatment-experienced patients) as indicated in the scope. These should be treated with caution as these were not pre-specified for the trials and are subject to large amounts of missing data (58% for treatment-naïve patients and 20% for treatment-experienced patients). Subgroup analyses are also presented for treatment-experienced patients, based on their prior response to therapy (relapsed, partial responder and non-responder).

The MS states special considerations, including issues relating to equity or equality, are not applicable and this is in line with the decision problem in the NICE scope.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

The manufacturer's literature searches were checked by an information scientist. Overall the search strategies were considered to be reasonably comprehensive, fit for purpose and reproducible, having a balance of descriptor and free text terms with correctly linked sets. The databases, hosts, dates and strategies were specified clearly in the MS. The MS record use of the Embase host platform, whereas the ERG use Ovid and therefore would be unable to exactly re-run the searches. However, the ERG anticipate that if the searches were to be re-run, results would be comparable.

Conference proceedings were searched on relevant websites/databases and dates were provided. Conference proceedings were searched from 2003 onwards. Abstracts were included in the searches. There is no overt search documenting the use of in-house company databases, nor recording of a strategy or sources used to identify on-going trials. However, two on-going trials were identified (MS p.15/16) and there is reference to records from clinicaltrials.gov in the MS text (MS p.16). It appears from the manufacturer's response to clarification questions that a specific search for on-going trials was not conducted but rather 'on-going trials were not excluded from the main clinical effectiveness searches.' The ERG consulted on-going trials databases to identify any additional unpublished data using the following sources: UK Clinical Research Network (UKCRN), controlled trials.com, clinicaltrials.gov and ICTRP (WHO International Clinical Trials Registry Platform). The results were checked by an ERG reviewer. One additional on-going trial relevant to the decision problem was identified (see Section 3.1.3). Although a thorough cost effectiveness search is documented for Medline and Embase, the MS omitted NHSEED and Econlit searches in their original submission. Further to the ERG's clarification questions, the manufacturer ran searches on these databases and reported that no additional references were identified on cross-checking with their prior Medline and Embase cost searches. The ERG also carried out searches on NHSEED and Econlit.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The MS clearly states the inclusion and exclusion criteria (MS Table 4 p.35-37) and these reflect the final scope issued by NICE and the licensed indication. No limits were placed on inclusion relating to the quality of the RCTs or the setting, but these were not requirements of the final scope. RCTs were limited to English language publications.

The MS presents a flow diagram illustrating the number of studies identified from searches and each stage of the inclusion/exclusion process (MS p.38). Citations identified from conference searches are presented separately in the diagram. Reasons for excluding citations and conference abstracts after first screening are provided in full, but reasons for exclusion of studies and conference abstracts at the full publication review stage are not provided.

Studies were restricted to randomised controlled trials (RCTs). Comparative observational studies would only be included to fill the data gaps in RCT evidence although none were identified by the systematic literature review. The MS states that smaller studies were excluded (n<30) 'as these are typically phase I and dose-ranging studies,' which is not unreasonable. The MS states that restricting the trials to English language publications only would not limit the results substantially due to data availability in the English language and the ERG would agree. While the MS does not explicitly consider issues of bias or study quality at this stage, a critical appraisal of the included RCTs is presented in Section 5.4 of the MS (p.64) and Appendix 8 (p.213).

3.1.3 Identified studies

The MS identified six studies from 70 publications (MS Table 5 p.39). However, whilst all six studies met the inclusion criteria, four studies were excluded from further consideration in the review of clinical effectiveness. The MS provided detailed reasons for the exclusions (MS p.45/46). Three studies were excluded as they evaluated unlicensed doses or dosing regimens, and did not incorporate response-guided therapy or an adverse effect management plan. The fourth trial was excluded as it was an on-going trial with interim results at 12 weeks only and reported no SVR results. Hence, the review of clinical effectiveness was based on two phase III studies: (1) the ADVANCE trial[1] (treatment-naïve patients); (2) the REALIZE trial[2] (previously treated patients), shown in Table 1. Both these studies had three trial arms, however the MS excluded one trial arm from each study due to the use of unlicensed dosing schedules of either

eight weeks of telaprevir treatment (ADVANCE[1]) or a four-week peginterferon alfa/ribavirin lead-in phase before telaprevir treatment (REALIZE[2]). The ERG would agree that this was appropriate. Both of the included RCTs were sponsored by the manufacturer in collaboration with Vertex and Tibotec Pharmaceuticals. Both of the included RCTs meet the inclusion criteria for the review and it would appear that the MS has identified all relevant published RCTs. However, the ERG did identify one further completed trial in the on-going trial searches (NCT00780416 Efficacy and safety of MP-424 (Telaprevir)/Peginterferon alfa-2b/ribavirin combination in treatment-naïve patients with chronic hepatitis C[4]) but have been unable to identify any publication. No non-randomised studies were included in the MS.

Electronic copies of the two included RCTS (ADVANCE[1] and REALIZE[2]) were provided, along with the three phase II PROVE studies,[5-7] which were later excluded. The interim analysis abstract on HIV patients[8] (the fourth study that was later excluded), and a conference proceeding (Pol and colleagues[9]) from which data were reported for the IL-28B subgroup analysis in the REALIZE trial, were also provided by the manufacturer.

Table 1 List of included studies

Trial	Intervention 1	Intervention 2*	Comparator
ADVANCE[1] (treatment-naïve)	**T12/PR**	**T8/PR**	**PBO/PR**
	T/PR 12 weeks + PR 12 or 36 weeks**	T/PR 8 weeks + PBO/PR 4 weeks + PR 12 or 36 weeks**	PBO/PR 12 weeks + PR 36 weeks
REALIZE[2] (treatment-experienced)	**T12/PR48**	**Lead-in T12/PR48**	**PR48**
	T/PR 12 weeks + PBO/PR 4 weeks + PR 32 weeks	PBO/PR 4 weeks + T/PR 12 weeks + PR 32 weeks	PBO/PR 16 weeks + PR 32 weeks

T, telaprevir; PR, peginterferon alfa-2a and ribavirin; PBO, placebo. *intervention arm excluded from MS due to unlicensed dose regímen; **received response guided therapy where those achieving an eRVR were treated for a shorter total duration of 24 weeks compared to 48 weeks.

Detailed summaries of the methodology of both included RCTs are provided in Table 7 (p.48-50) in the MS. The table summarises the location, design, duration of the studies, methods of randomisation and blinding, intervention and comparators, primary and secondary outcomes (with more details in Table 12 of the MS, p.57), as well as duration of follow-up. Whilst data have been reported from the published trial papers,[1;2] additional information has been taken from the unpublished CSRs.[10-13]

More detailed information about the eligibility criteria for both of the included RCTs[1;2] are presented separately in Table 8 (MS p.52) of the MS and appear to be reasonable. However, both trials excluded patients co-infected with hepatitis B or HIV and also intravenous drug users which raises a question over generalisability. Patient numbers for those eligible and randomised are presented in a flow diagram for each RCT (Figures 7 and 8 in the MS p.62-63). The reasons for drop outs are detailed for the majority of patients, but are only described as 'other reasons' for a small number of patients in both RCTs. Statistical analysis information is tabulated in the MS Table 13 p.59, including power/sample size calculations and data management (intention to treat (ITT) analysis).

The MS provided no commentary on any differences between groups at baseline, but tabulated baseline characteristics for both trials (MS Table 9 p.54). More detailed tables for each trial were presented in the appendices (MS Appendix 5 p.202 and Appendix 6 p.205). Upon visual inspection of the table, the two treatment arms in the ADVANCE trial[1] appear to be similar in baseline characteristics. The published trial[1] states that there were no statistically significant differences among the study groups (no p values are reported) for any characteristic except body mass index (BMI) for which there was a significant difference between the T12/PR and PBO/PR (control) group (p=0.02). There is no indication of whether this is for median BMI or in the proportion of patients who were classified in the three categories of healthy weight, overweight or obese. The two treatment arms in the REALIZE trial[2] also appear balanced with respect to baseline characteristics, with the exception of stage of fibrosis where the proportion of patients with 'no/minimal fibrosis' is higher in the PBO/PR (control) arm compared to the telaprevir arm (27% vs 19% respectively). In addition, the control arm has a higher proportion of Hispanic patients (15% vs 9% respectively) and black patients (8% vs 4% respectively). It is unclear if any of these differences are of statistical significance, as significance values are not provided in the MS or in the published RCT paper, although the published trial[2] does state that there were no statistically significant differences among the study groups for any characteristic.

In terms of differences in patient characteristics between the trials, the REALIZE trial[2] has a higher percentage of male patients (67-69% vs 58-59%) and a lower number of HCV genotype 1a patients (44-45% vs 58-59%) compared to patients in the ADVANCE trial.[1] However, MS Table 9 (p.54) reports different figures (for genotype) to those reported in the trial publication.[2] As disease severity (mild, moderate and compensated cirrhosis) is presented by age groups in the ADVANCE trial[1] and by prior response in the REALIZE trial,[2] it is not possible to interpret

any differences for this characteristic between the trials. However, there are a higher proportion of patients with no/minimal fibrosis (37-41% ADVANCE vs 19-27% REALIZE) and a lower proportion of patients with cirrhosis (6% ADVANCE vs 23-27% REALIZE) in the ADVANCE trial[1] compared to the REALIZE trial.[2] This would be expected given that the ADVANCE trial[1] is based on treatment-naïve patients whilst the REALIZE trial[2] is based on treatment-experienced patients. Clinical opinion concurs that previously treated patients would be expected to be at a more advanced stage of liver disease than treatment-naïve groups of patients given that CHC is a progressive disease.

The MS identified two on-going trials (MS p.15-16) (VX-950-TiDP24-C219 and VX08-950-110), with anticipated results for both due towards the end of 2012. The VX-950-TiDP24-C219 trial is an open-label, single-arm Phase III extension study of the REALIZE trial evaluating T/PR in the PBO/PR treated patients who failed treatment for virologic reasons. The VX08-950-110 trial is an on-going Phase IIa T/PR safety and efficacy trial in treatment-naïve, genotype 1 HCV patients co-infected with HIV. The ERG identified one additional on-going trial - NCT 01415141 'Peginterferon and ribavirin, with or without telaprevir, for genotype 1 hepatitis C and IL-28B CC polymorphism.'[14] However, this trial appears to be limited to only one IL-28 gene subgroup. The trial is currently recruiting subjects and has an estimated study completion date of June 2014.

3.1.4 Description and critique of the approach to validity assessment

The MS provides a summary of the quality assessment of the included RCTs in Table 15 (MS p.64) and a more detailed assessment of each RCT can be found in Appendix 8 (MS p.213-214). The manufacturer's quality assessment is appropriate and follows the NICE criteria. The published paper for the ADVANCE trial[1] reports no information relating to randomisation, concealment of treatment allocation or blinding but refers to a protocol available online. More methodological information was reported in the published paper for the REALIZE trial,[2] but further details are again given in an online protocol. Both these protocols are extensive (131 and 170 pages respectively) and the ERG therefore had limited time to search for information within them to check against the MS. Table 2 shows the assessment of study quality for each RCT by the manufacturer and the ERG. As the table shows, there are some differences in quality assessment between the MS and ERG. A large proportion of the clinical effectiveness data was sourced from unpublished CSRs[10;11] and it is not clear whether these have undergone quality

assessment. After seeking clarification from the manufacturer who stated that 'standard procedures were completed', this remains unclear.

Table 2 Manufacturer and ERG assessment of trial quality

		ADVANCE	REALIZE
1. Was randomisation carried out appropriately?	MS:	Yes	Not clear
	ERG:	Yes	Not clear
Comment: According to the details in the MS (MS p.48/49), the randomisation procedure for the ADVANCE trial appears appropriate, however there are no details in the trial publication[1] though details are available in the online protocol. The use of a predefined randomisation list constructed through random permuted blocks in the REALIZE trial[2] makes it unclear if randomisation was carried out appropriately (MS Appendix 8 p.213). It is also not clear why patients were randomised in a 2:2:1 ratio leading to smaller subgroups in one treatment arm in the subsequent analysis by prior treatment response.			
2. Was concealment of treatment allocation adequate?	MS:	Yes	Yes
	ERG:	Yes	Yes
Comment:			
3. Were groups similar at outset in terms of prognostic factors?	MS:	Yes	Yes
	ERG:	No	Unclear
Comment: Baseline characteristics between the treatment arms were not significantly different with respect to major baseline demographic and disease characteristics in the ADVANCE trial, except BMI which was statistically significantly different (p=0.02) between treatment arms (median BMI 25.7 T12/PR vs 26.4 PBO/PR).[1] Clinical opinion is that this is unlikely to have an impact on the SVR rate given that the BMI for both groups are within the normal range. Baseline characteristics and disease level between treatment arms in the REALIZE trial are described as similar by the trial authors,[2] however no p-values were provided and it is unclear if any of the differences were statistically significant.			
4. Were care providers, participants and outcome assessors blind to treatment allocation?	MS:	Not clear	Yes
	ERG:	No	Yes
Comment: The MS states that in the ADVANCE trial individual viral response monitoring was conducted by an unblinded independent reviewer until week 28 (MS Appendix 8 p.213) and HCV RNA results were available to lead investigator from week 28 onwards (Table 7 p.49).			
5. Were there any unexpected imbalances in drop-outs between groups?	MS:	Yes	Yes
	ERG:	Yes	Yes
Comment: In the MS this question was answered 'Yes' to both trials in the quality assessment (Table 15, p.64) but 'No' to both trials in the detailed quality assessment (Appendix 8, p.213). There are some imbalances in treatment discontinuation and reasons for discontinuation between treatment groups in both the ADVANCE and REALIZE trials. However, no p-values were reported and it is unclear if these differences were statistically significant.			
6. Is there any evidence that authors measured more outcomes than reported?	MS:	Yes	Yes
	ERG:	Yes	Yes
Comment: While the MS states that the authors did measure more outcomes than were reported (Table 15, p.64), their detailed quality assessment (Appendix 8, p.213) contradicts this by stating that the authors measured the same outcomes that were reported in the protocol or study methods of the trials. However, there are several outcomes reported in the MS that are not reported in the trial publications (e.g. HRQoL, fatigue).			
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	MS:	Yes	Yes
	ERG:	Unclear	Unclear

Comment: The MS states that both trials conducted an ITT analysis defined as all patients who had received at least one dose of study drug. Whilst a true ITT analysis should include all randomised patients, it is not unusual to restrict it to patients receiving at least one dose of study drug. The difference between these two analysis sets is small (N=7 ADVANCE and N=1 REALIZE) (see also comment in Section 3.1.6). It is unclear how missing data was accounted for (see Section 3.1.6). The MS reports that SVR rates were analysed using a conservative approach without imputation of missing values for SVR assessment (Table 7 p.50).

