NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Sofosbuvir for treating chronic hepatitis C

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report and additional analyses.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Data is lacking for some subgroups (e.g. for treatment experienced patients with genotype 1, 4, 5 or 6 chronic HCV). Does the Committee consider that sufficient evidence has been presented to allow recommendations to be made on the use of sofosbuvir for all populations (by genotype and treatment history) covered by the marketing authorisation?
- The data presented by the manufacturer was mainly from open label and single-arm studies with relatively short follow-up periods, some of which rely on historical controls. The studies also included very small numbers of patients in most subgroups. Does the Committee consider that the evidence presented is robust enough to allow recommendations to be made on the use of sofosbuvir in these populations?
- The manufacturer's economic model structure is a modified version of models previously used in NICE appraisals of treatments for hepatitis C. The manufacturer replaced the 'mild', 'moderate' and 'severe' cirrhosis starting health states of the previous models with 2 health states, non-cirrhotic and cirrhotic. The ERG commented that there were fewer studies that used the cirrhotic and non-

cirrhotic categories. What is the Committee's view on the robustness of the clinical efficacy data used in the model as a result?

Cost-effectiveness

- The manufacturer used a simple average of male and female mortality figures to calculate the age-specific mortality rates for use in the model. The ERG did not consider this to be appropriate as it does not reflect the proportion of men to women infected with HCV. What is the Committee's view on the manufacturer's approach to calculating age-specific mortality rates for the sofosbuvir model?
- The manufacturer presented a number of sensitivity analyses for different discount rates (ranging from 0 to 6%). Does the committee consider the use of 3.5% discounting for costs and benefits appropriate?
- The manufacturer has made a case that sofosbuvir is an innovative treatment and this should be taken into account when considering the manufacturer's base case. What is the Committee's view on the innovative aspects associated with sofosbuvir, when considering the uncertainties associated with the clinical evidence used to populate the manufacturer's economic model?
- There is some uncertainty around how representative the health-related quality of life results are of the wider trial populations. There was a decrement in some of the trials during treatment suggesting a worsening of quality of life with sofosbuvir-based regimens. These generally returned to baseline 12 weeks after treatment completion. The manufacturer has applied a utility increment attributed to achieving an SVR and propagated this through the model and it has a significant effect on the ICER in patients with different genotype and levels of liver disease. What is the Committee's view on the plausibility of patients gaining an improvement in their quality of life following a sustained virological response? Are there any equalities issues raised by the clinical and cost effectiveness evidence in subgroups where there is an unmet need?

1 Background: clinical need and practice

1.1 The hepatitis C virus (HCV) causes inflammation of the liver and affects the liver's ability to function. HCV is a blood-borne virus, meaning that it is spread by exposure to contaminated blood. Contaminated needles used

for injecting drugs are currently the most common route of transmission. Symptoms of chronic HCV infection are typically mild and non-specific, including fatigue, flu-like symptoms, anorexia, depression, sleep disturbance, pain, itching and nausea. Often, people with HCV do not have any symptoms, and 15 to 20% of infected people naturally clear their infections within 6 months. However, the remainder develop chronic hepatitis C which can be life-long.

1.2 Chronic hepatitis is categorised according to the extent of liver damage, as mild, moderate, or severe (where severe refers to cirrhosis). About 30% of people infected with HCV will develop cirrhosis; the time for progression to cirrhosis varies, but takes 40 years on average. Cirrhosis can progress to become ‘decompensated’, where the remaining liver can no longer compensate for the loss of function. A small percentage of people with chronic hepatitis and cirrhosis also develop hepatocellular carcinoma. Liver transplantation may be needed for people with decompensated cirrhosis or hepatocellular carcinoma.

1.3 The true prevalence of HCV infection is difficult to establish and likely to be underestimated because many people do not have symptoms. There are 6 major genotypes and several subtypes of HCV, the prevalence of each vary geographically. People can be infected with more than one genotype. The most recent national estimates (2012) suggest that approximately 160,000 people are chronically infected with HCV in England, and that most of this infection is genotype 1 (46%) and 3 HCV (43%). However, more than half of people with chronic hepatitis C are unaware of their infection.

1.4 The aim of treatment is to cure the infection, and prevent liver disease progression, hepatocellular carcinoma development, and HCV transmission. Sustained virological response at 12 weeks after the end of treatment is considered a good indicator of successful treatment. Most patients who achieve a sustained virological response at 12 weeks after the end of treatment maintain their HCV-negative status and have

reduced complications from liver disease and increased survival times. Viral genotype predicts the effectiveness of anti-viral treatment; people infected with genotypes 2 or 3 generally respond better than those with genotypes 1, 4, 5 or 6. People with HCV genotype 1 or 4 and people who have a single nucleotide polymorphism with 2 copies of the C allele near their IL28B gene (CC genotype IL28B polymorphism) are likely to have a better response to treatment than those who do not. People with HCV genotype 2 or 3 respond better to peginterferon with ribavirin treatment than people infected with the other HCV genotypes. For those with mild hepatitis C, a 'watchful waiting' approach may be agreed, on an individual basis, between the patient and clinician. NICE guidance on hepatitis C (TA75, TA106) recommends that standard treatment for the majority of people with chronic hepatitis C, regardless of disease severity, is combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b. Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended for patients who are unable to tolerate ribavirin or for whom ribavirin is contraindicated. NICE guidance on hepatitis C (TA200) also recommends that people who have been previously treated with peginterferon alfa and ribavirin or with peginterferon alfa monotherapy have an option to receive further courses of peginterferon alfa and ribavirin. Shortened courses of combination therapy are also recommended as an option for certain patient subgroups. For people with genotype 1 chronic hepatitis C, who have not been previously treated or who have been previously treated, NICE guidance also recommends telaprevir in combination with peginterferon alfa and ribavirin (TA252) or boceprevir in combination with peginterferon alfa and ribavirin (TA253).

2 The technology

2.1 Sofosbuvir (Sovaldi, Gilead Sciences) is a uridine nucleotide analogue that inhibits HCV polymerase, preventing viral replication. Sofosbuvir has a UK marketing authorisation 'in combination with other medicinal products for treating chronic hepatitis C in adults'. The recommended

dose is one 400mg tablet daily, taken orally. It should be used in combination with peginterferon alfa and ribavirin, or ribavirin only if the patient is ineligible or intolerant to peginterferon alfa. The recommended duration of treatment is 12 or 24 weeks depending on genotype and combination therapy prescribed (see Table 1). Peginterferon alfa-free regimens for patients with genotype 1, 4, 5 and 6 HCV infection have not been investigated in phase 3 studies. According to the summary of product characteristics, peginterferon alfa-free regimens should only be used to treat patients with genotype 1, 4, 5 and 6 HCV infection if the patients are intolerant to or ineligible for peginterferon alfa therapy and are in urgent need of treatment. The summary of product characteristics also states that for all genotypes consideration should be given to potentially extending the duration of therapy from 12 weeks up to 24 weeks especially for subgroups of people who have one or more factors historically associated with lower response rates to interferon-based therapies (such as people with advanced liver fibrosis or cirrhosis, high baseline viral concentrations, non CC genotype IL28B polymorphism , prior unresponsiveness to peginterferon and ribavirin combination therapy and people of African and Caribbean family origin).

Table 1 Sofosbuvir treatment duration with co-administered medicinal products by genotype

Patient population*	Treatment	Duration
Patients with genotype 1, 4, 5, or 6 HCV	sofosbuvir + peginterferon alfa + ribavirin	12 weeks
	sofosbuvir + ribavirin (for people ineligible or intolerant to peginterferon alfa)	24 weeks
Patients with genotype 2 HCV	sofosbuvir + ribavirin	12 weeks
Patients with genotype 3 HCV	sofosbuvir + peginterferon alfa + ribavirin	12 weeks
	sofosbuvir + ribavirin	24 weeks
Patients with chronic hepatitis C awaiting liver transplantation	sofosbuvir + ribavirin	Until liver transplantation
* Includes patients co-infected with HIV HCV – hepatitis C virus Note: Summary of product characteristics indicates that 12 week regimens may be extended to 24 weeks for some patients if appropriate		

Source: Sofosbuvir summary of product characteristics (Table 1)

2.2 Sofosbuvir has been studied in combination with ribavirin, with or without peginterferon alfa. The summary of product characteristics lists the following adverse reactions for sofosbuvir in combination with ribavirin only or ribavirin and peginterferon alfa: fatigue, headache, nausea and insomnia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost of sofosbuvir is £11,660.98 per 28-tab pack of 400mg tablets (excluding VAT, 'British national formulary' [BNF] June 2013). The cost of a 12 and 24 week course of treatment is £34,982.94 and £69,965.88 (excluding VAT), respectively not including the cost for ribavirin and peginterferon. Costs may vary in different settings because of negotiated procurement discounts.

2.4 Sofosbuvir has been funded since April 2014 by NHS England through an interim clinical commissioning policy in combination with daclatasvir or ledipasvir with or without ribavirin for patients who meet specific criteria and are considered to be at significant risk of death or irreversible damage within the next 12 months, irrespective of genotype. The combination of

sofosbuvir and daclatasvir or ledipasvir with or without ribavirin is not being considered in this appraisal. Both these combinations are currently within the NICE scoping programme. Full details of the clinical commissioning policy are available at: http://www.england.nhs.uk/wp-content/uploads/2014/04/sofosbuvir-pol-stat.pdf (also see Appendix B).

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of sofosbuvir within its licensed indication for treating chronic hepatitis C. The manufacturer's approach to the decision problem was in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	• Adults with chronic hepatitis C	
Intervention	• Sofosbuvir in combination with peginterferon alfa and ribavirin • Sofosbuvir in combination with ribavirin	
Comparators	• Peginterferon alfa with ribavirin • Telaprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only) • Boceprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only) • Best supportive care (including treatments to manage the liver disease without a treatment for the hepatitis C)	
Outcomes	• sustained virological response • mortality • adverse effects of treatment • health-related quality of life	

Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The manufacturer used a lifetime horizon. Costs were considered from an NHS and Personal Social Services perspective.
Other considerations	If evidence allows the following subgroups will be considered: • Co-infection with HIV • Response to previous treatment (non-response, partial response, relapsed)

3.2 The ERG stated that manufacturer's approach to the decision problem was appropriate for the NHS. However, it considered that the manufacturer did not adequately explain which patients would be considered 'ineligible' for treatment with peginterferon alfa and were of the opinion that given a choice, patients may decline interferon-based therapy.

4 Clinical-effectiveness evidence

4.1 The manufacturer identified and included 13 studies that investigated the effect of sofosbuvir in combination with ribavirin alone or ribavirin and peginterferon alfa in adults with HCV who were either treatment naïve or previously treated. Of the 13 included studies, 4 were phase 3 randomised controlled trials in people with genotype 2 and 3 HCV (FISSION [treatment naïve], FUSION [treatment experienced], POSITRON [treatment naïve and experienced], VALENCE [treatment naïve and experienced), 3 were phase 2 randomised controlled trials in treatment naïve people with genotype 1, 4, 5 and 6 HCV (QUANTUM, SPARE, ATOMIC), 1 was a phase 2 randomised controlled trial in treatment naïve people with genotype 2 and 3 HCV (ELECTRON). The manufacturer also included 4 non-randomised studies: NEUTRINO, LONESTAR-2, PHOTON-1, P7977-2025) and 1 study containing both a randomised controlled trial and single cohort (PROTON). For the clinical

effectiveness section of its submission, the manufacturer focused on the 5 phase 3 studies:

- genotype 1,4,5 and 6 – NEUTRINO
- genotype 2 and 3 - FISSION, FUSION, POSITRON and VALENCE.