3.1.5 Description and critique of manufacturer's outcome selection

The primary outcome is SVR, 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. This is appropriate and matches the decision problem.

The secondary outcomes reported in the MS are: eRVR, relapse rates, virologic failure, adherence, discontinuation rates, duration of treatment, HRQoL, fatigue, SVR rates by subgroups (IL-28B subtype, disease severity, other baseline characteristics) and SVR rates according to definition (published values and SmPC values). The outcomes are appropriate to the decision problem but the MS has included more outcomes than are specified in the NICE scope - relapse rate, virologic failure, adherence, discontinuation rates and fatigue. Several outcomes (HRQoL, fatigue and adherence) reported by the manufacturer to be addressed in the submission (p.31) were included as outcomes in the summary of the RCTs (MS.Table 7, p.50) but were not reported in the published papers[1;2] and the outcome data in the MS has been taken from the unpublished CSRs[10;11] which were not provided with the submission. Data for several other outcomes (virologic failure, duration of therapy, SVR by IL-28B subtype [ADVANCE[1]], SVR according to disease severity [REALIZE[2]]) also reported in the MS came from the unpublished CSRs.[10;11]

Adverse events (AE) are reported in the main AE results section (section 5.9) and in some more detail in Appendices 9.5 & 9.6 (p. 204 & 208). Mortality is specified in the final scope and is included in the AE section of the MS (section 5.9.2.5). The EQ-5D and the Fatigue Severity Scale were used to measure quality of life and both are validated measures. Neither are reported as outcomes by the published trials.[1;2]

There are a number of outcomes reported by the published RCTs[1;2] that were not reported in the main results section of the MS (e.g. mean HCV RNA levels during treatment, more complete list of AE or reasons for discontinuation). Some of these were presented in the MS Appendices

9.5 and 9.6, others were supplementary data not stipulated in the NICE scope or not of importance with regards to the decision problem.

3.1.6 Description and critique of the manufacturer's approach to trial statistics

Both trials[1;2] evaluated two telaprevir arms versus PBO/PR (control) but omitted reporting one of the telaprevir arms each in the MS due to the use of unlicensed doses or regimens (an approach which is considered appropriate). For both RCTs, analysis of the primary end point was based on a logistic regression model with treatment group and baseline HCV RNA (both trials), genotype 1 subtype (ADVANCE[1]) and type of prior response (REALIZE[2]) as factors. The ADVANCE[1] trial also conducted a pre-specified subgroup treatment effect analysis related to 10 baseline variables. The REALIZE[2] trial used a Hochberg procedure to adjust for multiple comparisons; the method used to adjust for multiple comparisons in the ADVANCE trial was not stated in the MS or the trial publication.[1] The sample size/power calculation was performed with the use of a two-sided continuity-corrected chi-square test for both trials. Neither the trial publications[1;2] nor the MS reported on the methods of analysis for secondary outcomes.

Results for all relevant outcomes are presented in the MS, but odds ratios (ORs), absolute differences, 95% confidence intervals (CIs) and p values are not reported for a number of outcomes. The percentage difference, 95% CIs and p values are reported for the primary outcome (SVR) in the published papers[1;2] and the MS. eRVR, relapse, virologic failure, adherence, discontinuation rates and AE were reported as n,N (%) only and HRQoL and fatigue as n, mean only with no indication of whether any differences were statistically significant. For the ADVANCE trial, 95% CIs and p-values were not reported for secondary outcomes, except for the subgroup analyses where point estimates and 95% CIs were shown graphically (in the published paper only[1]). For the REALIZE trial, 95% CIs and p values were not reported for secondary outcomes except for the subgroup analyses of SVR according to prior response (p value only) and changes in HCV RNA levels (mean and standard error (SE) only, shown graphically in the published paper[2]). No interim data is presented in the MS.

Strict ITT analyses of all patients randomised were not carried out in either study but rather all randomised patients who had received at least one dose of study medication. This population is referred to by the manufacturer as the 'Full Analysis' set. The numbers randomised who

subsequently did not receive study drugs was very small and this discrepancy is considered unlikely to have impacted the results.

The MS is not clear how missing data was dealt with/accounted for and it is not mentioned in the published papers.[1;2] The ERG sought clarification from the manufacturer and some of the statistical methods described (i.e. linear interpolation) in their response are not deemed best practice.

3.1.7 Description and critique of the manufacturer's approach to the evidence synthesis

On the whole, the tabulated data in the MS clinical effectiveness review reflect the data in the published trials with two minor incorrect values (MS Table 24 p.71, Table 27 p.72). However, as noted, a substantial amount of the data has been taken from the CSRs[10;11] (rather than the published papers[1;2]). Another problem with the narrative review is that much of the interpretation is based on comparisons of percentage values without any effect size (ORs or RRs), confidence intervals or statistical significance tests (p values).

A meta-analysis of the two included trials was not conducted. The MS states this was because 'ADVANCE[1] provides a comparison in treatment-naïve patients and REALIZE[2] in treatment-experienced patients and the trials provide a direct head-to-head comparison therefore a meta-analysis is not considered appropriate' (MS p.78). The ERG is in agreement that a meta-analysis would not be appropriate given that the trials are in different patient populations.

An indirect comparison was not necessary as the included trials evaluated a direct head-to-head comparison of the technology with the current standard of care. No mixed treatment comparison (MTC) was conducted.

Subgroups were analysed in both trials and presented in the MS. Both trials performed pre-planned subgroup analyses according to baseline demographics and characteristics – although pre-planned, some subgroups had very small numbers and were likely not statistically powered. Both trials also performed a post-hoc analysis according to IL-28B subtype as defined in the NICE scope. The MS states that this analysis should be viewed with caution due to it being post-hoc and having small numbers; the ERG concurs.

3.2 Summary statement of manufacturer's approach

The quality of the MS based on CRD questions[15] for a systematic review as assessed by the ERG is shown in Table 3.

Table 3 Quality assessment (CRD criteria) of MS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes, these are reported in the main document (MS Table 4 p.35-37) and also in MS Appendix 7 (p.211).
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	Yes, on the whole. The clinical effectiveness searches were considered to be reasonably comprehensive and reproducible, although no details were provided relating to searches of in-house databases or on-going trials (see Section 3.1.1)
3. Is the validity of included studies adequately assessed?	Yes. The validity of the included RCTs was undertaken using the standard CRD criteria for assessing the quality of RCTs and is presented in a summary table (MS Table 15, p.64) and in more detail in MS Appendix 8 (p.213). No narrative discussion was included.
4. Is sufficient detail of the individual studies presented?	Yes. Study methodology, eligibility criteria, participant characteristics, outcomes and statistical analysis of the two included RCTs are presented in the MS.
5. Are the primary studies summarised appropriately?	Yes, the primary RCTs are appropriately summarised in tables and corresponding narratives separately for the two RCTs (treatment-naïve and previously treated patients). However, much of the outcome data is derived from unpublished CSRs which were not provided with the MS. Strengths and weaknesses of the review are presented; the clinical interpretation reports the relevance of the evidence base to UK clinical practice.

The systematic review carried out by the MS is of good quality according to CRD criteria and the evidence reflects the decision problem defined in the MS. The processes for inclusion/exclusion, data extraction and quality assessment were fully reported and adequate. Two independent reviewers were used at all stages.

The ERG's opinion is that there is a low chance of systematic error in the systematic review undertaken by the manufacturer. However, concerns remain regarding the lack of transparency in the reporting of some of the data and the lack of statistical analysis to support the data.

3.3 Summary of submitted evidence

The outcomes presented here by the ERG are those stipulated in the NICE scope only with data from the included published RCTs,[1;2] with the addition of end of treatment relapse rate which is considered to be an important outcome with regards to treatment success. The data presented in the MS have been checked against the published RCTs[1;2] by the ERG. As previously noted, the extensive CSRs[10;11] have only been referred to in order to verify statistical comparisons reported in the MS.

Virologic failure, adherence, fatigue and some of the subgroup analyses are secondary outcomes presented by the MS that are not stipulated in the NICE scope, present data taken from an unknown source or the unpublished CSRs[10;11] and present no statistical analyses to support the data. These results have therefore not been presented by the ERG.

Summary of results for sustained virologic response (SVR)

The primary outcome was SVR (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). Results can be seen in Table 4.

Table 4 Achievement of sustained virological response

Trial name	T12/PR	PBO/PR	Absolute difference (95% CI) p value
ADVANCE SVR, % (n/N)	75% (271/363)	44% (158/361)	31% (95% CI 24-38%) p<0.0001
REALIZE SVR, % (n/N)	64% (171/266)	17% (22/132)	47% (95% CI 37-57%) p<0.001
Prior relapsers, % (n/N)	83% (121/145)	24% (16/68)	p<0.001
Prior partial responders, % (n/N)	59% (29/49)	15% (4/27)	p<0.001
Prior null responders, % (n/N)	29% (21/72)	5% (2/37)	p<0.001

SVR, sustained virological response.

In the treatment-naïve population (ADVANCE trial[1]), a significantly higher SVR rate was observed in the T12/PR group compared to the PBO/PR group (75% vs 44% respectively, p<0.0001) with a difference in response rates of 31% (95% CI 24-38%). (See MS p.66).

Similarly, in the previously treated population (REALIZE trial[2]), the proportion of patients who achieved an SVR was significantly higher in the T12/PR48 group compared to the PBO/PR48 group (64% vs 17% respectively, p<0.001; difference 47% [95% CI 37-57]). (See MS p.71). SVR in each of the prior response patient subgroups in the REALIZE trial was reported as a subgroup analysis (MS Figure 12 p.76). Significantly higher SVR rates were observed in T12/PR48 patients compared to PBO/PR48 for prior relapsers (83% vs 24%), prior partial responders (59% vs 15%) and prior null responders (29% vs 5%) (p<0.001 T12/PR48 vs PBO/PR for all subgroups). It should be noted that the numbers in these subgroups are small.

Summary of results for extended rapid viral response (eRVR)

Achievement of an eRVR (defined as undetectable HCV RNA at weeks 4 and 12) was used as the basis for shortening overall treatment duration from 48 weeks to 24 weeks in the ADVANCE trial.[1]

In treatment-naïve patients (ADVANCE trial[1]), higher eRVR rates were seen in the T12/PR treatment arm compared to the PBO/PR arm (58% vs 8% respectively, MS p.66-67). This was reported to be a statistically significant difference in the MS (p<0.0001, difference 50% [95% CI 45-56%]) but the statistics were not reported in the published trial paper.[1] However a subsequent check of the CSR[11] confirms the statistical significance. Of the patients who achieved an eRVR, more patients receiving PBO/PR (97%) than T12/PR (89%) subsequently achieved an SVR (MS p.203). However, patients achieving eRVR in the T12/PR group received 24 weeks of treatment compared to 48 weeks of treatment for the PBO/PR group. No p value or other statistical comparison was reported in the MS, the published RCT[1] or the unpublished CSR.[11]

The MS (Table 26 p.71) reports that for previously treated patients (REALIZE trial[2]), a greater proportion of T12/PR48 patients achieved an eRVR compared to PBO/PR48 patients for each of the prior response groups – 66% vs 3% (relapsers), 61% vs 0 (partial responders), 22% vs 3% (null responders) respectively. However, no statistical comparisons were reported in the MS,

the published RCT[2] or the unpublished CSR[10] and the numbers in each group were small. In addition, all the data were taken from the unpublished CSR[10] and are not available in the published RCT.[2]

Summary of results for relapse rates

Whilst relapse rates are not stipulated in the NICE scope, they are presented here due to being considered an important outcome with regards to treatment success.

The relapse rate among treatment-naïve patients (ADVANCE[1]) who had undetectable HCV RNA levels at the end of treatment was lower in the T12/PR group compared to the PBO/PR group (9% vs 28% respectively) (See MS p.67). It is not known if the difference was statistically significant as no p value or statistical comparison was reported in the MS, published RCT[1] or unpublished CSR.[11]

The relapse rate at 72 weeks for treatment-experienced patients (REALIZE[2]) who had undetectable HCV RNA levels at the end of treatment was lower in the T12/PR48 groups compared to the PBO/PR48 group for patients who had a previous relapse (7% vs 65%) or null response (27% vs 60%) (MS Table 27 p.72). In those with a prior partial response, a relapse rate of 21% was observed in T12/PR48 patients. The MS has reported that the number relapsing in the PBO/PR group is 'not applicable' based on zero patients in that group. However, given that four prior partial responders achieved an SVR, the ERG suggest this figure should be four (i.e. N=4) with zero relapsing. Despite the errors, the numbers remain small making comparisons between the groups difficult to interpret. No p values or statistical comparison was reported in the MS or published paper.[2] However, the CSR[10] reports a statistically significant difference ($p<0.001$) in favour of telaprevir in prior relapsers only.

Summary of Health related quality of life (HRQoL)

HRQoL was specified in the NICE scope and was reported in the MS for both treatment-naïve and treatment-experienced patients (MS Table 20 p.69, Table 32 p.74-75). The values appear to be generally higher than would be expected for hepatitis C patients and no statistical comparisons have been reported. In addition, all the data have been taken from unpublished papers.[12;13]

Subgroup analyses results

A number of subgroup analyses were undertaken in the ADVANCE[1] and REALIZE[2] trials. SVR according to IL-28B gene subtype was specified in the NICE scope to be considered if data were available as patients with a particular type of change in one of their genes (IL-28 polymorphism) are likely to have a better response to treatment than those who do not. Results are presented in the MS for both treatment-naïve and treatment-experienced patients (according to prior response) with both showing better SVR rates for all subtypes with T12/PR (see MS Table 22 p.70, Table 34 p.75-76). However, it should be noted that these are post-hoc subgroup analyses with small patient numbers and randomisation is broken within the IL-28B subgroups, points made in the MS with which the ERG concurs. No statistical comparisons are presented in the MS and they are likely not powered so results should be viewed with caution. For the ADVANCE trial it is not known where the data was taken from (MS Table 22 p.70). Answers to clarification questions to the manufacturer stated that the data were taken from a conference poster.[16] For the REALIZE trial, the MS also refer to data from a conference proceeding.[9] However, results are presented for the pooled TR groups (TR12 and lead-in TR12) so only the data for the PBO/PR could be checked by the ERG (MS Table 34 p.76).

Other subgroup analyses have been reported in the MS including SVR according to definition (published values and SmPC values) and SVR according to disease severity, but these are not presented here. None present any statistical analyses and the source of the data in MS Table 36 (p.77) is not known. In their response to clarification questions, the manufacturer stated that the data were 'taken directly from post-hoc analysis provided by biostatisticians' but provided no further information.

Mixed Treatment Comparison results

No MTC was conducted by the manufacturer.

Summary of adverse events

The MS presented safety data reported as secondary outcomes in the two included comparative trials. No trials focussed primarily on AE were included although the three dose-finding PROVE phase II trials[5-7] identified in the clinical effectiveness searches highlighted specific AE which were later addressed in the phase III included ADVANCE[1] and REALIZE[2] trials.

The MS tabulates the incidence of common AE as n (%) only, with no p values, RR or statistical support for any differences, and it is therefore unclear whether any differences between treatment groups highlighted by the MS are statistically significant. Furthermore, no p values were reported in the CSRs.[10;11] Some of the data presented in MS Table 37 (p.84) and MS Table 38 (p.85) are reported in the published papers[1;2] (or supplemental tables online) but other data are derived from the unpublished CSRs.[10;11]

Treatment-naïve patients

For treatment-naïve patients (ADVANCE[1]), the MS reports a number of AE that occurred more frequently in those receiving T12/PR compared to standard treatment (PBO/PR). MS Table 37 (p.84) shows a >10% difference in incidence for nausea (43% vs 31%), anaemia (37% vs 19%), rash (37% vs 24%) and pruritus (50% vs 36%). Similarly, the online supplemental Table 1 in the published RCT[1] reports a higher incidence of haemorrhoids and anorectal discomfort in the T12/PR group compared to the PBO/PR group (>10% difference), although these occurred less frequently compared to other AE. Conversely, the incidence of infections was greater in the PBO/PR vs T12/PR group (38% vs 28% respectively). The overall incidence of AE and serious AE were similar between groups but data from the unpublished CSR[11] (MS Table 37 p.84) reports grade 3 AE occurring more frequently in the T12/PR group vs PBO/PR (28% vs 19% respectively).

During the 48 week treatment period, more patients in the PBO/PR group than in the T12/PR group discontinued therapy prematurely (44% vs 26% respectively), with virologic failure largely accounting for the difference in discontinuation rates (33% vs 10% respectively). Four deaths were reported (MS p.88) during the 48 week study treatment period (2 T12/PR, 1 PBO/PR, 1 T8/PR [trial arm not included in the MS]) and were all considered to be unrelated to study treatment.

Treatment-experienced patients

The MS also reports a number of AE that occurred more frequently in those receiving T12/PR compared to standard treatment (PBO/PR) for previously treated patients (REALIZE[2]). MS Table 38 (p.85) shows a >10% difference in incidence for fatigue (55% vs 40%), pruritus (52% vs 27%), rash (37% vs 19%), nausea (35% vs 23%), anaemia (30% vs 15%) and diarrhoea (24% vs 14%). Online supplemental table 2 in the published RCT[2] also reports a higher incidence of haemorrhoids (15% vs 7%) in the T12/PR group compared to the PBO/PR group,

although this occurred less frequently compared to other AE. Conversely, the incidence of asthenia was greater in the PBO/PR vs T12/PR group (29% vs 19%). No p values were reported for any comparisons. The overall incidence of AE were similar between groups, but a greater proportion of serious AE (12% vs 5%) and severe (grade 3) AE (37% vs 22%) were observed in the T12/PR patients (MS Table 38 p.85).

During the 48 week treatment period, more previously treated patients in the PBO/PR group than in the T12/PR48 group discontinued therapy prematurely (62% vs 38% respectively) with virologic failure largely accounting for the difference in discontinuation rates (51% vs 16% respectively). The MS (p.88) reported two deaths during the 48 week study treatment period (1 PBO/PR, 1 Lead-in T12/PR [trial arm not included in the MS]) and one death (PBO/PR) occurred during the follow-up phase (not reported in the published paper[2]). The two deaths in the PBO/PR arm were considered unrelated to study treatment.

For both treatment-naïve and treatment-experienced patients, the MS highlights rash and anaemia as the most frequently reported AE that led to discontinuation of telaprevir-based treatment (MS p.83-84). Patients receiving T12/PR were observed to have a greater occurrence of rash and anaemia of any grade, of severe grade 3 and a higher discontinuation rate due to rash and anaemia. The majority of data relating to anaemia and rash presented in the MS (p.85-88) are not available in the published RCTs[1;2] but have been taken from the unpublished CSRs.[10;11] In their answers to clarification questions, the manufacturer stated that the data relating to rash severity (MS Table 39 p.86) was 'taken directly from post-hoc analysis provided by biostatisticians' but provided no further information.

The MS states (p.87) that anaemia in the trials was managed through licensed dose reductions of ribavirin therapy – the ERG's clinical expert indicated that this was acceptable and reflects practice currently used for standard PR treatment. The MS refers to an Adverse Event Management Plan in Figs 13 & 14 (MS p.86-87) [redacted] with regards to the management of rash. Clinical advice to the ERG indicated that this is acceptable and appropriate.

3.4 Summary

Results of the two included RCTs[1;2] show statistically significantly higher SVR rates when telaprevir is added to PR compared to PR alone, the current standard of care.

In patients receiving T12/PR, there was a significant increase in SVR rate of about 30% in treatment-naïve patients and almost 50% in treatment-experienced patients, with significantly higher rates being maintained across the treatment-experienced subgroups (previous relapsers, partial responders and null responders). Response guided therapy enables some treatment-naïve patients to reduce total PR treatment time from 48 to 24 weeks.

A number of AE occur more frequently with the use of telaprevir, particularly rash and anaemia. Patients receiving T12/PR were observed to have a greater occurrence of rash and anaemia of any grade, of severe grade 3 and a higher discontinuation rate due to rash and anaemia (although much of this data are in the CSRs[10;11]). However, the MS states that response guided therapy (enabling a shorter treatment duration) and an AE management plan for rash would be in place in clinical practice and help to address these issues. Clinical advisors to the ERG verify that this is the case.

On the whole, it appears that the MS contains an unbiased estimate of treatment effect within the stated scope of the decision problem. A key issue is that a large amount of the data has been taken from the unpublished CSRs[10;11] rather than the published papers.[1;2] In addition, interpretation of many of the outcomes is based on comparisons of percentage values without any effect size (ORs or RRs), CIs or statistical significance tests (p values). Subgroup analyses have small numbers and are likely not powered.

In general, the manufacturer's interpretation of the evidence is appropriate. It acknowledges the following limitations:

- all the clinical evidence is for peginterferon alfa-2a with no data for peginterferon alfa-2b. Clinical opinion concurs with the manufacturer's opinion that there is likely no difference in efficacy between the two formulations when used with telaprevir. However, there is no phase III clinical trial evidence to back this up;
- response guided therapy was not incorporated into the REALIZE trial[2] and thus has not been evaluated in treatment-experienced patients;

- the IL-28B subgroup analyses for both trials were post-hoc analyses with small patient numbers (particularly the REALIZE trial[2]) and randomisation was broken within the subgroups. The results should therefore be interpreted with caution.

The MS does not identify the lack of statistical testing between treatment groups as a limitation.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

i) a review of published economic evaluations of anti-viral treatment for adults with CHC;
ii) an economic evaluation undertaken for the NICE STA process to estimate the cost effectiveness of telaprevir in combination with peginterferon alfa and ribavirin (T12/PR) compared with standard therapy (peginterferon alfa and ribavirin alone(PR)) for adults with genotype 1 CHC.

Manufacturer's review of published economic evaluations

The manufacturer conducted a systematic search of the literature to identify economic evaluations of anti-viral treatment for CHC. See section 3.1.1 of this report for the ERG critique of the search strategy. The review did not identify any studies that included telaprevir as a treatment for adults with genotype 1 CHC.

CEA Methods

The cost effectiveness analysis uses a Markov model to estimate the cost-effectiveness of T12/PR compared with PR in adults with genotype 1 CHC. Separate base case analyses are reported for treatment-naïve patients and for those who had previously been treated. The model adopted a lifetime horizon, with an annual cycle length.

Base case results from the economic evaluation are presented for treatment-naïve and treatment-experienced patients separately. The MS presents subgroup analyses by IL-28B subtype for both patient populations (treatment-naïve and treatment-experienced) as well as by response to previous treatment (relapse, partial response or null response) for treatment-experienced patients.

The primary treatment outcome included in the economic model is SVR. At baseline patients are distributed across age and severity of compensated liver disease (mild CHC, moderate CHC and compensated cirrhosis (CC)) as observed in the phase III RCTs[1;2] with treatment outcome (SVR or non-SVR) assigned at the end of the first year of the model. Patients who do not achieve SVR are assumed to be at risk from progressive liver disease (those with mild or moderate CHC may progress to compensated cirrhosis, while those who have (or develop) CC are at high risk of decompensated cirrhosis (DC) or hepatocellular carcinoma (HCC)). Patients with DC or HCC are at increased risk of death compared with the general population – a proportion of patients with DC or HCC may be treated with a liver transplant (LT). Patients who achieve SVR are assumed to be free of risk from progressive liver disease (other than those who were cirrhotic prior to receiving treatment, who are assumed to be at higher risk of developing HCC than those who were not cirrhotic).

HRQoL is included in the model through severity of liver disease (health state) and adverse effects of treatment (applied using treatment-specific disutilities, derived from patient responses to the EQ-5D, rather than prevalence and HRQoL impact of specific adverse events). The health state utility values are the same as those adopted for a model developed for previous NICE appraisals of anti-viral treatment for CHC,[17;18] which were taken from a UK RCT of anti-viral treatment for CHC.[19] The approach to quantifying resource use is also largely based on previous NICE appraisals of anti-viral treatment for CHC,[17;18] in which treatment protocols were developed to estimate costs of on-treatment monitoring and health state costs were taken from a UK RCT of anti-viral treatment for CHC.[19]. Costs included in the model are intervention and comparator drug costs, on-treatment monitoring, management of adverse events and health state costs. Where necessary costs derived from published sources were inflated to 2010 prices, using the Hospital and Community Health Services (HCHS) Pay and Price Index.[20]

Deterministic sensitivity analyses (DSA), scenario analyses, and probabilistic sensitivity analyses (PSA) were performed. DSA results are presented in section 6.7.7, page 163-166 of the MS, as Tornado plots (Figure 20, page 164 of the MS, for treatment-naïve and Figure 21, page 165 of the MS, for treatment-experienced patients) and as tabulations of the twelve variables with greatest impact on the ICER. Scenario analyses for each patient population are presented in section 6.7.9, page 168-169 of the MS. PSA results are reported in section 6.7.8, page 166-168 of the MS including scatterplots on the cost-effectiveness plane and cost-

effectiveness acceptability curves (CEACs) for treatment-naïve (Figures 22 and 23 in the MS) and treatment-experienced patients (Figures 24 and 25 in the MS).

The MS states that the model assumptions and functionality were validated by an independent health economist with expertise in CHC modelling, and by further independent reviews of each model (for treatment-naïve and treatment-experienced populations) although no further details of the review process are provided. The MS does not report whether the models were validated against any external data.

CEA Results

Results from the economic model are presented in section 6.7, pages 159-169 of the MS, with the base case incremental cost per quality adjusted life year (QALY) gained for T12/PR compared with PR alone for treatment-naïve and treatment-experienced patients reported in section 6.7.6, page 162-163 of the MS. Model estimates are also presented (pages 159-162 of the MS) for life years, QALYs, incidence of cirrhosis, liver transplantation and death, undiscounted QALYs, undiscounted costs by health state and a cost breakdown (discounted drugs and health state costs) by patient population and by treatment cohort.

For the base case an incremental cost per QALY gained of £13,553 is reported for treatment-naïve patients and £8,688 for treatment-experienced patients (see Table 5).

Table 5 Base case cost effectiveness results (MS Tables 89 and 90)

	Costs (£)	QALYs	ICER (£/ QALY gained)
Treatment-naïve			
PR	24,722	13.03	
T12/PR	36,152	13.87	
Increment	11,430	0.84	13,553
Treatment-experienced			
PR	34,394	10.09	
T12/PR	44,589	11.26	
Increment	10,195	1.17	8,688

The manufacturer's DSA suggest that the cost effectiveness results for treatment-naïve patients are most sensitive to utility values applied to early disease states (mild or moderate CHC), treatment duration (in the T12/PR-treated cohort) and SVR, while for treatment-experienced

patients they are most sensitive to the costs and utility values applied to the cirrhosis (compensated or decompensated) health states, treatment duration (in the T12/PR-treated cohort) and SVR.

The MS summarises the results of the PSA stating that, for treatment-naïve patients, there is an 85.3% probability of T12/PR therapy being cost-effective, relative to PR alone, at a threshold willingness to pay of £20,000 per QALY gained, and 98.0% probability at a threshold of £30,000 per QALY gained (section 6.7.8, page 166-167 of the MS). The equivalent values for treatment-experienced patients are 94.0% and 97.4% (section 6.7.8, page 167-168 of the MS).

4.2 Critical appraisal of the manufacturer's submitted economic evaluation

Manufacturer's review of published economic evaluations

The manufacturer conducted a search of the literature to identify economic evaluations of anti-viral treatment for CHC from the date of the review undertaken for TA200 (see section 6.1.1, page 95 of the MS for an overview of the search and a list of databases searched, Appendix 10 of the MS for the search terms used and section 3.1.1 of this report for the ERG critique of the manufacturer's search strategy). The search was not specific to studies which included telaprevir-containing regimens.