Most of the data obtained from the VALENCE randomised controlled trial were reported after it had been converted to a non-randomised multi-cohort study (clarified by the manufacturer on request from the ERG). See Table 2 for a summary of the studies included in the manufacturer's submission.

Table 2 Summary of studies included in the manufacturer's submission

Population	Trial name	Phase	Trial arms
HCV genotype 1, 4, 5 and 6 treatment naïve	NEUTRINO (single cohort)	3	1. sofosbuvir + peginterferon alfa+ ribavirin 12 weeks
	QUANTUM (5-arm randomised controlled trial and single cohort)	2	1. sofosbuvir + ribavirin 12 weeks 2. sofosbuvir + ribavirin 24 weeks *Arms 3-5 excluded from manufacturer's submission and ERG report (drug outside scope)* *3. GS-0938 (an experimental treatment) up to 24 weeks* *4. GS-0938 + sofosbuvir up to 24 weeks* *5. GS-0938 + sofosbuvir + ribavirin up to 24 weeks* 6. *Single cohort 'retreatment group' in MS but excluded from ERG report (patients had atypical treatment history on an experimental drug)*
	ATOMIC (3-arm randomised controlled trial) [a]	2	1. sofosbuvir + peginterferon alfa+ ribavirin 12 weeks 2. sofosbuvir + peginterferon alfa+ ribavirin 24 weeks 3. *Arm included in MS but excluded from ERG report (unlicensed sofosbuvir monotherapy)*
	SPARE (2-arm randomised controlled trial, phase 2, and one non-randomised cohort) genotype 1 only	2	1. sofosbuvir + ribavirin 24 weeks single cohort 2. sofosbuvir + ribavirin 24 weeks randomised arm 3. sofosbuvir +low-dose (600mg) ribavirin 24 weeks randomised arm *(technically unlicensed ribavirin dosing - arm included in MS and also in ERG report for supporting information, based on clinical expert advice)*
HCV genotype 2/3 treatment naïve	FISSION (2-arm randomised controlled trial)	3	1. sofosbuvir + ribavirin 12 weeks 2. peginterferon alfa+ 800mg ribavirin 24 weeks

Population	Trial name	Phase	Trial arms
	ELECTRON (4-arm randomised controlled trial, and 4 non-randomised cohorts)	2	1. Randomised arm: sofosbuvir + ribavirin 12 weeks 2-3. *Randomised arms mentioned narratively in MS but excluded from ERG report (unlicensed durations of peginterferon alfa)* 4. Randomised arm: sofosbuvir + peginterferon alfa+ ribavirin 12 weeks 5-6. *Non-randomised cohorts mentioned narratively in MS but excluded from ERG report (unlicensed sofosbuvir regimens)* 7-8. *Non-randomised cohorts excluded from MS and ERG report (unlicensed sofosbuvir regimens)*
	PROTON (3-arm randomised controlled trial and single cohort)	*2*	*1-3. Randomised arms of response-guided sofosbuvir therapy excluded from MS and ERG report (unlicensed sofosbuvir regimens)* 4. sofosbuvir + peginterferon alfa+ ribavirin 12 weeks
HCV genotype 2/3 treatment experienced	FUSION (2-arm randomised controlled trial	3	1. sofosbuvir + ribavirin 12 weeks + matching placebo 4 weeks 2. sofosbuvir + ribavirin 16 weeks
	LONESTAR-2 (single cohort)	2	1. sofosbuvir + peginterferon alfa+ ribavirin 12 weeks
HCV genotype 2/3 treatment naive and experienced	POSITRON (2-arm randomised controlled trial)	3	1. sofosbuvir + ribavirin 12 weeks 2. Placebo 12 weeks
	VALENCE (initially 2-arm randomised controlled trial, subsequently modified to 3-cohort study)	3	Initial randomised design: 1. sofosbuvir + ribavirin 12 weeks (HCV genotype 2/3) 2. Placebo 12 weeks (HCV genotype 2/3) Modified design: 1. sofosbuvir + ribavirin 12 weeks (HCV genotype 2) 2. sofosbuvir + ribavirin 12 weeks (HCV genotype 3) 3. sofosbuvir + ribavirin 24 weeks (HCV genotype 3)
HCV genotype 1/2/3 with HIV co-infection	PHOTON-1 (4 cohort study)	3	1. sofosbuvir + ribavirin 24 weeks (HCV genotype 1, treatment naive) 2. sofosbuvir + ribavirin 12 weeks (HCV genotype 2, treatment naive) 3. sofosbuvir + ribavirin 12 weeks (HCV genotype 3, treatment naive) 4. sofosbuvir + ribavirin 24 weeks (HCV genotype 2/3, treatment experienced)
Any HCV genotype, pre-liver-transplant	P7977-2025 (single cohort) [a]	2	1. sofosbuvir + ribavirin 12-48 weeks

Source: ERG report pages 20-21; manufacturer's submission pages 57-62.

a. Note: This trial did not inform the manufacturer's economic model.

Evidence in people with genotype 1, 4, 5 or 6 HCV (treatment naïve)

4.2 One open-label, single-arm study (NEUTRINO) evaluated the efficacy and safety of sofosbuvir in combination with peginterferon alfa and ribavirin treatment for 12 weeks in treatment-naive patients with chronic genotype 1, 4, 5, or 6 HCV infection. The primary efficacy analysis assessed whether patients who received treatment for 12 weeks achieved a rate of sustained virological response at 12 weeks greater than the historical control rate of 60%. The 60% sustained virological response null rate was derived from Phase 3 telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data and took into account the higher number of cirrhotic patients in the NEUTRINO study, the improved safety profile of sofosbuvir combination treatment, and its shorter treatment duration. Superiority would be established if the p-value from a two-sided one-sample exact test was < 0.05. Treated subjects (n = 327) had a median age of 54 years (ranging in ages from 19 to 70 years); 64% of the subjects were male; 78% had baseline HCV RNA greater than 6 $\log_{10}$ IU/mL (viral load, or the number of virus particles floating in the blood; a viral load less than 6 $\log_{10}$ IU/mL has been linked to better response to treatment); 17% had cirrhosis; 89% had HCV genotype 1 and 11% had HCV genotype 4, 5 or 6.

Evidence in people with genotype 2 or 3 HCV

Treatment naïve

4.3 A randomised, open-label, active-controlled study (FISSION) evaluated the efficacy and safety of sofosbuvir and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 24 weeks in treatment-naive patients with chronic genotype 2 or 3 HCV infection. Treatment with peginterferon alfa and ribavirin for 24 weeks was selected as the control in this study because it is the recommended treatment for this patient population. The primary outcome was sustained virological response at 12 weeks. The noninferiority of sofosbuvir and ribavirin compared with peginterferon alfa and ribavirin for sustained virological

response at 12 weeks (primary endpoint) was tested first. If noninferiority was established, then the superiority of sofosbuvir and ribavirin relative to peginterferon alfa-2a and ribavirin was tested. Superiority was demonstrated if the 2-sided p-value associated with the test of superiority was < 0.05. Patients were randomised in a 1:1 ratio and stratified by the presence or absence of cirrhosis, HCV genotype (2 versus 3) and baseline HCV RNA level (<6 $\log_{10}$ IU/mL versus ≥6 $\log_{10}$ IU/mL). Patients with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio. Treated subjects (n = 499) had a median age of 50 years (ages ranging from 19 to 77 years); 66% of the subjects were male; 57% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU/mL; 20% had cirrhosis; 72% had HCV genotype 3.

Treatment experienced

4.4 One randomised, double-blind study (FUSION), evaluated the efficacy and safety of sofosbuvir and ribavirin treatment for either 12 or 16 weeks in treatment-experienced patients (who had no response to prior HCV treatment [25%] or who lost their initial response during prior treatment or after the end of prior HCV treatment [75%]) with chronic genotype 2 or 3 HCV infection. The 2 primary statistical hypotheses of this study were that the sustained virological response rate at 12 weeks in both treatment groups should be higher than a null rate of 25% for patients with genotype 2 or 3 HCV infection and an expected improved safety profile and shorter duration of treatment. Both hypotheses were tested at a significance level of 0.025. Subjects were randomised in a 1:1 ratio and stratified by the presence or absence of cirrhosis and HCV genotype (2 or 3). Treated subjects (n = 201) had a median age of 56 years (ranging in ages from 24 to 70 years); 70% of the subjects were male; 73% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU/mL; 34% had cirrhosis; 63% had HCV genotype 3.

Treatment naïve or treatment experienced

4.5 One randomised, double-blind, placebo-controlled, phase 3 study (VALENCE) evaluated sofosbuvir in combination with ribavirin (dosage amended by weight) for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve a sustained virological response with prior interferon-based treatment, including those with compensated cirrhosis. The study was designed as a direct comparison of sofosbuvir and ribavirin versus placebo for 12 weeks. However, based on emerging data, the study was unblinded and all patients with HCV genotype 2 continued to receive sofosbuvir and ribavirin for 12 weeks, whilst treatment for patients with HCV genotype 3 was extended to 24 weeks. Eleven patients with HCV genotype 3 had already completed treatment with sofosbuvir and ribavirin for 12 weeks at the time of the amendment. Treated subjects (n = 419) had a median age of 51 years (ages ranging from 19 to 74 years); 60% of the subjects were male; the mean baseline HCV RNA level was 6.4 $\log_{10}$ IU/mL; 21% had cirrhosis; 78% had HCV genotype 3; around 65% of previously treated patients included had lost their initial response during prior treatment, 25% lost their response after the end of prior treatment, and 7% were interferon intolerant..

Interferon treatment intolerant, ineligible or unwilling

4.6 One randomised, double-blind, placebo-controlled study (POSITRON) evaluated the efficacy and safety of sofosbuvir and ribavirin treatment compared with placebo for 12 weeks in patients with chronic genotype 2 or 3 HCV infection who were interferon intolerant, ineligible (medical conditions precluding interferon therapy), or unwilling. Similar proportions of patients with genotype 2 and 3 HCV infection were enrolled (51% and 49%, respectively). Patients were randomised in a 3:1 ratio to receive either sofosbuvir and ribavirin or placebo. The placebo control group in this study was selected because there is no current treatment available for HCV-infected patients who are interferon intolerant, interferon ineligible, or unwilling to receive treatment with interferon. The difference in sustained

virological response rate at 12 weeks between treatment groups was assessed for superiority. Superiority would be demonstrated if the p-value was < 0.05. Patients were stratified by the presence or absence of cirrhosis. Treated patients (n = 278) had a median age of 54 years (ages ranging from 21 to 75 years); 54% were male; 70% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU/mL; 16% had cirrhosis; 49% had HCV genotype 3. The proportions of patients who were interferon intolerant, ineligible, or unwilling were 9%, 44%, and 47%, respectively. Most patients had not received prior HCV treatment (81.3%).

HIV co-infected patients

4.7 Sofosbuvir was studied in PHOTON-1, an open-label clinical study evaluating the safety and efficacy of 12 or 24 weeks of treatment with sofosbuvir and ribavirin in patients with genotype 1, 2 or 3 chronic hepatitis C co-infected with HIV. Patients with genotype 2 or 3 HCV were either treatment-naïve or experienced, whereas those with genotype 1 HCV were all naïve to prior treatment. Treatment duration was 12 weeks in treatment-naïve patients with genotype 2 or 3 HCV infection, and 24 weeks in treatment-experienced patients with genotype 3 HCV infection, as well as patients with genotype 1 HCV infection. Patients received 400mg sofosbuvir and weight-based ribavirin (1000mg for subjects weighing <75kg or 1200mg for subjects weighing ≥75kg). Patients were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm^3 or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm^3. At the time of enrolment, 95% of patients received antiretroviral therapy. Preliminary sustained virological response rates at 12 weeks were available for 210 subjects.

Patients awaiting liver transplantation

4.8 An open-label clinical study (P7977-2025) evaluated the safety and efficacy of sofosbuvir and ribavirin in HCV infected patients prior to undergoing liver transplantation administered pre-transplant to prevent post-transplant HCV reinfection. The primary endpoint of the study was

post-transplant virological response (HCV RNA undetectable at 12 weeks post-transplant). HCV infected patients, regardless of genotype, with hepatocellular carcinoma (HCC) eligible for liver transplant received 400mg sofosbuvir and 1000-1200mg ribavirin daily for a maximum of 24 weeks, subsequently amended to 48 weeks, or until the time of liver transplantation, whichever occurred first. An interim analysis was conducted on 61 patients who received sofosbuvir and ribavirin; the majority of patients had HCV genotype 1. Of these patients, 44 underwent liver transplantation following up to 48 weeks of treatment with sofosbuvir and ribavirin; 41 had no detectable HCV RNA at the time of transplantation.

Clinical effectiveness of sofosbuvir

Evidence in people with genotype 1, 4, 5 or 6 HCV

Treatment naïve - NEUTRINO

4.9 The manufacturer reported a statistically significant improvement in sustained virological response rates following 12 weeks of treatment with sofosbuvir, peginterferon alfa and ribavirin in treatment naïve patients with genotype 1, 4, 5, or 6 HCV. At 12 weeks after the end of treatment, 90% of patients (95% confidence interval [CI] 87% to 93%, p<0.001) had a sustained virological response. Pre-specified analyses demonstrated that all subgroups (age, sex, race, ethnicity, cirrhosis, HCV genotype, HCV RNA level, body mass index (BMI), alanine aminotransferase (ALT) level (a biomarker of liver damage associated with the progression of fibrosis), and interleukin 28B (IL28B) host gene polymorphism) had sustained virological response rates at 12 weeks of ≥80%.

4.10 The manufacturer investigated covariate effects and found that cirrhosis and non-CC IL28B polymorphism (see section 1.4 for explanation) were both associated with a reduced sustained virological response rate at 12 weeks: 92% (95% CI 89% to 95%) among patients without cirrhosis and 80% (95% CI 67%, 89%) among those with cirrhosis (p=0.0018) and 98%

(95% CI 93% to 100%) among patients with the IL28B CC genotype polymorphism compared with 87% (95% CI 82% to 91%) among those with the non-CC IL28B polymorphism (p=0.006). Sustained virological response rates at 12 week were 90% for people with genotype 1 HCV and 97% for people with genotype 4, 5 or 6. Response rates did not appear to be affected by race or ethnicity. In all other subgroups, the differences in response rates were less than 10%. By week 2 and 4 of treatment, 91% (299/327) and 99% (321/325) of patients had undetectable HCV RNA. No patients experienced on-treatment virological failure. Relapse after virological response at the end of treatment occurred in 28 of 327 patients after stopping treatment, 25 of whom had completed 12 weeks of treatment and 3 who did not complete the treatment course. Results for the primary and secondary outcomes of the NEUTRINO study are presented in Table 3.

Table 3 Response rates in genotype 1, 4, 5 and 6 HCV, treatment naive patients (NEUTRINO)

Response	(N=327)
HCV RNA undetectable, n/N (%)	
During treatment	
At Week 2	299/327 (91)
At Week 4	321/325 (99)
At last observed measurement	326/327 (>99)
Post-treatment	
At Week 4 (sustained virological response)	302/327 (92)
At Week 12 (sustained virological response)	295/327 (90)
Virological breakthrough during treatment, n (%)	0
Relapse in patients with HCV RNA <LLOQ at end of treatment, n/N (%)	
Patients who completed treatment	25/320 (8)
Patients who did not complete treatment	3/6 (50)

Source: Manufacturer's submission, page 97, table 21

4.11 The manufacturer reported the health-related quality of life data obtained during the study, including the Chronic Liver Disease Questionnaire - Hepatitis C (CLDQ-HCV), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Work Productivity and Activity Impairment (WPAI), and Short Form-36 items (SF-36)for the NEUTRINO study which indicated that there were [redacted] differences in

health-related quality of life scales between baseline and the end-of treatment responses and that scores returned to baseline values by the post-treatment week 12 visit. The data suggest that treatment [redacted] (academic in confidence).

Treatment-experienced

4.12 No studies were identified which included treatment-experienced people with genotype 1, 4, 5, or 6 HCV.

Evidence in people with genotype 2 or 3 HCV

Treatment naïve

FISSION

4.13 Results from the FISSION study in treatment naïve patients with genotype 2 or 3 HCV showed that at 12 weeks after the end of treatment, the sustained virological response rate was 67% in both treatment groups. Sofosbuvir in combination with ribavirin was non-inferior to peginterferon alfa-2a and ribavirin with respect to the primary endpoint. The absolute difference between treatment groups after adjustment for stratification was 0.3% (95% CI −7.5 to 8.0, non-inferiority p<0.001). The proportion of patients with a sustained virological response at 24 weeks was 67% in the sofosbuvir and ribavirin arm of the study and 65% in the peginterferon alfa-2a and ribavirin arm. Results for the primary and secondary outcomes of the FISSION study are presented in Table 4.

4.14 The manufacturer investigated covariate effects and found that genotype 2 HCV and absence of cirrhosis were associated with higher sustained virological responses in people treated with sofosbuvir and ribavirin. The sustained virological response rate at 12 weeks among patients with genotype 2 or 3 HCV in the sofosbuvir and ribavirin arm was 97% (95% CI

90% to 100%) and 56% (95% CI 48% to 63%), respectively. The sustained virological response rate at 12 weeks among patients with genotype 2 or 3 HCV in the peginterferon alfa-2a and ribavirin arm was 78% (95% CI 66% to 87%) and 63% (95% CI 55% to 70%), respectively. When stratified by absence or presence of cirrhosis, the sustained virological response rate at 12 weeks for patients treated with sofosbuvir and ribavirin was 72% (95% CI 65% to 78%) among patients without cirrhosis and 47% (95% CI 33% to 62%) among those with cirrhosis. For people receiving peginterferon alfa-2a and ribavirin these rates were 74% (95% CI 67% to 80%) and 38% (95% CI 25% to 53%), respectively. The sustained virological response rate at 12 weeks in people with genotype 2 HCV was 98% in those without cirrhosis and 91% in those with cirrhosis, compared with 82% and 62% respectively in people receiving peginterferon alfa-2a and ribavirin. The sustained virological response rate at 12 weeks in people with genotype 3 HCV with cirrhosis was similar between both treatment groups (34% in people receiving sofosbuvir and ribavirin compared with 30% in people receiving peginterferon alfa-2a and ribavirin).

4.15 The manufacturer reported that relapse occurred in 29% (n=71) of the 242 patients who completed treatment with sofosbuvir and ribavirin, and in 43% (n=3) of the 7 patients who did not complete this treatment. In the peginterferon alfa-2a and ribavirin arm, 20% (n=37) of the 188 patients who completed treatment relapsed as did 31% (n=9) of the 29 patients who did not complete peginterferon alfa-2a and ribavirin treatment. There was a greater than 99% correlation between sustained virological response rates at 12 and 24 weeks following treatment among patients who received sofosbuvir and ribavirin. One of 166 patients who could be evaluated had a virological relapse after 12 weeks after the end of treatment.

Table 4 Response rates in genotype 2 or 3 HCV, treatment naive patients (FISSION)

Response	Sofosbuvir and ribavirin 12 weeks (N=253)	Peginterferon alfa- and ribavirin 24 weeks (N=243)
HCV RNA undetectable, n/N (%)		
During treatment		
At Week 2	231/251 (92)	76/241 (32)
At Week 4	249/250 (>99)	158/236 (67)
At last observed measurement	249/253 (98)	217/243 (89)
Post-treatment		
Sustained virological response at week 4	187/253 (74)	181/243 (74)
Sustained virological response at week 12	170/253 (67)	162/243 (67)
Sustained virological response at week 24	(67)	(65)
Virological breakthrough during treatment, n (%)	1 (<1)	18 (7)
Relapse in patients with HCV RNA undetectable at end of treatment†, n/N (%)		
Patients who completed treatment	71/242 (29)	37/188 (20)
Patients who did not complete treatment	3/7 (43)	9/29 (31)

Source: Manufacturer's submission, page 101, table 23.

4.16 The manufacturer collected data on health-related quality of life using SF-36 from the FISSION study. For the composite Physical Component score, patients in the sofosbuvir and ribavirin treatment group [redacted] and the peginterferon alfa ribavirin peginterferon alfa-2a and ribavirin treatment group [redacted] (academic in confidence).

Treatment-experienced patients

FUSION

4.17 The FUSION study compared sofosbuvir and ribavirin for 12 or 16 weeks in treatment-experienced patients (who had no response to treatment or who had relapsed) with chronic genotype 2 or 3 HCV infection. The sustained virological response rate at 12 weeks was 50% (95% CI 40 to 60%) in the "12-week-plus-placebo group" and 73% (95% CI 63 to 81%) in the 16-week therapy group. These response rates were statistically superior to an historic 'control' rate of 25% (Table 5).

Table 5 Response rates in genotype 2 or 3 HCV, treatment experienced patients (FUSION)

Response	Sofosbuvir and ribavirin 12 weeks (n=100)	Sofosbuvir and ribavirin 16 weeks (n=95)
HCV RNA undetectable, n/N (%)		
During treatment		
At Week 2	81/100 (81)	83/95 (87)
At Week 4	97/100 (97)	93/95 (98)
At Week 12	100/100 (100)	95/95 (100)
At Week 16	-	95/95 (100)
Post-treatment		
Sustained virological response at week 4	56/100 (56)	73/95 (77)
Sustained virological response at week 12	50/100 (50)	69/95 (73)
Virological breakthrough during treatment, n (%)	0	0
Relapse in patients with HCV RNA undetectable at end of treatment, n/N (%)		
Patients who completed treatment	46/99 (46)	26/95 (27)
Patients who did not complete treatment	1/1 (100)	0

Source: Manufacturer's submission, page 107, table 25.

4.18 The manufacturer investigated covariate effects and found that HCV genotype and cirrhosis were associated with differences in sustained virological response rates in people treated with sofosbuvir and ribavirin. Genotype 2 HCV was associated with a higher rate of sustained virological response at week 12 in both treatment arms compared with genotype 3 HCV (12-week: odds ratio [OR] 21.5; 95% CI 6.1 to 75.1; p<0.0001; 16-week: OR 10.5; 95% CI 2.3 to 49.2; p=0.0028). The absence of cirrhosis was associated with a higher rate of sustained

virological response among patients who received 12 weeks of treatment (OR 3.1; 95% CI 1.0 to 9.5; p=0.046), particularly among those with genotype 3 HCV infection. The manufacturer reported that the difference observed between the 12-week and 16-week treatment groups (irrespective of the presence of cirrhosis) suggested that patients with genotype 3 HCV infection would achieve additional benefit from the longer 16-week treatment duration with sofosbuvir (Table 6).

Table 6 Sustained virological response rate by genotype and presence of cirrhosis (FUSION)

Response n/N ,%	Sofosbuvir and ribavirin 12 weeks (n=100)	Sofosbuvir and ribavirin 16 weeks (n=95)	Sofosbuvir and ribavirin 12 weeks vs. sofosbuvir and ribavirin 16 weeks, proportional difference (95% CI)
genotype 2, no cirrhosis	25/26 96%	22/23 100%	−3.8% (−20.2%, 11.3%)
genotype 2 and cirrhosis	6/10 60%	7/9 78%	−17.8% (−58.0%, 26.8%)
genotype 3, no cirrhosis	15/38 37%	63% 25/40	−25.7% (−46.5%, −2.9%)
genotype 3 and cirrhosis	5/26 19%	14/23 61%	−41.6% (−65.0%, −11.8%)

Source: Manufacturer's submission, page 110, table 26.