Inclusion and exclusion criteria for the systematic review are listed in Table 40 of the MS (section 6.1.1, page 96). The inclusion criteria state that full economic evaluations which involved peginterferon alfa or ribavirin in adults with CHC would be included. The exclusion criteria state that non-model based studies (e.g. within trial analyses), in populations without CHC, which did not report both costs and outcomes and which were not published in English language would be excluded.

Screening of 224 identified 23 studies. Of these seventeen studies were excluded, mainly for not being cost effectiveness analyses (n=10) or being review articles (n=4) – full details of study exclusion are reported in Figure 15, page 98 of the MS. Six studies were included for full review – Fonseca and colleagues[21], Gheorghe and colleagues[22], Grishchenko and colleagues[23], Hartwell and colleagues[18], Saab and colleagues[24] and Siebert and colleagues[25]. Only two of these (Grishchenko and colleagues[23], Hartwell and colleagues[18]) were conducted in the UK.

The quality assessment checklist suggested by NICE has been applied to the included cost effectiveness studies (Table 42, section 6.1.3 page 101-102 of the MS). However no interpretation or conclusions from this quality assessment were provided in the MS. The MS also includes a summary table reporting the study year, country, interventions and comparators, a summary of model assumptions (including health states), patient population and brief results (Table 41, section 6.1.2, page 98-100), but no critique of these studies, comment on their NHS relevance or relevance to the current appraisal was reported.

While the inclusion criteria in Table 40 of the MS (section 6.1.1, page 96) specify the included interventions to be peginterferon alfa or ribavirin, telaprevir is included as a keyword in the search strategies listed in Appendix 9.10. The ERG assume that no economic evaluations of telaprevir were identified by the searches as none are reported in the tabulations in section 6.1, page 95 – 102 of the MS. However the MS does not state this explicitly.

The MS also reports systematic searches and narrative reviews of identified evidence on health-related quality of life and resource use. These will be discussed later in the relevant sections of this report.

Critical appraisal of manufacturer's submitted economic evaluation

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 6 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[26]).

Table 6 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	Statement of decision problem, MS section 4, page 31-32
Is there a clear description of alternatives?	Yes	Telaprevir in combination with peginterferon alfa and ribavirin versus peginterferon alfa and ribavirin alone.
Has the correct patient group / population of interest been clearly stated?	Yes	Genotype 1 CHC patients considered suitable for treatment with telaprevir. Separate analyses for treatment-naïve and treatment-experienced patients.
Is the correct comparator used?	Yes	Peginterferon alfa and ribavirin
Is the study type reasonable?	Yes	Cost-utility analysis
Is the perspective of the analysis clearly stated?	Yes	NHS and PSS

Item	Critical Appraisal	Reviewer Comment
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	Yes	Effectiveness evidence from phase III RCTs (SVR, adverse events)
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	
Are the costs and consequences consistent with the perspective employed?	Yes	
Is differential timing considered?	Yes	Costs and benefits discounted at 3.5% per year
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	One way sensitivity analyses - methods in section 6.6.2 (page 154-156 of MS), results in section 6.7.7 (page 163-166 of MS) Scenario analyses - methods in section 6.6.1 (page 149-154 of MS), results in section 6.7.9 (page 168-169 of MS) Probabilistic sensitivity analyses - methods in section 6.6.3 (page 156-158 of MS), results in section 6.7.8 (page 166-168 of MS) Unclear why arbitrary ranges were used in the one way sensitivity analyses for variables where standard errors, confidence intervals or original data were available to characterise uncertainty

NICE reference case

The NICE reference case requirements have also been considered for critical appraisal of the submitted economic evaluation in Table 7.

Table 7 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	
Comparator: Alternative therapies routinely used in the UK NHS	Yes	Additional stopping rules used in RCT – data on treatment duration may not be directly applicable to routine practice
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	Yes	
Type of economic evaluation: Cost effectiveness analysis	Yes	Cost utility analysis

NICE reference case requirements:	Included in submission	Comment
Synthesis of evidence on outcomes: Based on a systematic review	Yes	Clinical trial data presented – consistent with evidence reviewed in clinical effectiveness section (see section 3.3 and section 4.2.4 of this report)
Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes	EQ-5D
Method of preference elicitation for health state values: Choice based method (e.g. time trade-off (TTO), standard gamble (SG), not rating scale)	Yes	Clarification requested from manufacturer – confirmed valuation using time trade-off based value set[27]
Source of preference data: Representative sample of the public	Yes	Clarification requested from manufacturer – confirmed valuation using UK general population based value set[27]
Discount rate: 3.5% pa for costs and health effects	Yes	

4.2.1 Modelling approach / Model Structure

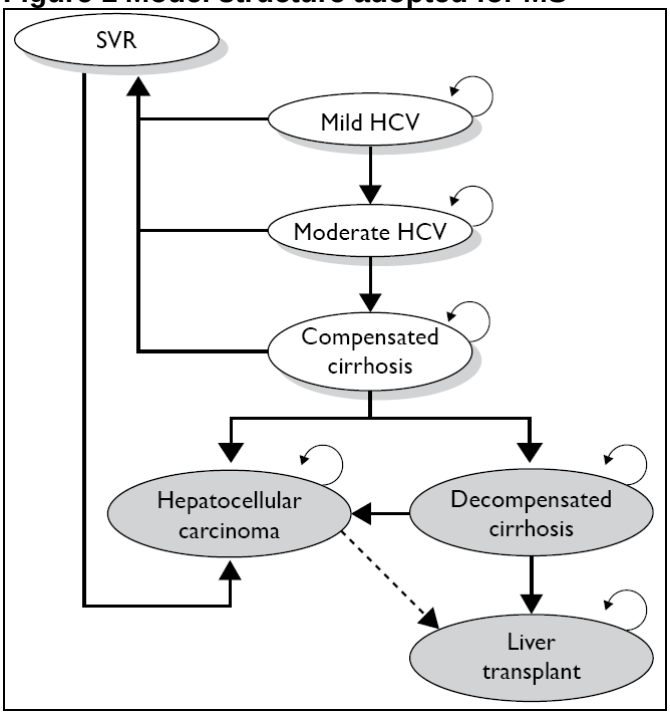
The CEA includes two models which are identical in structure: one for treatment-naïve patients, the second for treatment-experienced patients. The modelling approach is a Markov state transition model, based on that presented in the HTA report by Hartwell and colleagues,[18] and is developed in Excel. The model perspective is that of the NHS and PSS, with a lifetime horizon (70 years). Costs and utilities are discounted at 3.5%. The model has a cycle length of one year, and the MS states that a half-cycle correction has been applied.

The model structure is based on five previous economic models in CHC[17-19;28;29] which are referenced, but not described. Six previous cost-effectiveness studies are identified in the systematic review but these are not used to inform the model structure, the reasons for this are not discussed. The MS states that the model structure was developed with input from experts in CHC and health economics modelling and confirmed by a board of 'clinical opinion leaders'.

A schematic of the model is provided in the MS (see Figure 1). Patients enter the model in a 'mild', 'moderate' or 'cirrhotic' disease state and receive anti-viral therapy. Drug costs are applied in the first cycle. Patients then achieve an SVR or, if they do not, their disease can remain at their initial state, or progress as they move through the model, as illustrated by the model schematic. The MS states that all-cause mortality has been applied to each of the health

states. While not stated explicitly in the MS, it appears that no patients are assumed to die in the first year while on treatment.

Figure 1 Model structure adopted for MS



The disease states and patient pathway in the model appear to reflect the underlying biological and clinical process of CHC. In common with previous models 'decompensated cirrhosis'(DC) is retained as a single health state. Patients with compensated cirrhosis who achieve an SVR can either progress to HCC, or can remain in a 'cirrhotic post SVR' state.

There are a number of key structural assumptions. In addition to retaining DC as a collapsed health state (which is consistent with previous models and expert advice), patients with an SVR are assumed not to progress to more severe liver disease, (with the exception of those with cirrhosis who remain at risk of developing HCC and therefore do not progress to more severe health states).

Patients for whom treatment has failed may either remain in that health state or progress. Early transition probabilities (of 'mild to moderate' and 'moderate to compensated cirrhosis',) have been taken from Grishchenko and colleagues,[23] which is justified in the MS by stating that these are age-specific progression rates (see section 4.2.4 for further discussion of this assumption).

The remaining transition probabilities used for progression through the health states have been taken from Hartwell and colleagues.[18] Excess mortality risk attributable to chronic liver disease is applied to the health states of DC, HCC and LT. Finally, disutilities and costs associated with treatment are applied in the first cycle. These assumptions are clearly stated. The first has been justified by reference to previous studies and expert opinion.

In summary, the modelling approach and structure adopted appear reasonable, and are based on previous models in this disease area. The structural assumptions are clearly stated. Whilst a lifetime horizon is appropriate in order to reflect the differences in the alternatives, the lifetime horizon of 70 years appears long as the patient starting age in the model is 50 years. This results in patients being alive in the model and potentially accruing QALYs, theoretically at 120 years old. However, these numbers are a small proportion, and do not appear to substantially impact on the overall ICER.

4.2.2 Patient Group

The patients included in the manufacturer's model are defined as genotype 1 CHC patients, including treatment-naïve and treatment-experienced patients (although these two populations are analysed separately). This definition generally agrees with the scope for this appraisal and with the licensed indication for telaprevir, although it does not specifically refer to adult populations (telaprevir is not recommended for use in children and adolescents younger than 18 years of age, see SmPC page 9). The distribution of patients across age and stage of compensated liver disease in the models for treatment-naïve and treatment-experienced patients is based on the overall populations recruited to the ADVANCE and REALIZE trials, respectively (see Table 8). Since both trials specified patients should be between the age of 18 and 70 the modelled populations are, by definition, adult. For the treatment-naïve population, patients are distributed across three broad age categories (35 years or less, 36 to 45 years and older than 45 years), while for the treatment-experienced population a baseline age of 50 years is applied for all patients in the modelled cohort (mean age in the REALIZE trial was 51 years for T12/PR arm and 50 years for PR). The MS does not present any comparison of this population to available data on the distribution of CHC population in the UK (e.g. Health Protection Agency (HPA)[30]) or to baseline assumptions adopted for treatment-naïve patients in models developed for previous NICE appraisals.[17;18] The MS acknowledges that the clinical advisory board recruited to offer clinical validation of the modelling approach suggested that the patient populations in the ADVANCE and REALIZE trails were approximately 5 years older (on

average) than would be expected in normal clinical practice. Clinical advice to the ERG suggests this is a reasonable assumption.

The distribution of treatment-experienced patients across categories of prior response is also derived from the overall REALIZE trial population.

Table 8 Proportion of total patients in each trial by severity (and by age [treatment-naïve], or by prior response to treatment [treatment-experienced])

	Mild	Moderate	Cirrhosis	Overall
Treatment-naïve (ADVANCE[1])				
35 years or younger	9.7%	5.0%	0.6%	15.2%
36 to 45 years old	10.5%	9.8%	3.9%	24.2%
Older than 45 years	18.6%	26.2%	15.7%	60.6%
Overall	38.8%	41.0%	20.2%	
Treatment-experienced (REALIZE[2])				
Relapse	13.6%	16.3%	23.6%	53.5%
Partial	4.3%	6.0%	8.8%	19.1%
Null	3.8%	8.0%	15.6%	27.4%
Overall	21.6%	30.4%	48.0%	

Percentages calculated by ERG based on data reported in MS Table 10 (for treatment-naïve) and Table 11 (treatment-experienced) (see page 55 of the MS).

As discussed in section 3.1.3 of this report, patients co-infected with HIV and HBV as well as current alcohol or illicit drug abusers (including those with a history of alcohol or illicit drug abuse within two years of screening visit) were excluded from both ADVANCE and REALIZE trials. As a result the models for treatment-naïve and treatment-experienced patients do not apply to these groups of patients.

Closer examination of the baseline populations in the electronic model has uncovered a discrepancy in the patient groups defined as cirrhotic in the MS compared with the trial publications. In the trial publications[1;2] patients with bridging fibrosis are not included under the heading of cirrhosis (see Table 9 (page 54 of MS), Figure 6 (page 60 of MS) and Table 14 (page 61 of MS)) whereas they are included in group of cirrhotic patients when calculating the baseline populations in the MS. This has the impact of making the baseline populations appear to have more severe liver disease than might be the case if patients with bridging fibrosis are categorised as having moderate disease (see Table 9).

Table 9 Impact of classification of bridging fibrosis on baseline severity distribution in treatment-naïve and treatment-experienced patients

	Mild	Moderate	Cirrhosis
Treatment-naïve (ADVANCE[1])			
Overall (Bridging fibrosis included in cirrhosis)	38.8%	41.0%	20.2%
Overall (Bridging fibrosis included in moderate CHC)	38.8%	55.4%	5.8%
Treatment-experienced (REALIZE[2])			
Overall (Bridging fibrosis included in cirrhosis)	21.6%	30.4%	48.0%
Overall (Bridging fibrosis included in moderate CHC)	21.6%	52.8%	25.6%

The MS presents subgroup analyses by IL-28B subtype (for treatment-naïve and treatment-experienced patients) and by response to prior treatment (for treatment-experienced patients). Both of these subgroups were indicated in the scope issued by NICE, where data were available. However these subgroup analyses were not pre-specified and it is unlikely the trials were powered for these comparisons. The subgroup analysis by IL-28B subtype suffers due to incomplete data. This is particularly the case for the treatment-naïve population (derived from the ADVANCE trial[1]) where IL-28B subtype is only available for 42% of patients and no baseline characteristics are available for the patients included in this analysis. These data are more complete for the treatment-experienced population. However there are still 20% of trial participants whose IL-28B subtype is not known.

Complete data are available for the subgroup analysis of treatment-experienced patients by prior treatment response. The robustness of the SVRs derived in this analysis is hampered by the small numbers in some cells, particularly for the PR regime, when broken down by severity of liver disease (see Table 36, page 77 of the MS).