4.19 The manufacturer reported the health-related quality of life data obtained during the study. The CLDQ-HCV score did not decrease significantly in either treatment group and there were no significant differences in overall scores between the groups. The FACIT-F, WPAI, and SF-36 quality of life scores [redacted] (academic in confidence).

Treatment naïve and treatment experienced combined

POSITRON (interferon intolerant, ineligible or unwilling)

4.20 The POSITRON study compared sofosbuvir and ribavirin for 12 weeks with placebo in people with genotype 2 or 3 HCV who were interferon

intolerant, ineligible (medical conditions precluding interferon therapy), or unwilling to receive interferon treatment, regardless of treatment history. The manufacturer reported that the sustained virological response rate at 12 weeks was 78% (95% CI 72% to 83%) for people receiving sofosbuvir and ribavirin compared with 0% in the placebo group (p<0.001) (Table 7).

Table 7 Response during and after treatment period for treatment naïve and experienced patients with genotype 2 or 3 (POSITRON)

Response	sofosbuvir and ribavirin 12 weeks (N=207)	placebo 12 weeks (N=71)
HCV RNA undetectable, n/N (%)		
During treatment		
At Week 2	186/205 (91)	0/70
At Week 4	202/204 (99)	0/70
At Week 12	202/202 (100)	0/71
Post-treatment		
Sustained virological response at Week 4	172/207 (83)	0/68
Sustained virological response at Week 12	161/207 (78)	0/68
Virological breakthrough during treatment, n (%)	0	-
Relapse in patients with HCV RNA undetectable at end of treatment, n/N (%)		
Patients who completed treatment	40/201 (20)	-
Patients who did not complete treatment	2/4 (50)	-

Source: Manufacturer's submission, page 114, table 28.

4.21 The manufacturer investigated covariate effects and showed that genotype 2 HCV was associated with a higher rate of sustained virological response at 12 weeks compared with genotype 3 HCV (OR 8.7; 95% CI 3.6, 20.7; p<0.0001). Among patients treated with sofosbuvir and ribavirin, sustained virological response rates at 12 weeks after treatment were 93% with genotype 2 HCV and 61% with genotype 3 HCV. The sustained virological response rates in patients with genotype 2 HCV were similar in people with and without cirrhosis (94% vs. 92% for no cirrhosis). The sustained virological response rate in people with genotype 3 HCV without cirrhosis was higher than in those with cirrhosis (68% compared with 21%) (Table 8).

Table 8 Sustained virological response rate by genotype and presence of cirrhosis (POSITRON)

Classification	Genotype 2 HCV (N=109)	Genotype 3 HCV (N=98)
Sustained virological response at 12 weeks after treatment end, n/N (%)		
All	101/109 (93)	60/98 (61)
No cirrhosis	85/92 (92)	57/84 (68)
Cirrhosis	16/17 (94)	3/14 (21)

Source; Manufacturer's submission, page 117, table 29

4.22 The manufacturer reported the health-related quality of life data obtained during the treatment period (baseline through to week 12) which showed decreases (worsening) in the eight SF-36 scales and the Mental Component and Physical Component scores in both treatment groups. In the sofosbuvir and ribavirin group, the differences were statistically significant ($p<0.001$) from baseline in the Physical Function scale, Role Physical, Vitality, Social Functioning, Role Emotional, and Mental Health scales; however, there were no significant differences from placebo at any time point.

VALENCE

4.23 The manufacturer provided results for some outcomes derived from an interim analysis of the VALENCE study which showed that people with genotype 2 HCV receiving sofosbuvir and ribavirin for 12 weeks had a sustained virological response rate at 12 weeks following treatment of [redacted]. People with genotype 3 HCV receiving sofosbuvir and ribavirin for 24 weeks had a sustained virological response rate at 12 weeks following treatment of [redacted]The manufacturer reported that in all subgroups of patients with genotype 2 HCV treated with sofosbuvir and ribavirin for 12 weeks, the sustained virological response rates were 88% or higher at 12 weeks following treatment, irrespective of prior treatment experience and presence/absence of cirrhosis. In treatment-naive patients with genotype 3 HCV, sofosbuvir and ribavirin treatment for 24 weeks resulted in sustained virological response rates greater than 90% at 12 weeks following treatment, irrespective of cirrhosis status. In treatment-experienced patients with genotype 3 HCV, sofosbuvir and ribavirin

treatment for 24 weeks resulted in sustained virological response rates of 60% and 85% in those with or without cirrhosis, consistent with other studies (academic in confidence).

HCV/HIV co-infection

PHOTON-1

4.24 Results from the PHOTON 1 study (of patients with HCV/HIV co-infection) showed that treatment with sofosbuvir and ribavirin for 12 weeks in people with genotype 2 or 3 HCV and 24 weeks in people with genotype 1 HCV resulted in sustained virological response rates at 12 weeks following treatment similar to those reported for patients with HCV mono-infection irrespective of HCV genotype (≥93%; interim analysis). Similar safety, efficacy and tolerability was reported in HIV/HCV co-infected patients compared to HCV mono-infected patients.

Pre-Liver Transplant

P7977-2025 Study

4.25 The manufacturer provided results for the P7977-2025 study in people awaiting a liver transplant who received treatment with sofosbuvir and ribavirin for up to 48 weeks ending immediately prior to transplantation. Results suggested that treatment prevented HCV recurrence in 64% of patients compared with a 100% historical risk of reinfection in the absence of prophylaxis. During sofosbuvir and ribavirin treatment, HCV RNA suppression in patients with well-compensated cirrhosis awaiting transplantation for hepatocellular carcinoma was rapid and similar to other patient populations treated with sofosbuvir regimens.

Meta-analysis

4.26 The manufacturer did not conduct a meta-analysis of the available clinical studies. The ERG considered that this decision appeared to be appropriate, given that most studies focused on comparing different sofosbuvir combination treatments for varying durations, and included

different patient populations based on genotype, cirrhotic involvement and treatment experience.

Mixed treatment comparison

4.27 The manufacturer conducted a mixed treatment comparison to explore the comparative data for sofosbuvir versus other relevant comparators. The manufacturer reported several limitations to the mixed treatment comparison (MTC) it conducted, explaining that the results could not be considered robust. Due to the absence of data, a mixed treatment comparison network could not be formed for all the relevant populations and the comparison was only conducted for treatment naive interferon-eligible patients with genotype 1, 2 or 3 HCV infection. The manufacturer's economic model required that efficacy data were split out by cirrhotic and non-cirrhotic status and these data were not available for all trials. In patients with genotype 1 HCV, a network including sofosbuvir was only possible by linking two small phase 2 trials (ATOMIC and PROTON) which only included non-cirrhotic patients. In patients with genotype 2 or 3 HCV, the MTC results were based on cirrhotic and non-cirrhotic patients combined. The ERG stated that the manufacturer's justification for not using the mixed treatment comparison results in the economic model was reasonable.

Adverse effects of treatment

4.28 The manufacturer presented data on adverse events for the 5 phase 3 studies (NEUTRINO, FISSION, FUSION, POSITRON and VALENCE). The most common adverse events among patients receiving sofosbuvir and ribavirin therapy (with or without peginterferon alfa) were fatigue, headache, anaemia, nausea, insomnia, irritability, rash, pruritis, myalgia, decreased appetite, influenza-like illness, chills, pyrexia, and neutropenia. Among these events, fatigue and headache were usually the most frequent, affecting more than 40% of the patients in some studies. Adverse events from these studies are generally consistent with adverse events reported in other publications on sofosbuvir which were not

included in the manufacturer's submission. In the studies comparing sofosbuvir and ribavirin with placebo, common adverse events occurred more frequently or at similar frequencies in both groups, whereas in studies comparing sofosbuvir and ribavirin with peginterferon alfa-2a and ribavirin, the common adverse events that occurred in 10% or more of patients in at least one group were consistently more frequent in the peginterferon alfa-2a and ribavirin arms which the ERG stated was suggestive that sofosbuvir had an improved safety profile compared to standard of care (peginterferon alfa plus ribavirin).

Health-related quality of life

4.29 Generally health-related quality of life, assessed using the SF-36 in the FISSION, FUSION and POSITRON studies, [redacted] The ERG noted that no comparisons were made of 12 week or 24 week regimens of sofosbuvir and ribavirin and only 40-42% of health related quality of life questionnaire responses were received from each arm of the trial and used in the manufacturer's health-related quality of life analyses. In FUSION, both the 12- and 16-week durations of sofosbuvir and ribavirin [redacted] In NEUTRINO, [redacted]

[redacted].

4.30 The ERG commented that the manufacturer's interpretation of the clinical evidence is on the whole justified and unbiased. However, the ERG considered that most of the evidence does not directly address the decision problem, due to the lack of head-to-head studies against current standard of care comparators. Additionally, the ERG highlighted the following areas of particular uncertainty in the manufacturer's submission:

- no studies were included which examined the efficacy of sofosbuvir within its licenced indication for treatment experienced patients with genotype 1 HCV, a patient group who have a high unmet treatment need
- data supporting the treatment regimens licensed for use in patients with genotype 3 HCV predominantly come from 2 small phase 2 studies and from 1 phase 3 study (VALENCE), The results from the VALENCE study need to be interpreted with caution because randomisation was broken, with patients being switched from 12 to 24 weeks of sofosbuvir and ribavirin during the study. 11 patients were not moved over to 24 weeks of therapy. Consequently, the ERG believes it is uncertain what the sustained virological response rate at 12 weeks after treatment would have been if these patients had been included in the 24 week treatment arm.
- health-related quality of life results have uncertain relevance in the FISSION trial as results were only reported for 40-42% of the participants randomised per arm, and in the VALENCE trial because only unpublished summary results are available.

5 Comments from other consultees

5.1 The clinical specialists stated that a cure for hepatitis C would prevent progression of HCV-related liver disease and hence life-threatening conditions such as cirrhosis and liver cancer and would even result in

fibrosis regression and the restoration of a normal liver. According to clinical specialists, a cure for hepatitis C could also reduce the symptoms of chronic HCV infection, such as (sometimes extreme) tiredness, joint pain, cognitive impairment, depression, thus restoring quality of life. The clinical specialists stated that chronic HCV infection could often significantly impair people's social life, libido, ability to work because of the physical and mental symptoms. In addition, many people experience stigma because of HCV's association with drug use.

5.2 The clinical specialists commented that the side effects seen in the studies of sofosbuvir predominantly relate to the side effects observed during interferon and ribavirin treatment alone. Pegylated interferon is a difficult drug to tolerate for most but not all patients, as are boceprevir and telaprevir (licensed for people with genotype 1 HCV infection). The clinical specialists stated that there is some evidence that interferon induces long term side effects that persist after the end of treatment in an as yet undetermined sub-set of patients. The use of sofosbuvir will lessen the amount of interferon and ribavirin needed due to the shorter treatment duration and in the case of patients with genotype 2 (and possibly 3) HCV, they may be able to receive peginterferon-free treatment. The clinical specialists highlighted that sofosbuvir on its own has a relatively mild side effect profile. According to clinical specialists, sofosbuvir would most benefit those who are likely to be unable to be treated with interferon for a full standard treatment course and those with genotype 2 or 3 HCV who are intolerant of or unwilling to be treated with peginterferon alfa. However, clinical specialists commented that not all genotypes will get the same benefit. According to clinical specialists sofosbuvir would also be particularly useful for pre and post liver transplant patients with active HCV.

5.3 According to patient experts, sofosbuvir offers a better chance of a cure for HCV infection than the current standard of care. Currently, the length and difficulty of peginterferon alfa and ribavirin treatment is a major barrier for people seeking treatment. The patient experts also believe that the

improvements offered by sofosbuvir will encourage more people to get tested and seek treatment, potentially saving their lives and preventing onward transmission.

5.4 The clinical specialists highlighted that there has been a reluctance to treat people who take intravenous drugs, partly from erroneous beliefs that they would not adhere to treatment or that they would become re-infected. There is evidence to show that neither of these happens to any significant degree. According to clinical specialists, failure to specifically include intravenous drug users in some form in the final guidance may lead to their continued exclusion. Nevertheless, the complexity and duration of current standard of care regimens can be a substantial barrier to treating many patients. The clinical specialists highlighted the importance of simplifying treatment by adopting the use of new direct-acting antiviral drugs, such as sofosbuvir.

6 Cost-effectiveness evidence

6.1 The manufacturer identified 112 cost-effectiveness studies in people with chronic HCV that reported results from treatments currently used for HCV. No studies were identified that compared sofosbuvir to alternative treatments.

Manufacturer's economic model

6.2 The manufacturer submitted a de novo economic analysis that assesses the cost effectiveness of sofosbuvir treatment in people with chronic hepatitis C who are considered suitable candidates for treatment with sofosbuvir. These analyses included the following populations:

- Genotype 1 HCV treatment-naïve patients, including those who are interferon eligible or unsuitable for interferon
- Genotype 2 HCV or Genotype 3 HCV
  - Treatment-naïve patients, including those who are interferon eligible or unsuitable for interferon

  - Treatment-experienced patients, including those who are interferon eligible or unsuitable for interferon
- Genotype 4, 5 or 6 HCV treatment-naïve patients

An NHS and Personal and Social Services perspective was taken and a lifetime horizon was used, with costs and outcomes discounted at 3.5%.

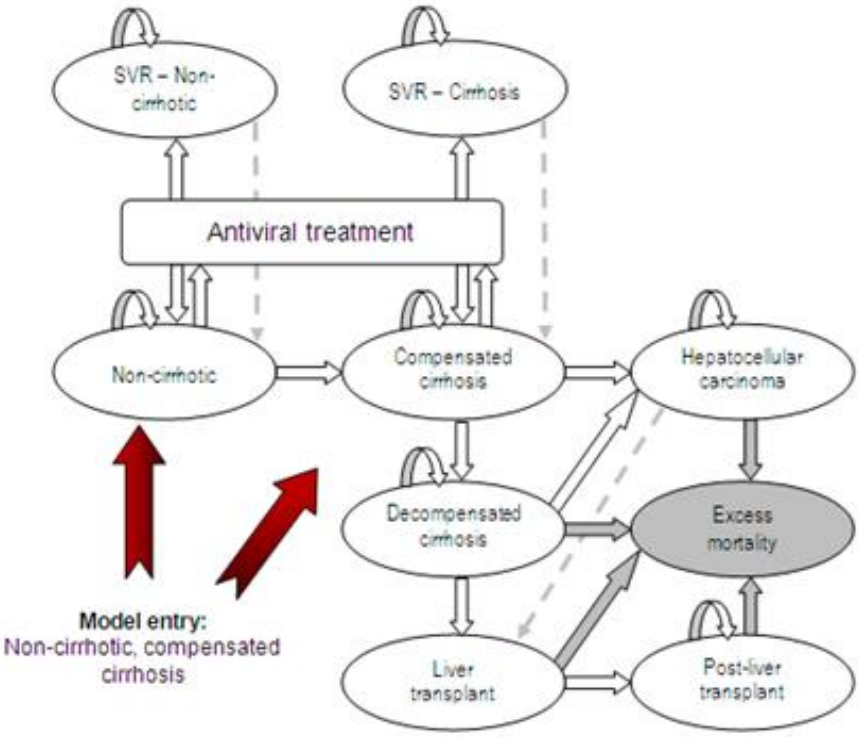
6.3 The manufacturer stated that the licence for sofosbuvir also covers patients with genotype 1 HCV infection who are HCV treatment-experienced due to the high unmet need and lack of suitable treatment. However, the manufacturer stated that it extrapolated the sustained virological response rates for this population using an FDA model and as such an economic analysis in this population was not conducted. The manufacturer also stated that the main economic analyses presented in the manufacturer's submission only consider the HCV mono-infected populations and data inputs and incremental cost effectiveness ratios (ICERs) for HCV/HIV co-infected populations were reported separately in the manufacturer's appendix 10 to its submission.

6.4 The manufacturer developed a Markov model to estimate the expected costs and benefits associated with the treatment strategies applied in the clinical trials relative to the sofosbuvir UK marketing authorisation. The structure of the model is based on other published health economic models of chronic HCV, previously considered by NICE. The structure of the model was amended by the manufacturer to reflect the data available from its pivotal phase 3 randomised clinical trials by combining both mild and moderate chronic hepatitis C patients as non-cirrhotic patients. The model only distinguishes between cirrhotic and non-cirrhotic patients. Data from clinical trials were used to inform model inputs for treatment effects and adverse events. The model simulates treatment and subsequent natural history of chronic HCV, depending on whether the patient is cured. The same model structure is used for all patients irrespective of HCV genotype or treatment experience. For the first 2 years a 3-month cycle was used in the model, then the remaining cycles

each last 1 year. A half-cycle correction was applied, which is consistent with previous hepatitis C appraisals. Treatment effect data were based on the sustained virological response rates taken from the sofosbuvir clinical trials and where data for sustained virological response rates of comparators were not available in these trials, they were taken from other studies identified by the manufacturer. The main determinants of quality of life in the model were taken from utilities from the UK mild chronic hepatitis C trial. The manufacturer used transition probabilities for disease progression from 2 UK health technology assessments and 1 UK study: Hartwell et al. (2011), Shepherd et al. (2007), and Grishchenko et al. (2009), which used estimates of disease progression from the Trent database (a large representative sample of patients with HCV who only attended non tertiary centres in the UK).

6.5 The model has a total of 9 health states according to disease stage and treatment response (Figure 1). Although not represented on the transition diagram, the manufacturer applied age-specific general population mortality rates to each health state in the model.

Figure 1 Manufacturer's Markov model schematic for chronic hepatitis C (page 169, figure 20)



6.6 Patients enter the model in either the non-cirrhotic or compensated cirrhosis stages of disease. Patients receiving antiviral treatment can have the virus cleared, depicted by transitioning to the sustained virological response health states. Those who do not clear the virus after treatment remain in their respective health states, or progress to more severe stages of chronic HCV. The model assumes that a patient may progress to more severe stages of liver disease or remain in their current health state, and that patients who experience a sustained virological response will not progress to more severe health states during or after therapy. Reversion to less severe health states is not permitted if treatment is unsuccessful. The sustained virological response health state is stratified by the patient's original cirrhosis status.

6.7 The manufacturer compared sofosbuvir in combination with ribavirin (with/without peginterferon alfa) with telaprevir in combination with peginterferon alfa and ribavirin, boceprevir in combination with peginterferon alfa and ribavirin, peginterferon alfa with ribavirin and best

supportive care. Sofosbuvir, telaprevir, boceprevir and peginterferon alfa-2a and ribavirin were implemented in the model according to the marketing authorisations for each treatment. The interventions and comparators used by the manufacturer in its model are shown in Table 9. The manufacturer applied no stopping rules, lead in phase, or additional treatment for sofosbuvir, in line with sofosbuvir clinical trials.

Table 9 Manufacturer's modelled treatment strategies per indication

Indication	Intervention	Comparator(s)
Genotype 1		
genotype 1 treatment naive interferon eligible	sofosbuvir (400 mg) + peginterferon alfa (180 micrograms/wk) + weight-based ribavirin (1,000-1,200 mg) for 12 weeks	Telaprevir (750 mg) + peginterferon alfa (180 micrograms/wk) + weight-based ribavirin (15 mg/kg) for 24 or 48 weeks based on stopping rules and rapid virological response status
		Boceprevir (800 mg TID) + PEG-interferon-2b (1.5 micrograms/kg/wk) + weight-based ribavirin (15 mg/kg OD for 28 or 48 weeks based on futility rules (patients discontinued all study drugs at specific time points if they had detectable HCV RNA)
		peginterferon alfa (180 micrograms/wk) + weight-based ribavirin (15 mg/kg) for 48 weeks
genotype 1 treatment naive unsuitable for interferon	sofosbuvir (400 mg) + weight-based ribavirin (1,000-1,200 mg) for 24 weeks	no treatment
genotype 1 treatment experienced interferon eligible	sofosbuvir (400 mg) + peginterferon alfa (180 micrograms/wk) + weight-based ribavirin (1,000-1,200 mg) for 12 weeks(recommended extending treatment up to 24 weeks)	The licence for sofosbuvir also covers genotype 1 treatment experienced patients. The sustained virological response for these patients was extrapolated based on an FDA model and as such an economic analysis in this population has not been conducted
Genotype 2		
genotype 2 treatment naive interferon eligible	sofosbuvir (400 mg) + weight-based ribavirin (1,000-1,200 mg) for 12 weeks	peginterferon alfa (180 micrograms/wk) + ribavirin (800 mg) for 24 weeks
genotype 2 treatment naive unsuitable for interferon	sofosbuvir (400 mg) + weight-based ribavirin (1,000-1,200 mg) for 12 weeks	no treatment
genotype 2 treatment experienced interferon eligible	sofosbuvir (400 mg) + weight-based ribavirin (1,000-1,200 mg) for 12 weeks	peginterferon alfa (180 micrograms/wk) + ribavirin (800 mg) for 48 weeks
		no treatment

Indication	Intervention	Comparator(s)
genotype 2 treatment experienced unsuitable for interferon	sofosbuvir (400 mg) + weight-based ribavirin (1,000-1,200 mg) for 12 weeks	no treatment
Genotype 3		
genotype 3 treatment naive interferon eligible	sofosbuvir (400 mg) + peginterferon alfa (180 micrograms/week) + weight-based ribavirin (1,000-1,200 mg) for 12 weeks Alternative regimen sofosbuvir (400 mg) + weight-based ribavirin (1,000-1,200 mg) for 24 weeks	peginterferon alfa (180 micrograms/wk) + ribavirin (800 mg) for 24 weeks
genotype 3 treatment naive unsuitable for interferon	sofosbuvir (400 mg) + weight-based ribavirin (1,000-1,200 mg) for 24 weeks	no treatment
genotype 3 treatment experienced interferon eligible	sofosbuvir (400 mg) + peginterferon alfa (180 micrograms/wk) + weight-based ribavirin (1,000-1,200 mg) for 12 weeks Alternative regimen sofosbuvir (400 mg) + weight-based ribavirin (1,000-1200 mg) for 24 weeks	peginterferon alfa (180 micrograms/wk) + ribavirin (800 mg) for 48 weeks no treatment
genotype 3 treatment experienced unsuitable for interferon	sofosbuvir (400 mg) + weight-based ribavirin (1,000-1200 mg) for 24 weeks	no treatment
Genotype 4/5/6		
genotype 4/5/6 treatment naive	sofosbuvir (400 mg) + peginterferon alfa (180 micrograms/wk) + weight-based ribavirin (1,000-1,200 mg) for 12 weeks	peginterferon alfa (180 micrograms/wk) + weight-based ribavirin (15 mg/kg) for 48 weeks

Source: Manufacturer's submission, pages 174-175, table 42.