4.2.3 Interventions and comparators

The comparator in the model is peginterferon alfa in combination with ribavirin. This is the current standard of care for patients with CHC who are suitable for anti-viral therapy (supported by NICE guidance[31-33]) and is the comparator specified in the scope issued by NICE. There are two forms of peginterferon alfa with marketing authorisation for use in the NHS - peginterferon alfa-2a (manufactured by Roche) and peginterferon alfa-2b (manufactured by Schering-Plough/ Merck Sharp and Dohme). Peginterferon alfa-2a is used in the model, since this formulation was used in both the ADVANCE[1] and REALIZE[2] trials. The SmPC for telaprevir[3] acknowledges that

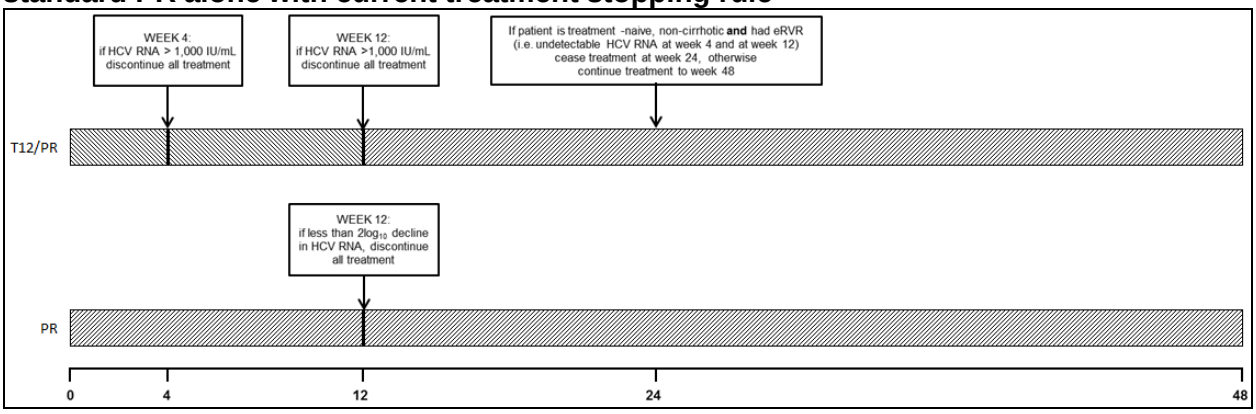
there is limited data on its use in combination with peginterferon alfa-2b and ribavirin (from a relatively small, open-label study for treatment-naïve patients and none in treatment-experienced patients).

Stopping rules within the current treatment pathway are presented in Figure 4 (section 2.4, page 25) of the MS, where patients who have failed to achieve a <2-$\log_{10}$ drop in HCV RNA at 12 weeks discontinue treatment. However clinical advice to ERG suggests that many centres would also discontinue treatment if a patient has detectable HCV RNA at 24 weeks of treatment. A number of additional stopping rules were applied in the ADVANCE and REALIZE trials (discussed below).

Treatment regimens and stopping rules

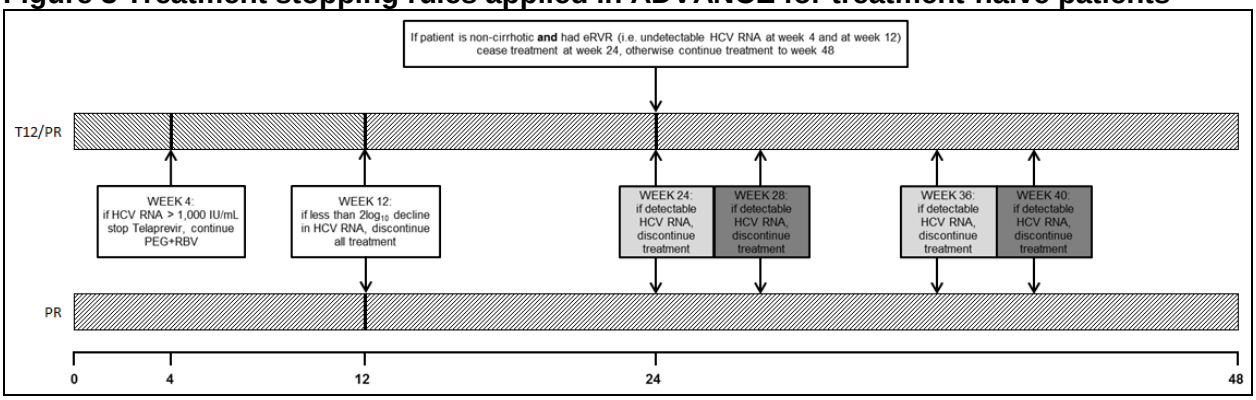
The standard treatment regimen (for treatment-naïve and treatment-experienced patients) described in the SmPC for telaprevir[3] involves 12 weeks of treatment with telaprevir (750mg three times daily) in combination with peginterferon alfa and ribavirin, followed by a further 36 weeks of treatment with peginterferon alfa and ribavirin alone. An additional regimen, with a shorter overall treatment duration, is recommended for non-cirrhotic, treatment-naïve patients who achieve an eRVR. Such patients would receive 12 weeks of treatment with telaprevir in combination with peginterferon alfa and ribavirin, followed by a further 12 weeks of treatment with peginterferon alfa and ribavirin alone. These treatment regimens are summarised in Figure 2 below.

Figure 2 Treatment regimens – T12/PR with treatment stopping rules from SmPC and standard PR alone with current treatment stopping rule



Stopping rules associated with telaprevir in treatment-naïve and treatment-experienced patients imply at least one additional HCV RNA test than is current practice (at week 4), but may require a total of three additional tests. Two additional tests were included in the ADVANCE trial to support stopping rules at weeks 28 and 40 (see Figure 3). As a result the treatment durations derived from the ADVANCE trial may not be generalisable to normal practice as fewer stopping rules are expected in routine practice.

Figure 3 Treatment stopping rules applied in ADVANCE for treatment-naive patients



4.2.4 Clinical Effectiveness

Clinical evidence included in the model is drawn from a range of sources and relates to:

- response to anti-viral therapy, measured as SVR. This is regarded as a clinical meaningful end-point and was the primary outcome for the phase III clinical trials. SVR (as discussed in section 4.2.1 of this report) is treated, in the model, as a durable "cure" with a substantially reduced risk of advanced liver disease;
- a natural history model which extrapolates patients' lifetime risk of advanced liver disease, based on their initial stage of compensated liver disease and their response to anti-viral treatment.

SVRs applied in the model are derived directly from the phase III clinical trials reviewed in the clinical effectiveness section of the MS – see section 5.3, page 47-63, for a presentation of the methodology and section 5.5, page 65-77, for results. Overall SVRs from the ADVANCE trial are reported in Figure 9, page 66, of the MS and SVRs by stage of liver disease in subgroup analyses in Figure 6, page 60 of the MS. Overall SVRs from the REALIZE trial are reported in Table 25, page 71, of the MS and SVRs by stage of liver disease in subgroup analyses in Figure 7, page 61 of the MS. These data are again reported in Table 47, page 110, of the MS

which reports the overall SVR for the ADVANCE trial and SVRs by prior response for the REALIZE trial. None of the tables in the MS report the breakdown of SVR used in the model for treatment-naïve patients. However the summary Table 49 does include the breakdown of SVR for treatment-experienced patients used in the model.

The data sources for the SVRs are clearly described and the methods for deriving the SVRs are clearly presented in the MS. No transformations or additional pre-model analysis are applied to the values used in the economic models.

The model applies age- and liver-disease-stage-specific SVRs for treatment-naïve patients (derived from the ADVANCE trial) and prior-treatment-response- and liver-disease-stage-specific SVRs for treatment-experienced patients (derived from the REALIZE trial). The age categories used in calculating SVRs for treatment-naïve patients are (a) less than or equal to 35 years, (b) 36 to 45 years and (c) greater than 45 years, while the categories of prior treatment response are (a) relapse, (b) partial response and (c) null response. In both cases the liver disease stages are defined as mild CHC, moderate CHC and compensated cirrhosis. However there appears to be a discrepancy in the patient groups defined as cirrhotic in the MS compared with the trial publications, as described in section 4.2.2 of this report.

Some of the cells involved in the calculation of SVRs from the REALIZE trial involve very small denominators when broken down by prior treatment response and stage of liver disease (discussed in section 4.2.2 of this report), which may lead to unreliable estimates of the SVR, particularly for the PR arm in which 132 patients were enrolled, compared with 266 for the T12/PR arm. In the base case analysis, two cells have zero value SVRs for PR. However it is not clear whether this is a robust estimate of the SVR, as the SVRs have been estimated for small denominators (5 and 10). Table 10 below illustrates the impact of using the observed SVRs or a commonly used method (add one to each cell numerator and denominator) to adjust for small cell counts.

Table 10 Effect on overall SVR of adjusting for small cell counts

		Stage of liver disease			Overall
		Mild	Moderate	CC	
T12/PR	Observed				
	Relapse	85.3%	80.9%	84.4%	83.4%
	Partial	71.4%	76.5%	44.0%	59.2%
	Null	10.0%	42.1%	27.9%	29.2%
	"Adjusted" for small cell counts				
	Relapse	85.7%	81.3%	84.6%	83.8%
	Partial	75.0%	77.8%	46.2%	61.2%
	Null	18.2%	45.0%	29.5%	32.0%
PR	Observed				
	Relapse	35.0%	27.8%	13.3%	23.5%
	Partial	0.0%	42.9%	10.0%	14.8%
	Null	0.0%	7.7%	5.3%	5.4%
	"Adjusted" for small cell counts				
	Relapse	38.1%	31.6%	16.1%	26.7%
	Partial	9.1%	50.0%	18.2%	23.1%
	Null	16.7%	14.3%	10.0%	12.4%

The MS does not discuss the comparability of the observed SVRs for PR with response to treatment for this population (adults with genotype 1 CHC) in other clinical trials.

The natural history model, implementing the state transition model outlined in 4.2.1 of this report, uses transition probabilities derived from a range of sources. The majority of the transition probabilities applied to later disease states (CC onward) are taken from a model developed for previous NICE appraisals.[17;18] The exception to this is the probability of liver transplant for patients with HCC which was derived in the MS based on the reported number of patients in the UK having liver transplant due to HCC and the number of HCC patients in the UK. The value applied in the model appears to be an over-estimate (see Table 11). However this does not seem likely to have a substantial biasing effect on the model results. The transition probabilities for early disease – from mild to moderate CHC and from moderate CHC to compensated cirrhosis – are taken from a recently published economic evaluation.[23] The MS does not indicate whether these data were searched for specifically or whether this source was selected after being included in the systematic review of economic evaluations of anti-viral

therapy reported in section 6.1, page 95-102 of the MS. There is limited discussion in the MS of the advantage of using these updated transition probabilities, suggesting that patient age is an important determinant of disease progression. It is not clear whether these transition probabilities, which were estimated for age at treatment, capture this. Table 11 summarises the differences between the transition probabilities included in the model reported in the MS and those adopted in previous appraisals for NICE.

Table 11 Differences between MS economic and the model adopted for previous NICE appraisals.

Transition probability	MS Model	Previous appraisals[17;18]	Comment
Mild to moderate CHC	0.015 (≤35 years) 0.023 (36 to 45 yrs) 0.035 (>45 yrs)	0.025	Transition probabilities from Grishchenko and colleagues[23] appear to be interpreted in model as age-specific (see section 6.2.5, page 105-106 of the MS) but paper describes them as being based on age at treatment
Moderate CHC to CC	0.021 (≤35 years) 0.032 (36 to 45 yrs) 0.048 (>45 yrs)	0.037	
HCC to liver transplant	0.04	0.0	Calculated in MS as total number of transplants in UK due to HCC (32) divided by total cases of HCC assumed to have CHC (2867 * 0.25). Re-estimate as 32/2867 = 0.01

Adverse events included in the model are rash, pruritis, nausea, diarrhea and anaemia – all of these are more common in T12/PR than PR alone. All grades of rash were included in the model, but only grade 3 for other AEs – the MS does not report any reason for this discrepancy. Adverse events are only explicitly modelled in relation to estimating the costs of managing adverse events. The effect of adverse events on health outcomes is assumed to be captured by the treatment-specific disutilities derived from the phase III clinical trials and the impact on treatment discontinuation by using the treatment duration from the phase III clinical trials.

Overall the clinical evidence used to populate the model appears to be appropriate. The methods used to derive transition probabilities are clearly reported in the MS and appear to be appropriate. Transition probabilities applied in the model are generally consistent, although not always identical with those applied in previous NICE appraisals of anti-viral therapy for CHC. The ERG has some concerns about the derivation of SVRs, where sub-division of trial

populations lead to small numbers in the denominators (reducing the reliability/ robustness of the SVR estimates) and over the definition of cirrhosis including patients with bridging fibrosis.

4.2.5 Patient outcomes

QALYs associated with each treatment strategy are estimated by applying state-specific utility estimates to patients' life expectancy in each of the model health states. Progression of liver disease is assumed to have a negative impact on HRQoL, hence progressive disease states are associated with increasingly lower health state utility. In addition (as discussed in the previous section) more advanced stages of liver disease (DC and HCC) are also associated with higher mortality risks, hence are associated with lower life expectancy as well as poorer HRQoL. This is discussed in section 6.4.1 and section 6.4.2, page 121-122 of the MS. In contrast, SVR is assumed to be associated with an improvement in HRQoL. This may be due to reduced anxiety (by removal of chronic disease and risk of disease progression), reduction in restrictions on normal activities that may be associated with chronic infection status, or may be due to absence of psychological symptoms that may be associated with CHC.

The MS reports a systematic search (see 6.4.5, page 123-125 of MS with the search strategy reported in Appendix 11, page 219-223 of MS) for HRQoL estimates to populate the model. Their inclusion criteria state that studies were eligible if they reported HRQoL or utility (assessed using generic preference-based measure **or** a disease-specific measure that can be mapped to utility) in populations of adults patients with CHC. Studies reported as conference abstracts or in non-English language publications were excluded. Thirteen references were included in the review although the majority of the discussion in the review is limited to studies that used the EQ-5D[18;23;34] or direct elicitation of utilities with the time trade off (TTO) method.[35;36] Two of these were UK studies (Grishchenko and colleagues[23] and Hartwell and colleagues[18]) which both used utilities from EQ-5D in CHC patients valued using UK general population tariff (derived from the UK Mild Hepatitis C Trial[19]).

The MS briefly reviews each of the studies which reported utilities[18;23;34-36] noting a lack of consistency in the values reported. Without any further discussion, section 6.4.9 states that values sourced from Hartwell and colleagues[18] (which are ultimately derived from the UK Mild Hepatitis C Trial[19]) are used in the model which appears to be justified primarily on the grounds of consistency with previous economic analyses.[17;19;23;29] It is worth noting that the utilities derived in the UK Mild Hepatitis C Trial[19] – which were adopted by two studies[18;23] included in

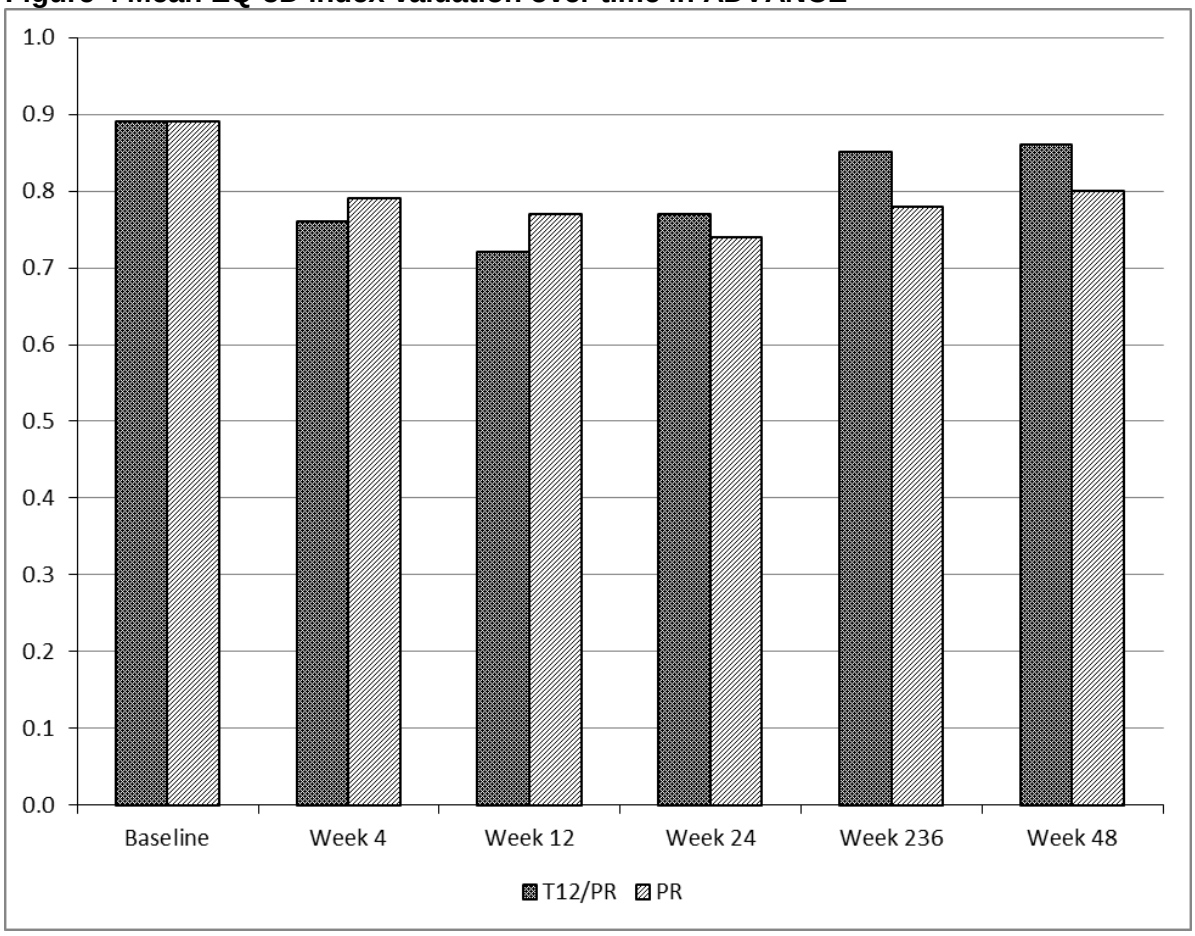
the manufacturer's review – are the only estimates that provide the required breakdown of early disease stages (mild/ moderate CHC and CC) and for SVR by stage prior to treatment (SVR from mild and SVR from moderate CHC). However these estimates are noticeably lower than the utility estimates, derived using identical methods (established following clarification from manufacturer), in the ADVANCE and REALIZE trials (Table 12).

Table 12 Health state utility (EQ-5D index) estimates from ADVANCE, REALIZE and UK Mild Hepatitis C Trials, by stage of liver disease

	ADVANCE[1]	REALIZE[2]	Wright et al[19]
Mild CHC	0.92	0.92	0.77
Moderate CHC	0.88	0.91	0.66
Compensated cirrhosis	0.85	0.87	0.55

The estimates of on-treatment disutility (associated with adverse effects of treatment) were based on utility values reported over the course of treatment in the ADVANCE and REALIZE trials (reported in section 6.4.8, page 132-133 of the MS). Separate utility decrements were estimated for T12/PR and PR alone to capture the impact of adverse events that occur more commonly while patients are treated with telaprevir (rash and anaemia). The disutility was estimated based on the difference between patients' baseline utility values and the average value estimated from week 4 to week 48 of treatment. The MS does not report how missing observations were handled in the calculation of these averages (although Table 20 and Table 32, showing the EQ-5D index scores over time in the ADVANCE and REALIZE trial respectively and which include the number of observations at each time point, indicate there may be substantial numbers of missing observations at some time points). Table 58, Page 133 of the MS, reports the utility decrements applied during the first year of the model, indicating a slightly lower disutility for T12/PR (-0.102) compared with PR alone (-0.109) for treatment-naïve patients, which the MS suggests is primarily attributable to patients, in the T12/PR, who achieved an eRVR stopping treatment at 24 weeks. This view appears to be borne out by the mean EQ-5D index values reported in Table 20, page 69 of the MS (see Figure 4).

Figure 4 Mean EQ-5D index valuation over time in ADVANCE



Overall, the patient outcome estimates used by the manufacturer conform to the NICE Reference Case and are consistent with the approach adopted in previous appraisals for NICE. However the ERG have some reservations regarding the calculation of on-treatment disutility given the lack of clarity over the handling of missing observations.

4.2.6 Resource use

Resource use reported in the MS includes drug costs, on-treatment monitoring and health state costs. On-treatment monitoring includes out-patients appointments, tests and investigations, and non-invasive tests associated with the evaluation of new patients with confirmed CHC and those patients considered for treatment. Monitoring during active treatment (which includes tests and investigations) comprises basic checks for weeks 2, 16 and 20, and for those still receiving treatment up to week 48, basic checks at weeks 28, 32 40 and 44. Further detailed assessments are undertaken at weeks 4 and 8 and week 12 and 24. Resource use for each of these is presented in Table 62 (page 141-143 of the MS) and Table 64 (page144 of the MS).

Drug acquisition and resource use for management of adverse events is detailed in Tables 67, 68 and 69 (page146-147 of the MS).

A systematic search was undertaken in order to identify publications reporting resource use and costs in CHC patients in order to populate the model. This was conducted as an update to the review by Hartwell and colleagues,[18] and therefore the searches were limited to 2009 onwards. NHS EED and EconLit were not searched. The studies by Hartwell and colleagues[18] and Grischenko and colleagues[23] were identified by the searches. However, resource use for evaluating new patients, further investigations, monitoring during active treatment and monitoring to 48 weeks appears to have been taken directly from Shepherd and colleagues[17] although this publication was not identified by the systematic searches. Each of these studies has employed the resource use estimates from the Mild Hepatitis C Trial, by Wright and colleagues,[19] although this is not stated in the MS.

The resource use in the MS differs notably from Shepherd and colleagues[17] in two key respects. The first is that no consultant time is costed for monitoring during active treatment. The MS states that the opinion of the clinical advisors has confirmed the assumptions around resource use concerning consultation appointments, monitoring and testing and the assumption that patients treated with T12/PR and PR alone would receive the same monitoring, testing and appointments. However, clinical experts also advised that patients receiving telepravir would be likely to receive consultant appointments (particularly during early adoption), which has not been included in the base case.

HCV quantitative PCR monitoring during active treatment at week 4 is additional to the resource use reported in Shepherd and colleagues,[17] and this is stated in the MS to be required to ascertain whether eRVR had been achieved.

The marketing authorisation and licensed doses of the drugs are applied in the model. The licensed treatment duration of telaprevir is 12 weeks in the marketing authorisation. The mean treatment duration applied in the model is derived from the phase III clinical trials. For both treatment-naïve and treatment-experienced patients the mean treatment duration with telaprevir was 10.7 weeks. In the treatment-naïve model the mean duration of treatment with peginterferon alfa and ribavirin was 26.9 weeks in the T12/PR arm and 38.6 weeks in the PR alone arm. In the treatment-experienced model the mean duration of treatment with

peginterferon alfa and ribavirin was 36.5 weeks in the T12/PR arm and 30.0 weeks in the PR alone arm.

Stopping rules applied in the model do not reflect the marketing authorisation but those applied in the phase III clinical trials. The week 4 stopping criteria in the SmPC is HCV RNA >1000 IU/mL. This is the same as the ADVANCE trial (treatment-naïve) but less restrictive than the rule applied in the REALIZE (treatment-experienced) trial. In addition the SmPC week 4 criteria indicate that all therapy should be stopped whereas peginterferon alfa and ribavirin was continued in the trials. The SmPC indicates that stopping rules should only be applied at week 4 and week 12 whereas the trials contained stopping rules for patients receiving PR alone beyond week 12. The numbers of patients reported in the MS as being affected by the modified stopping rules appears small, but the impact remains unclear.

Monitoring and investigations resource data during the initial year of treatment are taken from Shepherd and colleagues[17] (see Table 62 and 63, page 141-144 of the MS). It is assumed that these costs are incurred at the same time in the treatment year for those receiving telaprevir and those receiving PR alone. The MS states that these were ratified by a clinical advisory board.

Treatment for anaemia is not included in the base case. This is clearly stated and justified: erythopoietin is not included in the base case for treatment of anaemia as it is not licensed for anaemia as a result of anti-viral treatment for CHC, it was not included in the trials (ribavirin treatment is reduced) and clinical advice indicated its use varies substantially across centres. In current clinical practice, anaemia resulting from anti-viral treatment of CHC is usually managed by adjusting the dose of ribavirin.

There are further sources of uncertainty in the estimates of drug resource use. Although there is potential for drug wastage, with patients being given a month’s supply in advance, wastage is not referred to in the MS. In addition peginterferon alfa-2a and -2b are stated to be broadly equivalent in efficacy and cost in the MS, however peginterferon alfa-2b is administered by weight and is not considered explicitly in the MS.

The included resource use generally appears relevant and comprehensive. The assumptions applied in the model are consistent with the trials undertaken, and where resource use has been

excluded, such as drug treatment for anaemia, this has been clearly stated and justified with reference to expert opinion. However the stopping rules in the trial differ to those in the license and the omission of consultant time differs from clinical opinion. The impact of these differences is unclear.

4.2.7 Costs

As noted previously, the searches for evidence on resource use and cost were conducted together. The two studies identified (Hartwell and colleagues[18] and Grischenko and colleagues[23]) were used to inform health state costs. However, the costs attached to the resource use in Shepherd and colleagues{30} were inflated to 2010 prices, using the Hospital and Community Health Services (HCHS) inflation index, and used in the model. Costs from Wright and colleagues[19] were applied for routine monitoring.

Drug acquisition costs are presented in Table 13.

Table 13 Intervention costs

Intervention	Dose	Unit cost/ dose (£)	Weekly cost (£)	Treatment course	Total cost (£)
Telaprevir	750g every 8 hours[a]	88.88	1,866.50	12 weeks[c]	22,398
Peginterferon alfa-2a	180µg per week		124.40	24 or 48 weeks[c]	5,971[b]
Ribavirin	1000 mg per day		77.08	24 or 48 weeks[c]	3,700[b]

[a]Administered with food; [b]Cost for 48 weeks; [c]Maximum indicated treatment duration

Adverse events costs for drugs appear to have been supplied by the clinical advisory board; no further sources have been given. The source for staff costs for rash management is stated as the Unit Costs of Health and Social Care,{8} although advisors are again referenced for these cost assumptions. The cost year for costs of drugs and staff costs to manage adverse events is not explicitly stated.

Costs of monitoring and investigations during the initial year of treatment (Tables 62 and 63, page 141-144 of the MS) are taken from Shepherd and colleagues[17] and these were inflated to 2010 prices using the HCHS inflation index. It is assumed that these costs are incurred at the same time in the treatment year for those receiving T12/PR and those receiving PR alone. The MS states that these were ratified by the clinical advisory board.

Health state costs have been taken from Hartwell and colleagues[18] and are presented in Table 14 below. The exceptions are:

- on-going health state costs associated with disease severity specific post-SVR health state costs, which were taken from Grischenko and colleagues[23]
- estimates for two post-liver transplant costs (0-12 months and 12-24 months) from Wright and colleagues[19] are applied as opposed to the collapsed state of liver transplant applied in the Hartwell study.[18]

Table 14 Health state costs

Health state	Annual cost (£)	Source[a]
Mild CHC		
• Without treatment	175.37	Hartwell and colleagues[18]
• SVR following treatment	219.55	Grischenko and colleagues[23]
Moderate CHC		
• Without treatment	910.63	Hartwell and colleagues[18]
• SVR following treatment	268.46	Grischenko and colleagues[23]
Compensated cirrhosis		
• Without treatment	1,445.18	Hartwell and colleagues[18]
• SVR following treatment	474.96	Grischenko and colleagues[23]
Decompensated cirrhosis	11,582.59	Hartwell and colleagues[18]
HCC	10,321.23	Hartwell and colleagues[18]
Liver transplant		
• Liver transplant	46,720.18	Hartwell and colleagues[18]
• Post-liver transplant 0-12 months	12,016.13	Wright and colleagues[19]
• Post-liver transplant 12-24 months	1,759.60	Wright and colleagues[19]

[a]All inflated to 2010 prices; Taken from Table 66:Health state costs, p147 of the MS.

Measures of variability around costs are not reported in the MS. Arbitrary ranges for monitoring costs, health state costs and adverse events costs are reported in the deterministic sensitivity analysis, and are all varied by arbitrary ranges: duration of treatment is varied by 10%, monitoring costs by 10%, health state costs have been varied by 50% and adverse events costs by 50%. Drug prices do not appear to have been varied in the sensitivity analysis.