6.8 The manufacturer calculated the patient characteristics used in the model from the HCV research database, including mean age at treatment initiation, disease severity distribution and weight. The manufacturer obtained sustained virological response rates of sofosbuvir for each patient group from the corresponding sofosbuvir head-to-head trial. The

manufacturer obtained the sustained virological response rate for each comparator from sofosbuvir trials where possible; otherwise, relevant literature identified was used. The manufacturer obtained the utility decrement associated with sofosbuvir therapy from the SF-6D utility decrements from SF-36 data collected during the sofosbuvir phase 3 trials. Comparator utility decrements were obtained from published appraisals (for boceprevir and telaprevir) or from systematic reviews (for peginterferon alfa-2a and ribavirin). Adverse events rates were obtained from the sofosbuvir clinical trials and published studies. The manufacturer incorporated rates of grade 3 and 4 pruritus, diarrhoea and nausea, vomiting, rash, anaemia, thrombocytopenia, neutropenia, and depression from the trials into the model so that drug acquisition costs could be assigned for interventions associated with managing these side effects. The manufacturer did not use its mixed treatment comparison results to populate its base case model as it was not considered robust enough. However, the manufacturer did provide the economic results derived from the mixed treatment comparison in an economic scenario analysis provided in appendix 10.14.10 to their submission.

Utility values

6.9 The manufacturer obtained utility values from the most current models used in Hartwell et al. (2011) and Shepherd et al. (2007) and were based on the UK trial of mild HCV by Wright et al. (2006) The manufacturer calculated treatment-related utilities by applying treatment-related utility decrements to the baseline utility estimates. See table 10 for details of the utility values used by the manufacturer and its source.

Table 10 Summary of utility values used by the manufacturer

Health-state	Utility	Source	Comments
Baseline – non-cirrhotic	0.74	Wright et al., 2006 (UK mild HCV trial)	Average of mild and moderate utilities assuming 77% mild and 23% moderate EQ-5D Publications that used this utility: -Hartwell et al., 2011 -Grishchenko et al., 2009 -Shepherd et al., 2007
Baseline – compensated cirrhosis	0.55	Wright et al., 2006 (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011 -Grishchenko et al., 2009
sustained virological response (utility increment)	0.05	Wright et al., 2006 (UK mild HCV trial)	
After treatment at non-cirrhotic stage	0.79	Calculation	Calculated as baseline – non-cirrhotic + utility increment after reaching sustained virological response (0.74 + 0.05)
After treatment at cirrhotic stage	0.60	Calculation	Calculated as baseline – non-cirrhotic + utility increment after reaching sustained virological response (0.55 + 0.05)
Decompensated cirrhosis	0.45	Wright et al., 2006 (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011 -Grishchenko et al., 2009 -Shepherd et al., 2007
Hepatocellular carcinoma	0.45	Wright et al., 2006 (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011 -Grishchenko et al., 2009 -Shepherd et al., 2007
Liver transplant	0.45	Wright et al., 2006 (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011 -Shepherd et al., 2007
Post-liver transplant	0.67	Wright et al., 2006 (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al., 2011

Source: Manufacturer's submission, pages 214-215, table 57.

Costs

6.10 The manufacturer used costs within the model that reflected the UK NHS perspective, comprising treatment related costs (drug acquisition and patient monitoring), health-state costs and adverse event costs. Drug costs were based on the list price in the BNF (June 2013). The cost of an average course of 11.84 weeks of sofosbuvir based on the model for treatment naïve, genotype 1 HCV interferon eligible patients was £34,504.

Table 11 Treatment unit costs

Drug	Cost per pack	Unit dose	Quantity/pack	Source	Cost over time frame[a]
Sofosbuvir	£416.46	400 mg	1	Manufacturer	£34,504
Ribavirin	£246.65	400 mg	56	BNF, June 2013	£1,095
peginterferon alfa-2a	£124.40	180 micrograms	1	BNF, June 2013	£1,472
Telaprevir	£1,866.50	375 mg	42	BNF, June 2013	£22,461
Boceprevir	£2,800.00	200 mg	336	BNF, June 2013	£18,978
[a]based on the average treatment duration in the model for the HCV genotype 1, treatment naive, eligible group					

Source: ERG report, page 82, table 25.

6.11 Costs for the health states in the model were identified using published sources taken from the resource/costs systematic review conducted by the manufacturer. The costs for the non-cirrhotic health state was based on a calculation of the costs associated previously with mild and moderate cirrhosis (Wright et al. [2006]) using an assumed 77%/23% split between mild and moderate cirrhosis. Costs were inflated to 2011-12 (using the HCHS Pay and Prices index). The key health state costs have been reproduced below (Table 12). The ERG commented that the manufacturer's health-state costs were not current, but they were consistent with previous NICE appraisals. The ERG identified a more recent source for the cost of liver transplant with a much lower cost of £18,019 from National Reference costs 2011/12. However, the ERG commented that changing this cost in the model had a negligible impact on the results.

Table 12 Key health state costs used in the manufacturer's economic model

Health state	Annual inflated costs	Source
Non-cirrhotic, no treatment	£367	Calculation based on mild and moderate chronic hepatitis C in Wright et al 2006
Non-cirrhotic, sustained virological response	£243	Calculation based on mild and moderate chronic hepatitis C in Grishchenko et al 2009
Compensated cirrhosis, no treatment	£1,521	Wright et al 2006
Compensated cirrhosis, sustained virological response	£500	Grishchenko et al 2009
Decompensated cirrhosis	£12,193	Wright et al 2006
HCC	£10,865	Wright et al 2006
Liver transplant	£52,768	Longworth et al 2001
Post-liver transplant		
Follow-up phase (0-12 months)	£12,645	Longworth et al 2001
Follow-up phase (12-24 months)	£1,852	Longworth et al 2001

Source: ERG report, page 83, table 26.

6.12 Costs for monitoring patients included resource unit costs of outpatient appointments, inpatient care, tests and investigations (virology, pathology, haematology, immunology, radiology) and procedures (liver biopsy). The source for monitoring costs was the National Schedule of Reference Costs or was taken from studies identified or expert opinion. Adverse event costs include the costs of various drugs used to treat adverse events which were sourced by the manufacturer from the BNF

6.13 The ERG commented that the approach used by the manufacturer to value resource use was consistent with the NICE reference case.

Results

6.14 The manufacturer presented base-case analyses for sofosbuvir in combination with ribavirin with or without peginterferon compared with current standards of care based on HCV genotype, interferon eligibility and treatment history (Table 13). The manufacturer’s results show that sofosbuvir increased the cost of treatment but was associated with more quality-adjusted life years gained, a greater probability of cure, and a reduction in end-stage liver disease and death.

Table 13 Manufacturer's summary of base-case cost-effectiveness results (ICER for sofosbuvir against each comparator: £/QALY gained)

Indication	Sofosbuvir regimen	Comparator			
		No treatment	peginterferon alfa +ribavirin (48 weeks)	telaprevir+ peginterferon alfa +ribavirin	boceprevir+ PEG-interferon-2b+ribavirin
genotype 1					
Treatment-naïve, interferon eligible	sofosbuvir +peginterferon alfa +ribavirin (12 weeks)	-	£14,930	£11,836	£7,292
Treatment-naïve, unsuitable for interferon	sofosbuvir +ribavirin (24 weeks)	£49,249	-	-	-
genotype 2					
Treatment-naïve, interferon eligible	sofosbuvir +ribavirin (12 weeks)	-	£46,324	-	-
Treatment-naïve, unsuitable for interferon		£8,154	-	-	-
Treatment-experienced, interferon eligible		£9,274	£12,519	-	-
Treatment-experienced, unsuitable for interferon		£8,591	-	-	-
genotype 3					
Treatment-naïve, interferon eligible	sofosbuvir +peginterferon alfa +ribavirin (12 weeks)	-	£20,613	-	-
Treatment-naïve, unsuitable for interferon	sofosbuvir +ribavirin 24 (weeks)	£21,478	-	-	-
Treatment-experienced, interferon eligible	sofosbuvir +peginterferon alfa +ribavirin (12 weeks)	£8,557	£12,246	-	-
Treatment-experienced, unsuitable for interferon	sofosbuvir +ribavirin (24 weeks)	£28,569	-	-	-
genotype 4/5/6					
Treatment-naïve	sofosbuvir +peginterferon alfa /ribavirin (12 weeks)	-	£26,797	-	-

Source: Manufacturer's submission, page 246-247, table 81

Genotype 1

6.15 For treatment-naïve, interferon eligible patients with genotype 1 HCV, the manufacturer's base case ICER for sofosbuvir with peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £14,930 per QALY gained. For treatment naïve patients with genotype 1 HCV who are ineligible or unable to receive interferon treatment, the manufacturer's base case ICER for sofosbuvir with ribavirin treatment for 24 weeks compared with no treatment was £49,249 per QALY gained. See Table 14 for the manufacturer's fully incremental base case cost effectiveness results for the genotype 1 HCV subgroup.

Table 14 Manufacturer's base case cost effectiveness results for genotype 1 HCV.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)[a]	Incremental LYGs[a]	Incremental QALYs[a]	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
GT1 TN IFN eligible								
PEG2a+RBV (48 wks)	£24,994	19.3	13.8	NA	NA	NA	NA	NA
Telaprevir+PEG2a+RBV	£38,835	19.9	14.6	£13,841	0.6	0.8	£16,587	Extended dominance
Boceprevir+PEG2b+RBV	£39,221	19.8	14.4	£14,227	0.4	0.6	£23,360	Dominated
SOF+PEG2a+RBV (12 wks)	£44,123	20.2	15.1	£19,129	0.9	1.3	£14,930	£14,930
GT1 TN unsuitable for IFN								
No treatment	£20,225	18.7	13.0	NA	NA	NA	NA	NA
SOF+RBV (24 wks)	£84,129	19.5	14.3	£63,903	0.8	1.3	£49,249	£49,249

GT: genotype; ICER: incremental cost-effectiveness ratio; IFN: interferon; LYG: life years gained; NA: not applicable; QALY: quality-adjusted life year; TE: treatment naive; TN: treatment experienced; wks: weeks

Source: MS, pages 58-59.

6.16 The manufacturer did not conduct an economic analysis for treatment experienced patients with genotype 1 HCV as there was no clinical evidence available to populate the economic model for this subpopulation.

Genotype 2

6.17 In treatment naïve, interferon eligible patients with genotype 2 HCV, the manufacturer's base case ICER for sofosbuvir with peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £46,324 per QALY gained. In treatment naive patients with genotype 2 HCV who are ineligible or unable

to receive interferon treatment, the manufacturer's base case ICER for sofosbuvir and ribavirin treatment for 12 weeks compared with no treatment was £8154 per QALY gained.

6.18 In treatment experienced, interferon eligible patients with genotype 2 HCV, the manufacturer's base case ICER for sofosbuvir with peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £9274 per QALY gained. In treatment experienced patients with genotype 2 HCV who are ineligible or unable to receive interferon treatment, the manufacturer's base case ICER for sofosbuvir with ribavirin treatment for 12 weeks compared with no treatment was £8591 per QALY gained. See Table 15 for the manufacturer's fully incremental base case cost effectiveness results for the genotype 2 HCV subgroup.

Table 15 Manufacturer's base case cost effectiveness results for genotype 2 HCV.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)[a]	Incremental LYGs[a]	Incremental QALYs[a]	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
GT2 TN IFN eligible								
PEG2a+RBV (24 wks)	£14,492	21.1	15.6	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£42,271	21.6	16.2	£27,779	0.5	0.6	£46,324	£46,324
GT2 TN unsuitable for IFN								
No treatment	£21,426	18.6	12.8	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£41,477	20.4	15.3	£20,051	1.8	2.5	£8,154	£8,154
GT2 TE IFN eligible								
No treatment	£20,771	18.6	12.8	NA	NA	NA	NA	NA
PEG2a+RBV (48 wks)	£24,022	19.3	13.7	£3,251	0.7	0.9	£3,778	£3,778
SOF+RBV (12 wks)	£42,269	20.2	15.1	£21,498	1.6	2.3	£9,274	£12,519
GT2 TE unsuitable for IFN								
No treatment	£20,771	18.6	12.8	NA	NA	NA	NA	NA
SOF+RBV (12 wks)	£41,468	20.3	15.2	£20,697	1.7	2.4	£8,591	£8,591

GT: genotype; ICER: incremental cost-effectiveness ratio; IFN: interferon; LYG: life years gained; NA: not applicable; QALY: quality-adjusted life year; TE: treatment naive; TN: treatment experienced; wks: weeks

Source: MS, pages 58-59.