4.2.8 Consistency/ Model validation

The ERG has examined the submitted electronic model for internal and external consistency and accuracy. Random checking has been done for some of the key equations of the model although this has not been a comprehensive 'checking' process of all cells in the model.

Internal consistency

The electronic model is coded in Microsoft Excel and is fully executable. Models inputs can be varied by changing values on the relevant input worksheets and the results of the base case analyses are presented on the '*Results*' worksheet. Deterministic one-way sensitivity analyses are run from the '*DSA def'* worksheet by clicking on the '*Run the DSA*' button. Results of the DSA are reported on the *'DSA Results'* worksheet as a tabulation, ordered by decreasing range of ICER, and a tornado plot of the same information. The PSA is run from the '*PSA def*' worksheet with results reported in the '*PSA results*' worksheet (table of mean costs and QALYs for intervention and comparator, along with percentile-based 95% confidence interval, and a scatterplot of incremental costs and effects) and '*PSA results (2)*' worksheet (cost-effectiveness acceptability curve).

The MS reported that an independent external methodologist reviewed both assumptions around data inputs and the functionality of the model during model development. It is further reported that two independent reviewers then separately reviewed the treatment-naïve and treatment-experienced models. While the models were stated to have been found to be 'clear, transparent, intuitive and fully functional', there is no further documentation or evidence in the model of internal validation checks, or detailed reporting of what these procedures showed.

External consistency

The MS does not state that the model has been calibrated against independent data, and does not report further techniques for external validation. It is stated in the 'interpretation of economic evidence' that there are no published economic models exploring the cost effectiveness of telaprevir. However, there are published models in peginterferon alfa-2a and ribavirin which could have been used for external comparison. The model structure, and data inputs including transition probabilities, resource use and costs are substantially based upon, or derived directly from, previously published models in patients with CHC, and therefore there are unlikely to be

concerns over external consistency. The economic evaluation was consistent with the NICE reference case.

4.2.9 Assessment of Uncertainty

The MS reports the results of univariate sensitivity analyses, scenario analyses and PSA. These are primarily concerned with parameter uncertainty – consideration of methodological uncertainty is restricted to the use of alternative discount rates for outcomes, while structural uncertainty is addressed only by a reduction in the model time horizon (both reported as scenario analyses). Heterogeneity in patient populations is addressed by reporting separate base case analyses for treatment-naïve and treatment-experienced populations, and within these populations via subgroup analyses by IL-28B subtype and by prior treatment response (for the treatment-experienced population).

One-way sensitivity analyses

A range of one-way sensitivity analyses are reported in the MS (methods in section 6.6.2, page 154-156 of the MS, and results in section 6.7.7, page 163-166 of the MS). There is no discussion or rationale provided in the MS for the choice of variables included or excluded from the sensitivity analyses. Categories of variables included in the sensitivity analyses are: transition probabilities in the natural history model, health state utilities, SVR; treatment duration, treatment-related disutility, on-treatment monitoring costs, health state costs and adverse event costs. The sensitivity analyses do not include adverse event incidence or any variation in baseline characteristics of the treated populations (patient age, severity of liver disease or prior treatment response, for treatment-experienced patients).

The ranges applied in the sensitivity analyses are a mixture of 95% confidence intervals (for SVR and treatment-related disutility) and arbitrary ranges (transition probabilities (±25%), treatment duration (±10%), on-treatment monitoring costs (±10%), health state costs (±50%) and adverse event costs (±50%)). A number of arbitrary ranges have been applied for health state utilities without providing any rationale or explanation – although it appears that, for each health state, the maximum and minimum values may have been selected with respect to relevant reference states (for example, the minimum value for CC without SVR is equal to the base case value for DC and HCC (progression states from CC) while the maximum value for CC without SVR is equal to the base case value for moderate CHC (the health state prior to CC

in terms of disease progression)). The MS does not provide a rationale for the ranges chosen for any of the included variables, nor does it include a discussion of why arbitrary ranges have been chosen when appropriate information on variation is available. Arbitrary ranges of ±25% are applied to transition probabilities in the sensitivity analyses, despite standard errors being reported in the publications from which these transition probabilities are reported as being sourced (Grishchenko and colleagues[23] and Hartwell and colleagues[18]). Similarly Grishchenko and colleagues[23] report standard errors for health state utilities (consistent with those reported by the UK Mild Hepatitis C Trial,[19] and which were adopted by Shepherd and colleagues[17] and Hartwell and colleagues[18]) and health state costs. There are some additional problems in the one-way sensitivity analyses for variables whose base case value is zero (for example, SVR for null responders to previous treatment, with mild disease, treated with PR and SVR for partial responders to previous treatment, with mild disease, treated with PR), where the minimum and maximum values (derived using 95% CIs based on the normal approximation to the binomial) are also both zero. A better option might have been to use exact binomial confidence interval (estimated by ERG as 0% to 52.2% for SVR in null responders to previous treatment, with mild disease, treated with PR and 0% to 30.8% for SVR in partial responders to previous treatment, with mild disease, treated with PR).

The results of the one-way sensitivity analyses are presented as tornado plots, including all variables (Figure 20, page 164 of the MS for treatment-naïve patients and Figure 21, page 165 of the MS for treatment-experienced patients) and tabulations of the 12 variables associated with the greatest variation in ICER. The MS does not provide a rationale for choosing this number of variables for tabulation.

The greatest variation in ICER for treatment-naïve patients is associated with the health state utility for mild CHC with a difference of £6,774 (ranging from £10,966 to £17,739 per QALY gained). The range is very similar for the health state utility for moderate CHC. Apart from the utility values applied to early disease states the sensitivity analyses suggest that the cost effectiveness results for treatment-naïve patients are most sensitive to variation in treatment duration (in the T12/PR-treated cohort) and SVR. The MS reports that the ICER remained below £18,000 per QALY gained in all instances for this population.

The greatest variation in ICER for treatment-experienced patients is associated with the health state cost for DC with a difference of £5,329 (ranging from £11,353 to £6,024 per QALY

gained). Overall the sensitivity analyses suggest that the cost effectiveness results for treatment-experienced patients are most sensitive to the costs and utility values applied to the cirrhosis (compensated or decompensated) health states, treatment duration (in the T12/PR-treated cohort) and SVR. The MS reports that the ICER remained below £13,000 per QALY gained in all instances for this population.

Interpreting the one-way sensitivity analyses is complicated by the fact that variables that may logically be expected to be correlated are varied independently – for example, there may be questions over the interpretation of an analysis that varies the transition probability from mild to moderate for age ≤35 years, without also including variation for age 36-45 and 45+, or that treat SVRs by disease stage or prior treatment response completely independently. Treating all these variables independently may underestimate the uncertainty associated with a group of variables, derived from a single source.

Scenario Analysis

The methods and rationale for the scenario analyses in the MS are reported in section 6.6.1, page 149-154 of the MS and the results are reported in in section 6.7.9, page 168-169 of the MS. The scenarios considered relate to: adoption of response-guided treatment (reducing treatment duration (to 24 weeks) for PR-treated, treatment-naïve, patients with undetectable HCV RNA at weeks 4 and 24 and for T12/PR-treated, treatment-experienced non-cirrhotic, patients who demonstrate eRVR); definition of SVR (SmPC definition rather than the trial definition adopted in the base case); health state utility values; use or erythropoietin for grade 3 anaemia; patient age (treatment-naïve model run for population aged 30, 40 and 50 years separately, while mean age for treatment-experienced patients was reduced to 40); discount rate (for health outcomes set to 1.5% rather than 3.5%) and model time horizon (reduced from lifetime to 30 years).

The ICERs for the treatment-naive population were generally insensitive to changes, except when adopting a shorter time horizon where incremental QALYs markedly reduce (and the ICER increases to £20,689). Incremental QALYs reduce (hence ICER increases) with older patient age and with alternative utility values, while QALYs markedly increase with outcomes discounted at 1.5%.

The ICERs for the treatment-experienced population were generally insensitive to changes. Incremental QALYs reduce (hence ICER increases) with alternative utility values. Incremental QALYs increase (and costs decrease a little leading to lower ICER) for younger start age. QALYs markedly increase with shorter treatment duration for prior relapsers (costs also more than halved so that ICER reduces to 2,840) and where outcomes discounted at 1.5% (ICER reduces to 5,806). QALYs reduce with shorter time horizon (and costs increase a little leading to increased ICER of 11,566).

The MS does not include any commentary or interpretation of the scenario analysis results.

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis can be run by clicking on the '*Run the PSA*' button on the '*PSA def*' worksheet in the Excel model. The number of simulations to be run in the PSA is set in an input box that is displayed after the '*Run the PSA*' button is selected. The '*PSA def*' worksheet contains a table of input values for the model parameters included in the PSA, which lists the point estimate used in the deterministic base case analysis (labelled "base case"). Values in the "base case" column are linked within to the model to the input worksheets in which the variables are defined and where sources are clearly indicated. In contrast, the column headed "SE", presumed to stand for Standard Error are hard-coded on this sheet with no source specified.

Table 80, page 157-158 of the MS, lists the variables included in the PSA and the distribution associated with the variable, but no information on the methods used to parameterise the distribution and in many cases no estimate of variability has been included in the description of included variables (for example, transition probabilities in the natural history model are presented in Table 48, page 112 of the MS, but no standard errors are reported). The PSA includes the majority of variables in the model, but excludes patient baseline characteristics (age, stage of disease and (for treatment-experience patients) response to prior treatment) and also appears to exclude the incidence as well as treatment costs associated with adverse events. There is no discussion or rationale in the MS for the inclusion, or exclusion of variables from the PSA.

The PSA takes approximately 30 seconds to run (on a computer with 3.16 GHz dual core processor and 4 Gb memory) for 1,000 simulations. Results of the PSA are reported in section

6.7.8, page 166-168 of the MS, as a scatterplot on the cost-effectiveness plane (Figure 22, page 166 of MS, for treatment-naïve patients and Figure 24, page 167 of the MS, for treatment-experienced patients), cost-effectiveness acceptability curves (CEACs) (Figure 23, page 167 of MS, for treatment-naïve patients and Figure 25, page 168 of the MS, for treatment-experienced patients) and as the probability of T12/PR being cost effective, relative to PR alone, at thresholds of £20,000 and £30,000 per QALY gained. The MS does not report mean costs or outcomes for each intervention from the PSA, although this is estimated in the submitted electronic models (see Table 15 for a summary of these results). These appear to be consistent with the deterministic base case results (see Table 5 in this report).

Table 15 Probabilistic sensitivity analysis – mean cost and outcomes from submitted models, not reported in MS

	Cost	QALY
Treatment-naïve patients		
T12/PR	£36,021 (£33,909 - £38,414)	13.87 (13.05 - 14.71)
PR	£24,609 (£21,424 - £28,595)	13.04 (12.46 - 13.64)
Difference	£11,413 (£8,618 - £13,595)	0.83 (0.44 - 1.28)
Treatment-experienced patients		
T12/PR	£44,423 (£40,991 - £48,316)	11.29 (10.43 - 12.09)
PR	£34,211 (£28,255 - £41,168)	10.11 (9.14 - 11.06)
Difference	£10,212 (£5,522 - £14,166)	1.19 (0.42 - 1.98)

The distributions used in the model appear to be generally reasonable, with beta distributions used for probabilities (transition probabilities and SVRs) and health state utilities, gamma distributions used for costs and for disutilities, and log-normal distributions used for treatment durations. However, it is unclear why a uniform distribution is applied, as presented in Table 80 of the MS without reporting any rationale, for the transition probability from HCC to liver transplant. As noted earlier, the MS does not provide any information on the parameterisation of the distributions used in the PSA. It would be more typical to report the parameterisation along with the distributions used in a summary table (such as Table 80 in the MS) or to refer back to tables defining each model input (if these included standard errors, 95% CIs or other measures

of variation) and indicate how distribution parameters were derived from the reported mean and measures of variation. Examination of the electronic models suggests that appropriate values have been adopted for parameterising the distributions in the model.

Examination of the electronic model by the ERG revealed some errors in the PSA, where certain variables (treatment duration and health state utilities for mild and moderate CHC as well as CC) appear not to be simulated, but are included at their mean values due to errors in Excel formulae. A number of other variables (related to incidence of adverse events and their treatment costs) also appear to have been omitted from the PSA. The ERG re-ran the PSA after updating the model to include these variables in the PSA - these appear to have little impact on the ICER (see later section 4.3 reporting additional analyses undertaken by the ERG).

4.2.10 Comment on validity of results with reference to methodology used

The model structure adopted for the economic model is consistent with previous economic evaluations of anti-viral treatment for CHC, including those conducted to support previous NICE appraisals.[17;18] Data for the main clinical effectiveness parameter were sourced from phase III clinical trials, in patient populations relevant to this appraisal (genotype 1 CHC treatment-naïve and treatment-experienced patients) and were estimated separately for those with mild CHC, moderate CHC and compensated cirrhosis. This is appropriate since cirrhotic patients with CHC who receive anti-viral therapy generally show poorer response than those without cirrhosis. However, as noted in section 4.2.2, patients with bridging fibrosis were classified as cirrhotic in the calculation of baseline characteristics (by severity of disease) and of SVRs. This has the impact of making the baseline populations appear to have more severe liver disease and may have misrepresented the SVR for cirrhotic patients in the model.

The model parameters are generally similar to those adopted in previous economic evaluations and appear to be appropriate for this appraisal. The MS uses different (age-at-treatment-related) transition probabilities for early disease progression, compared with models used in previous NICE appraisals. However the differences are not large and are unlikely to have a substantially impact on the cost effectiveness results.

The cost of drug regimens in the economic model, calculated using the mean duration of treatment in the phase III clinical trials, may not fully reflect the cost of drugs prescribed in

normal clinical practice as patients are typically prescribed sufficient medication to last until the next follow-up visit. Costing using mean treatment duration assumes there is no wastage associated with patients discontinuing treatment between scheduled follow-up visits and will reflect the stopping rules adopted in the trials (which do not accord with routine clinical practice).