Genotype 3

6.19 In treatment naïve, interferon eligible patients with genotype 3 HCV, the manufacturer's base case ICER for sofosbuvir with peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £20,613 per QALY gained. In treatment naive patients with genotype 3 HCV who are ineligible or unable to receive interferon treatment, the manufacturer's base case ICER for sofosbuvir and ribavirin treatment for 24 weeks compared with no treatment was £21,478 per QALY gained.

6.20 In treatment experienced, interferon eligible patients with genotype 3 HCV, the manufacturer's base case ICER for sofosbuvir with peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £8557 per QALY gained. In treatment experienced patients with genotype 3 HCV who are ineligible or unable to receive interferon treatment, the manufacturer's base case ICER for sofosbuvir with ribavirin treatment for 24 weeks compared with no treatment was £28,569 per QALY gained. See Table 16 for the manufacturer's fully incremental base case cost effectiveness results for the genotype 3 HCV subgroup.

Table 16 Manufacturer's base case cost effectiveness results for genotype 3 HCV.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)[a]	Incremental LYGs[a]	Incremental QALYs[a]	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
GT3 TN IFN eligible								
PEG2a+RBV (24 wks)	£19,704	20.3	14.7	NA	NA	NA	NA	NA
SOF+PEG2a+RBV (12 wks)	£44,674	21.5	15.9	£24,970	1.2	1.2	£20,613	£20,613
GT3 TN unsuitable for IFN								
No treatment	£23,406	18.3	12.4	NA	NA	NA	NA	NA
SOF+RBV (24 wks)	£78,543	20.3	15.0	£55,137	2.1	2.6	£21,478	£21,478
GT3 TE IFN eligible								
No treatment	£22,740	18.3	12.4	NA	NA	NA	NA	NA
PEG2a+RBV (48 wks)	£25,531	19.1	13.4	£2,791	0.9	0.9	£3,037	£3,037
SOF+PEG2a+RBV (12 wks)	£42,374	20.1	14.7	£19,634	1.9	2.3	£8,557	£12,246
GT3 TE unsuitable for IFN								

No treatment	£22,740	18.3	12.4	NA	NA	NA	NA	NA
SOF+RBV (24 wks)	£81,568	19.8	14.5	£58,828	1.5	2.1	£28,569	£28,569
GT: genotype; ICER: incremental cost-effectiveness ratio; IFN: interferon; LYG: life years gained; NA: not applicable; QALY: quality-adjusted life year; TE: treatment naive; TN: treatment experienced; wks: weeks								

Source: MS, pages 58-59.

Genotypes 4, 5 or 6

6.21 In treatment naïve, interferon eligible patients with HCV genotype 4, 5 or 6, the manufacturer's base case ICER for sofosbuvir with peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £26,797 per QALY gained. See Table 17 for the manufacturer's fully incremental base case cost effectiveness results for the genotype 4, 5 and 6 HCV subgroups.

Table 17 Manufacturer's base case cost effectiveness results for genotype 4, 5 and 6 HCV

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)[a]	Incremental LYGs[a]	Incremental QALYs[a]	ICER vs. baseline (QALYs)	ICER incremental (QALYs)
GT4/5/6 TN								
PEG2a+RBV (48 wks)	£22,631	19.5	13.9	NA	NA	NA	NA	NA
SOF+PEG2a+RBV (12 wks)	£46,573	19.8	14.8	£23,942	0.3	0.9	£26,797	£26,797
GT: genotype; ICER: incremental cost-effectiveness ratio; IFN: interferon; LYG: life years gained; NA: not applicable; QALY: quality-adjusted life year; TE: treatment naive; TN: treatment experienced; wks: weeks								

Source: MS, pages 58-59.

6.22 The manufacturer tested the robustness of the model using deterministic sensitivity analyses. Structural sensitivity analyses showed that the ICERS were most sensitive to changes in the discount rates for both costs and outcomes and the utility increment after reaching sustained virological response. For some subgroups, the results were also sensitive to changes in sustained virological response rates for cirrhotic patients receiving the comparator treatment.

6.23 The manufacturer also undertook probabilistic sensitivity analyses to explore uncertainty and the results suggest that the ICER for sofosbuvir compared to its appropriate comparator has less than a 50% probability of

being less than £20,000 per QALY gained in 6 subgroups and of being less than £30,000 per QALY gained in 4 subgroups (Table 14). The ERG recalculated the probabilistic sensitivity analyses as it found a slight error in the settings of the slider control used to set the probability of cost-effectiveness at the £20,000 and £30,000 willingness to pay (WTP) thresholds. The comparison of the probabilistic sensitivity analyses conducted by the manufacturer and ERG are shown below.

Table 18 Probabilistic sensitivity analyses results– comparison of manufacturer and ERG results

Indication and comparator	Probability of being less than £20,000 per QALY gained		Probability of being less than £30,000 per QALY gained	
	Manufacturer	ERG	Manufacturer	ERG
sofosbuvir +peginterferon alfa +ribavirin (12 weeks) versus peginterferon alfa +ribavirin (48 weeks) in genotype 1 treatment naïve, interferon eligible	63	68	90	94
sofosbuvir +peginterferon alfa +ribavirin (12 weeks) versus telaprevir+ peginterferon alfa +ribavirin in genotype 1 treatment naïve interferon eligible	68	69	85	83
sofosbuvir+peginterferon alfa-2a+ribavirin (12 weeks) versus boceprevir+PEG2b+ribavirin (48 weeks) in genotype 1 treatment naive interferon eligible	85	86	95	96
sofosbuvir+ribavirin (24 weeks) versus no treatment in genotype 1 treatment naive unsuitable for interferon	<5%	1	10	10
sofosbuvir+ribavirin (12 weeks) versus peginterferon alfa-2a+ribavirin (24 weeks) in genotype 2 treatment naive interferon eligible	<5%	4	10	14
sofosbuvir+ribavirin (12 weeks) versus no treatment in genotype 2 treatment naive unsuitable for interferon	98	99	100	100
sofosbuvir+ribavirin (12 weeks) versus no treatment in genotype 2 treatment experienced interferon eligible	95	97	100	100
sofosbuvir+ribavirin (12 weeks) versus peginterferon alfa-2a+ribavirin (48 weeks) in genotype 2 treatment experienced interferon eligible	78	82	95	97
sofosbuvir+ribavirin (12 weeks) versus no treatment in genotype 2 treatment experienced unsuitable for interferon	97	99	100	100
sofosbuvir+peginterferon alfa-2a+ribavirin (12 weeks) versus peginterferon alfa-2a+ribavirin (24 weeks) in genotype 3 treatment naive interferon	37	42	80	79

Indication and comparator	Probability of being less than £20,000 per QALY gained		Probability of being less than £30,000 per QALY gained	
	Manufacturer	ERG	Manufacturer	ERG
eligible				
sofosbuvir+ribavirin (24 weeks) versus no treatment in genotype 3 treatment naive unsuitable for interferon	30	35	80	78
sofosbuvir+peginterferon alfa-2a+ribavirin (12 weeks) versus no treatment in genotype 3 treatment experienced interferon eligible	96	98	100	100
sofosbuvir+peginterferon alfa-2a+ribavirin (12 weeks) versus peginterferon alfa-2a+ribavirin (48 weeks) in genotype 3 treatment experienced interferon eligible	75	80	98	96
sofosbuvir+ribavirin (24 weeks) versus no treatment in genotype 3 treatment experienced unsuitable for interferon	12	14	48	48
sofosbuvir+peginterferon alfa-2a+ribavirin (12 weeks) versus peginterferon alfa-2a+ribavirin (48 weeks) in genotype 4/5/6 treatment naive	24	26	50	48

Source: ERG report, page s 90-92, tables 28 and 29.

6.24 The ERG stated that the manufacturer's methods of economic evaluation and the model produced were acceptable. The ERG validated the manufacturer's model by comparing the total costs and QALYs predicted by the model for the genotype 1 treatment naive, interferon eligible indication with the corresponding figures for peginterferon alfa and ribavirin, boceprevir and telaprevir obtained from the NICE STAs for boceprevir and telaprevir. The ERG found that the manufacturer's model for sofosbuvir is broadly consistent with previous models considered in STAs for hepatitis C, in terms of peginterferon alfa and ribavirin total costs and QALYs, and with telaprevir total costs and QALYs. However, the ERG noted that there was a discrepancy between models in boceprevir total costs but could not account for the differences without reviewing the data used in the boceprevir submission. The ERG also stated that the manufacturer's economic model captures most of the important aspects of the disease pathway although it does not include a transition from the sustained virological response-cirrhotic health state to the hepatocellular carcinoma health state. The ERG showed this discrepancy not to affect the ICERs substantively. The ERG commented that the manufacturer's

model extrapolates intermediate outcomes to final outcomes in a consistent manner, drawing upon standard sources from the literature.

HIV co-infected subpopulations

6.25 The manufacturer provided a separate economic analysis for patients co-infected with HIV and HCV(section 10.14.8 of manufacturer's appendices). According to the manufacturer, it is expected that co-infected patients will responds to sofosbuvir treatment in a similar manner to mono-infected patients. In treatment naïve, interferon eligible co-infected patients with genotype 1 HCV, the manufacturer's base case ICER for sofosbuvir and ribavirin treatment for 24 weeks compared with no treatment or peginterferon alfa-2a and ribavirin treatment for 48 weeks was £28,504 or £43,836 per QALY gained, respectively. The manufacturer's base case ICER for treatment-naïve people with genotype 2 HCV and HIV-co-infection who received sofosbuvir and ribavirin treatment for 12 weeks compared to peginterferon alfa-2a and ribavirin treatment for 48 weeks was £55,867 per QALY gained. The manufacturer's base case ICER for treatment-experienced people with genotype 2 HCV and HIV-co-infection, who received sofosbuvir and ribavirin treatment for 24 weeks compared to no treatment or peginterferon alfa-2a and ribavirin treatment for 48 weeks was £10,572 or £128,248 per QALY gained, respectively. For people with genotype 3 HCV/HIV co-infection, 12 weeks of sofosbuvir and ribavirin treatment dominated treatment with peginterferon alfa and ribavirin in treatment-naïve patients, while in treatment experienced people, the ICERs for 24 weeks of sofosbuvir and ribavirin treatment compared with no treatment or peginterferon alfa-2a and ribavirin for 48 weeks were £10,646 and £90,822, respectively. The manufacturer did not provide an economic analysis for people co-infected with HIV and genotype 4, 5, or 6 HCV (see Table 19). The ERG noted that the transition probabilities used by the manufacturer in its economic model for the HIV co-infected population from non-cirrhotic to compensated cirrhosis health states were higher than those assumed for the mono-infected population. The ERG further noted

that people with HIV co-infection are likely to have a higher mortality rate than the population with HCV mono-infection, regardless of sustained virological response, and this is not currently taken into account in the manufacturer's model. The ERG noted that a study by Van Der Helm et al (2013) had concluded that the effects of HCV treatment on HIV progression needed to be evaluated further, and on this basis, the ERG commented that the evidence required to accurately evaluate the cost-effectiveness of sofosbuvir in the HIV co-infected population was not currently available.