The methods of analysis are generally appropriate and conform to NICE methodological guidance.[37]

4.3 Additional work undertaken by the ERG

The following additional analyses have been undertaken by the ERG:

a) Applying baseline characteristics (mean age and distribution of disease severity) consistent with previous NICE appraisals (as reported in Hartwell and colleagues[18]);
b) Applying SVRs based on definitions of cirrhosis consistent with the original trial publications (grouping bridging fibrosis under moderate CHC rather than cirrhosis, see discussion in section 4.2.2 and section 4.2.4);
c) Applying baseline characteristics (disease severity) based on definitions of cirrhosis consistent with the original trial publications;
d) Applying early transition probabilities (from mild to moderate-CHC and moderate CHC to CC) consistent with definition in source publication (from Grishchenko and colleagues[23]) – i.e. dependent on age of treatment and not as age-specific probabilities;
e) Applying baseline characteristics consistent with previous NICE appraisals and age-of-treatment-dependent early transition probabilities (combining a) and d) above)
f) Applying baseline characteristics consistent with previous NICE appraisals, age-of-treatment-dependent early transition probabilities and SVRs based on definitions of cirrhosis consistent with the original trial publications (combining d), a) and b) above).
g) Re-running the manufacturer's PSA, including those variables which were not sampled (treatment duration and health state utilities for mild CHC, moderate CHC and CC were included at mean values due to errors in paramterisation in the treatment-naïve model, while adverse event incidences were not sampled in either model), or which were included with a value of zero (adverse events costs in the treatment-experienced model);
h) Re-running the manufacturer's PSA, including omitted variables and with assumptions as for f) above.

Applying baseline characteristics (mean age and distribution of disease severity) consistent with previous NICE appraisals

The mean age and distribution of disease severity at treatment was varied to those applied in previous NICE appraisals of anti-viral therapy for CHC[17;18] (see Table 16). For both populations the proportion with cirrhosis is lower than in the manufacturer's base case (10% compared with 20% for treatment-naïve and 32% compared with 48% for treatment-experienced patients). The mean ages are approximately five years younger than the respective trail populations (the MS reports mean ages of 51 (T12/PR) and 50 (PR) for patients in the REALIZE, but only the median age for ADVANCE. The CSR submitted by the manufacturer includes the mean age for patients in ADVANCE [redacted][11]).

Table 16 Distribution of patients across liver disease severity adopted in previous NICE appraisals

Patient population	Mean age (years)	Severity of liver disease		
		Mild (%)	Moderate (%)	CC (%)
Treatment-naive	40	46	44	10
Treatment-experienced	45	33	35	32

Source: Foster and colleagues[38]

The effect of this change in baseline assumptions is a slight reduction in ICER both for treatment-naïve patients (from £13,553 to £11,916 per QALY gained) and treatment-experienced patients (from £8,688 to £8,086 per QALY gained), see Table 17.

Table 17 Cost effectiveness results with baseline populations as in previous NICE appraisals

	Cost (£)	QALYs	ICER (£/QALY gained)
Treatment-naïve			
PR	23,278	14.36	
T12/PR	34,553	15.31	
Increment	11,275	0.95	11,916
Treatment-experienced			
PR	31,803	11.59	
T12/PR	42,295	12.89	
Increment	10,492	1.30	8,086

Applying SVRs using definitions of cirrhosis consistent with the original trial publications

As discussed in section 4.2.4 of this report, the SVRs applied in the MS included patients with bridging fibrosis under the heading of cirrhosis. This is inconsistent with the definition of cirrhosis adopted in the trial publications and in the clinical effectiveness section of the MS. The ERG recalculated the SVRs with patients with bridging fibrosis classified under moderate CHC.

The effect of applying this change to the calculation of SVR baseline assumptions is a slight reduction in ICER for treatment-naïve patients (from £13,553 to £13,368 per QALY gained) resulting from a small reduction in incremental cost and also a small increase in QALY gain. For treatment-experienced patients the ICERs increases (from £8,688 to £9,521 per QALY gained), see Table 18.

Table 18: Cost-effectiveness results with SVR for inclusion of bridging fibrosis under moderate disease

	Cost (£)	QALYs	ICER (£/QALY gained)
Treatment-naïve			
PR	25,162	12.98	
T12/PR	36,530	13.83	
Increment	11,368	0.85	13,368
Treatment-experienced			
PR	34,566	10.06	
T12/PR	45,351	11.20	
Increment	10,785	1.13	9,521

Applying baseline characteristics (disease severity) from trial using definitions of cirrhosis consistent with the original trial publications

As discussed in section 4.2.2 of this report the baseline distribution of disease severity includes patients with bridging fibrosis under the heading of cirrhosis – this has the effect of making the baseline population appear to have more severe liver disease. The ERG recalculated the baseline distribution of disease severity, including patients with bridging fibrosis under the heading of moderate CHC (see Table 9).

The MS doesn't report the number of patients with bridging fibrosis classified as cirrhotic in the baseline populations, by the age groups used in the treatment-naïve economic model. As a result this analysis was undertaken for the mean age of patients in the ADVANCE trial – as a

result the incremental cost, incremental QALYs and ICER reported in the scenario analysis by patient age (Table 93, page 168 of the MS) are more relevant for this population.

The effect of applying this change to the calculation of the baseline distribution of disease severity is a slight increase in ICER for treatment-naïve patients (from £15,104, for patients aged over 45 to £15,782 per QALY gained) and a slight reduction for treatment-experienced patients (from £8,688 to £8,630 per QALY gained), see Table 19.

Table 19 Cost-effectiveness results with correct baseline population and SVR for inclusion of bridging fibrosis under moderate disease

	Cost (£)	QALYs	ICER (£/QALY gained)
Treatment-naïve			
PR	21,364	12.68	
T12/PR	33,343	13.44	
Increment	11,979	0.76	15,782
Treatment-experienced			
PR	31,096	10.83	
T12/PR	41,575	12.04	
Increment	10,478	1.21	8,630

Applying early transition probabilities consistent with definition in source publication

As discussed in section 4.2.2 of this report, the MS has applied age-specific transition probabilities for early disease (transitions from mild to moderate disease and from moderate disease to cirrhosis). However the source publication (from Grishchenko and colleagues[23]) states that these transition probabilities relate to patients' age at treatment, not their current age. The ERG updated the manufacturer's model for treatment-naïve patients to use appropriate age at treatment probabilities.

Table 20 Cost-effectiveness results applying age at treatment transition probabilities

	Cost (£)	QALYs	ICER (£/QALY gained)
Treatment-naïve			
PR	23,858	13.18	
T12/PR	35,810	13.93	
Increment	11,952	0.75	15,903

The effect of applying this change is to reduce the QALY gain and slightly increase incremental costs, resulting in an increased ICER (from £13,553 to £15,903 per QALY gained) see Table 20.

Applying baseline characteristics consistent with previous NICE appraisals and age-of-treatment-dependent early transition probabilities

Combining two of the scenarios reported above – applying baseline characteristics from previous appraisals and using appropriate age at treatment early transition probabilities – results in increased incremental costs for both patient populations (increasing from £11,430 to £12,726 for treatment-naïve patients and from £10,195 to £11,566 for treatment-experienced patients) and comparatively large reduction in incremental QALYs for treatment-naïve patients (from 0.84 to 0.69). As a result the ICERs for both patient populations are higher than in the manufacturer's base case (increasing from £13,533 to £18,360 for treatment-naïve patients and from £8,688 to £10,369 for treatment-experienced patients), see Table 21.

Table 21 Cost-effectiveness results with age at treatment transition probabilities and baseline population as in previous appraisals

	Cost (£)	QALYs	ICER (£/QALY gained)
Treatment-naïve			
PR	20,839	14.79	
T12/PR	33,565	15.49	
Increment	12,726	0.69	18,360
Treatment-experienced			
PR	30,214	11.86	
T12/PR	41,781	12.98	
Increment	11,566	1.12	10,369

Applying baseline characteristics consistent with previous NICE appraisals, age-of-treatment-dependent early transition probabilities and SVRs based on definitions of cirrhosis consistent with the original trial publications

Combining three of the scenarios reported above – applying baseline characteristics from previous appraisals, using appropriate age at treatment early transition probabilities and recalculating the SVRs to include patients with bridging fibrosis under moderate CHC – results in increased incremental costs for both patient populations (increasing from £11,430 to £12,660 for treatment-naïve patients and from £10,195 to £11,617 for treatment-experienced patients) and comparatively large reduction in incremental QALYs for treatment-naïve patients (from 0.84

to 0.70). The ICERs for both patient populations are higher than in the manufacturer's base case (increasing from £13,533 to £18,091 for treatment-naïve patients and from £8,688 to £10,388 for treatment-experienced patients), see Table 22.

Table 22 Cost-effectiveness results with age at treatment transition probabilities and baseline population as in previous appraisals and SVR calculated with bridging fibrosis included in moderate disease

	Cost (£)	QALYs	ICER (£/QALY gained)
Treatment-naïve			
PR	21,280	14.75	
T12/PR	33,941	15.45	
Increment	12,660	0.70	18,091
Treatment-experienced			
PR	30,624	11.82	
T12/PR	42,242	12.93	
Increment	11,617	1.12	10,388

Probabilistic sensitivity analysis

The results of re-running the manufacturer's PSA on both models, including omitted variables are reported in Table 23. The inclusion of these additional variables in the PSA appears to have little impact on the mean cost and outcomes, or on the percentile-based confidence intervals.

Table 23 Probabilistic sensitivity analysis – including variables omitted from manufacturer's PSA

	Cost (£)	QALY
Treatment-naive		
T12/PR	£36,039 (£34,033 - £38,336)	13.89 (12.92 - 14.82)
PR	£24,588 (£21,744 - £28,293)	13.05 (12.24 - 13.85)
Difference	£11,451 (£8,933 - £13,613)	0.84 (0.46 - 1.26)
Treatment-experienced patients		
T12/PR	£44,468 (£41,047 - £48,340)	11.28 (10.38 - 12.16)
PR	£34,247 (£28,454 - £41,320)	10.12 (9.20 - 11.02)
Difference	£10,222 (£5,316 - £14,071)	1.16 (0.37 - 1.98)

In this analysis there is an 87.4% probability of T12/PR being cost effective, relative to PR alone, at a threshold willingness to pay threshold of £20,000 per QALY gained and 98.6% at a threshold of £30,000 per QALY gained, for treatment-naïve patients. The equivalent values for treatment-experienced patients are 92.3% and 97.2%. These compare with probabilities of 85.3% and 98.0%, respectively for treatment-naïve patients, and 94.0% and 97.4%, respectively for treatment-experienced patients, in the manufacturer's analysis.

The PSA was run again, including variables omitted from the manufacturer's PSA, and after applying baseline characteristics consistent with previous NICE appraisals, age-of-treatment-dependent early transition probabilities and amended SVRs as described above. The mean cost and outcomes, and percentile-based confidence intervals are reported in Table 24. As with the deterministic analysis reported above, the changes result in lower total costs for both T12/PR and PR alone, increased incremental costs for T12/PR compared with PR alone, higher total QALYs, and smaller QALY gains for T12/PR compared with PR alone. In this analysis there is a 59.1% probability of T12/PR being cost effective, relative to PR alone, at a threshold willingness to pay threshold of £20,000 per QALY gained and 88.5% at a threshold of £30,000 per QALY gained, for treatment-naïve patients. The equivalent values for treatment-experienced patients are 92.2% and 97.4%.

Table 24 Probabilistic sensitivity analysis – applying baseline characteristics consistent with previous appraisals, age-of-treatment dependent early transition probabilities and amended SVRs

	Cost (£)	QALY
Treatment-naïve		
T12/PR	£33,883 £32,403-£35,655	15.46 14.42-16.45
PR	£21,173 £19,056-£23,912	14.77 13.93-15.56
Difference	£12,710 £10,679-£14,431	0.69 0.29-1.14
Treatment-experienced patients		
T12/PR	£42,153 £39,360-£45,443	12.97 12.14-13.81
PR	£30,539 £25,743-£36,185	11.87 11.04-12.71
Difference	£11,613 £8,149-£14,795	1.10 0.41-1.80

4.4 Summary of uncertainties and issues

- It is unclear whether the trial populations reflect the UK CHC population treated in secondary care, in terms of average age at treatment and the stage of liver disease.
- The clinical trials used to estimate response to treatment excluded patients co-infected with HIV and HBV, as well as current drug and/ or alcohol abusers. As a result the models for treatment-naïve and treatment-experienced patients do not apply to these groups of patients.
- The phase III clinical trials adopted different stopping rules than those applied in routine clinical practice for peginterferon alfa and ribavirin, and those in the SmPC for telaprevir. The impact of these additional stopping rules on the cost effectiveness of telapravir in combination with peginterferon alfa and ribavirin is unclear.
- Costs of drug regimens in the economic model were calculated assuming no wastage and were based on the mean duration of treatment in the phase III clinical trials. However patients attending for periodic, on-treatment monitoring are typically prescribed sufficient medication to last until the next follow-up visit, so that the mean treatment duration may not fully reflect the cost of drugs prescribed.

5 End of life

NICE end of life criteria were not applicable and not included in the MS.

6 DISCUSSION

6.1 Summary of clinical effectiveness issues

The MS includes evidence on the clinical effectiveness of telaprevir in combination with peginterferon alfa and ribavirin for the treatment of genotype 1 CHC from two Phase III RCTs. One trial was based on treatment-naïve and one on treatment-experienced patients. Results presented in the MS suggest that triple therapy containing telaprevir is superior to standard therapy of peginterferon alfa and ribavirin for the primary outcome of SVR. These appear to be unbiased estimates of effectiveness. Telaprevir also appears to be more favourable for other outcomes. However, due to the lack of statistical testing and small subgroups, the interpretation of some of these outcomes should be treated with caution.

6.2 Summary of cost effectiveness issues

The MS includes evidence on the cost effectiveness of telaprevir in in combination with peginterferon alfa and ribavirin, compared with the current treatment standard of peginterferon alfa and ribavirin. The model structure and methods adopted for the economic evaluation are reasonable and generally appropriate. The model structure and model parameters are consistent with previous economic evaluations of anti-viral therapy for CHC.

The ERG identified some inconsistencies in data included in the model (inclusion of patients with bridging fibrosis under the heading of cirrhosis and the use of age-at-treatment probabilities as age-specific). Additional analyses have been presented by the ERG, including changes to baseline characteristics to values consistent with previous NICE appraisals. While these have had some effect on costs and outcomes in the model they did not have a substantial impact on the cost effectiveness estimates for telaprevir.

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