Table 19 Summary of manufacturer's base-case cost-effectiveness results for people with HCV/HIV co-infection

Indication	Sofosbuvir regimen	Comparator	
		No treatment	Peginterferon alfa-2a + ribavirin(48 weeks)
GT1			
Treatment naïve	SOF+RBV 24 weeks	£28,504	£43,836
GT2			
Treatment naive	SOF+RBV 12 weeks	-	£55,867
Treatment experienced	SOF+RBV 24 weeks	£10,572	£128,248
GT3			
Treatment naive	SOF+RBV 12 weeks	-	Dominated
Treatment experienced	SOF+RBV 24 weeks	£10,646	£90,822

Source: Manufacturer's appendices, page 486, table 198.
Key: SOF: sofosbuvir; RBV: ribavirin; GT: genotype

Additional exploratory ERG Analyses

6.26 The ERG undertook several exploratory analyses, which included:

- Adding a transition probability from the sustained virological response in people with cirrhosis health state to the hepatocellular carcinoma health state.
- Exploring the impact on the ICERs of a discount rate set to 1.5% for costs and health effects
- Assessing the effect of variations to all-cause mortality probabilities
- Conducting exploratory analysis in treatment experienced patients with genotype 1 HCV

- Using Peginterferon alfa-2b and Rebetol (ribavirin) costs used instead of peginterferon alfa-2a and Copegus (ribavirin) costs

6.27 The ERG explored the effect of including the transition probability (0.005) from the sustained virological response in people with cirrhosis health state (and the upper and lower 95% confidence intervals for the transition probability [0.013 and 0.002, respectively]) to the hepatocellular carcinoma health state in the economic model. The ERG heard from its clinical advisers that this transition should be included in the sofosbuvir model in order to better reflect the clinical course of the disease. The ICERs from the ERG's exploratory analyses were slightly higher than those estimated in the manufacturer's base case (Table 16).

Table 20 ERG exploratory analyses including transition probabilities from sustained virological response in people with cirrhosis health state to hepatocellular carcinoma health state compared with the manufacturer's base case ICERs

Indication	Comparison	Manufacturer's base case ICER (£/QALY)	Transition probability from SVR-cirrhosis health state to HCC: 0.005 (£/QALY)	Lower confidence interval for SVR-cirrhosis transition probability : 0.002 (£/QALY)	Upper confidence interval for SVR-cirrhosis transition probability : 0.013 (£/QALY)
genotype 2 treatment naive interferon eligible	sofosbuvir vs. peginterferon +ribavirin (24 weeks)	46,324	49,617	47,636	54,957
genotype 2 treatment naive interferon ineligible	sofosbuvir vs. no treatment	8,154	8,694	8,371	9,544
genotype 2 treatment experienced interferon eligible	sofosbuvir vs. no treatment	9,274	9,825	9,496	10,684
	sofosbuvir vs. peginterferon +ribavirin (48 weeks)	12,519	13,189	12,788	14,227
genotype 2 treatment experienced interferon ineligible	sofosbuvir vs. no treatment	8,591	9,149	8,815	10,027

Indication	Comparison	Manufacturer's base case ICER (£/QALY)	Transition probability from SVR-cirrhosis health state to HCC: 0.005 (£/QALY)	Lower confidence interval for SVR-cirrhosis transition probability : 0.002 (£/QALY)	Upper confidence interval for SVR-cirrhosis transition probability : 0.013 (£/QALY)
genotype 3 treatment naive interferon eligible	sofosbuvir vs. peginterferon +ribavirin (24 weeks)	20,613	22,850	21,489	26,771
genotype 3 treatment naive interferon ineligible	sofosbuvir vs. no treatment	21,478	23,032	22,096	25,574
genotype 3 treatment experienced interferon eligible	sofosbuvir vs. no treatment	8,557	9,273	8,842	10,442
	sofosbuvir vs. peginterferon +ribavirin (48 weeks)	12,246	13,214	12,631	14,796
genotype 3 treatment experienced interferon ineligible	sofosbuvir vs. no treatment	28,569	30,190	29,219	32,758
genotype 1 treatment naive interferon eligible	sofosbuvir vs. telaprevir	11,836	12,743	12,197	14,216
	sofosbuvir vs. boceprevir	7,292	7,829	7,507	8,684
	sofosbuvir vs. peginterferon +ribavirin (48 weeks)	14,930	16,070	15,384	17,934
genotype 1 treatment naive interferon ineligible	sofosbuvir vs. no treatment	49,249	51,294	50,074	54,434
genotype 4/5/6	sofosbuvir vs. peginterferon +ribavirin (48 weeks)	26,797	27,468	27,071	28,451

Source: ERG report, page 96, table 34.

6.28 The ERG also recalculated the manufacturer's base case ICERs using a discount rate of 1.5% for costs and health effects. In previous appraisals for hepatitis C treatments, the ICERs were not very sensitive to the discount rate that was used for costs and outcomes. However, in this

case, the manufacturer's results from the deterministic sensitivity analyses suggested that the ICERs for sofosbuvir were very sensitive to the discount rate used. The NICE Methods Guide advises that sensitivity analyses using discount rates of 1.5% for both costs and health effects may be presented alongside the base case analysis in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years). The resulting ICERs for all subgroups were below £30,000 per QALY gained when the revised discount rate was applied (Table 17).

Table 21 Revised ICERs with discount rate set to 1.5% for costs and health effects

Indication	Comparison	Manufacturer's Base case ICER (£/QALY)	ERG's revised ICER (£/QALY)
genotype 1 treatment naive interferon eligible	sofosbuvir vs. telaprevir	11,836	6,078
	sofosbuvir vs. boceprevir	7,292	3,949
	sofosbuvir vs. peginterferon +ribavirin (48 weeks)	14,930	8,069
genotype 1 treatment naive interferon ineligible	sofosbuvir vs. no treatment	49,249	29,726
genotype 2 treatment naive interferon eligible	sofosbuvir vs. peginterferon +ribavirin (24 weeks)	46,324	28,120
genotype 2 treatment naive interferon ineligible	sofosbuvir vs. no treatment	8,154	3,390
genotype 2 treatment experienced interferon eligible	sofosbuvir vs. no treatment	9,274	4,092
	sofosbuvir vs. peginterferon +ribavirin (48 weeks)	12,519	6,356
genotype 2 treatment experienced interferon ineligible	sofosbuvir vs. no treatment	8,591	3,668
genotype 3 treatment naive interferon eligible	sofosbuvir vs. peginterferon +ribavirin (24 weeks)	20,613	11,268
genotype 3 treatment naive interferon ineligible	sofosbuvir vs. no treatment	21,478	11,999
genotype 3	sofosbuvir vs. no treatment	8,557	3,678

Indication	Comparison	Manufacturer's Base case ICER (£/QALY)	ERG's revised ICER (£/QALY)
treatment experienced interferon eligible	sofosbuvir vs. peginterferon +ribavirin (48 weeks)	12,246	6,200
genotype 3 treatment experienced interferon ineligible	sofosbuvir vs. no treatment	28,569	16,492
genotype 4/5/6	sofosbuvir vs. peginterferon +ribavirin (48 weeks)	26,797	16,032

Source: ERG report, page 97-98, table 35.

6.29 The ERG noted that in the manufacturer used the simple average of male and female mortality figures to calculate the age-specific mortality rates used in the model. The ERG commented that the population most likely to be treated in clinical practice in England is male. During clarification, the manufacturer re-ran the model with weighted average mortality probabilities, but did not indicate which weights were used to obtain its results. The ERG conducted an exploratory analysis using a weighting of 61% men and 39% women as used in Wright et al. (2006). The resulting ICERs from the manufacturer and ERG are seen in Table 22.

Table 22 Revised ICERs using weighted average of all-cause mortality

Indication	Comparison	Manufacturer's base case ICER	Manufacturer's Clarification ICER	ERG calculated ICER
genotype 1 treatment naive interferon eligible	sofosbuvir vs. telaprevir	11,836	11,714	12,057
	sofosbuvir vs. boceprevir	7,292	7,202	7,453
	sofosbuvir vs. peginterferon alfa-2a+ribavirin (48 weeks)	14,930	14,778	15,205
genotype 1 treatment naive interferon ineligible	sofosbuvir vs. no treatment	49,249	48,777	50,083
genotype 2 treatment naive interferon eligible	sofosbuvir vs. peginterferon +ribavirin (24 weeks)	46,324	46,010	46,909
genotype 2 treatment naive interferon ineligible	sofosbuvir vs. no treatment	8,154	8,050	8,340
genotype 2 treatment experienced interferon	sofosbuvir vs. no treatment	9,274	9,159	9,479

Indication	Comparison	Manufacturer's base case ICER	Manufacturer's Clarification ICER	ERG calculated ICER
eligible	sofosbuvir vs. peginterferon +ribavirin (48 weeks)	12,519	12,379	12,770
genotype 2 treatment experienced interferon ineligible	sofosbuvir vs. no treatment	8,591	8,483	8,784
genotype 3 treatment naive interferon eligible	sofosbuvir vs. peginterferon +ribavirin (24 weeks)	20,613	20,458	20,900
genotype 3 treatment naive interferon ineligible	sofosbuvir vs. no treatment	21,478	21,257	21,867
genotype 3 treatment experienced interferon eligible	sofosbuvir vs. no treatment	8,557	8,452	8,746
	sofosbuvir vs. peginterferon alfa-2a+ribavirin (48 weeks)	12,246	12,112	12,488
genotype 3 treatment experienced interferon ineligible	sofosbuvir vs. no treatment	28,569	28,281	29,079
genotype 4/5/6	sofosbuvir vs. peginterferon alfa-2a+ribavirin (48 weeks)	26,797	26,538	27,265

Source: ERG report, page 99, table 36.

6.30 The ERG's additional exploratory analyses in treatment experienced patients with genotype 1 HCV, and in which peginterferon alfa-2b and Rebetol costs were used instead of peginterferon alfa-2a and Copegus costs resulted in ICERs similar to those in the manufacturer's base case for the respective indications (refer to page 100 of ERG report for more information).

6.31 The ERG was requested by NICE to undertake further exploratory analyses to inform the Appraisal Committee's discussions. The ERG noted that the manufacturer's model used an estimate drawn from a single source in instances where multiple efficacy estimates were available for the same treatment and indication. The ERG examined alternative efficacy estimates in a scenario analysis exploring the impact on the manufacturer's ICERs of using a range of alternative sustained virological response estimates from studies of comparator treatments. . For HCV genotype 1 treatment-naive patients, the ERG used alternative

estimates of sustained virological response for boceprevir in combination with peginterferon alfa-2a and ribavirin from the SPRINT-2 study used in NICE technology appraisal of boceprevir (68.2% for people with no cirrhosis and 41.7% for people with cirrhosis). The sustained virological response rates for boceprevir in combination with peginterferon alfa-2a and ribavirin used in the manufacturer's base case for BOC+PEG2b+RBV were 64.1% for people with no cirrhosis and 55.0% for people with cirrhosis.). Applying the alternative boceprevir sustained virological response estimates decreased the ICER compared to the manufacturer's base case in genotype 1 HCV treatment naïve patients (the ICER was not reported by the ERG in its additional analyses).

6.32 The ERG also used alternative sustained virological response rates for the HCV genotype 3 treatment-naive interferon-eligible group. First, the ERG used an alternative sustained virological response of 90.7% for the sofosbuvir in combination with peginterferon alfa-2a and ribavirin. This response rate was the lower end of the 95% confidence interval for the non-cirrhotic population from the sofosbuvir (an estimate of 97.4% was used in the manufacturer's base case). The resulting ICER for sofosbuvir in combination with peginterferon alfa-2a and ribavirin compared with peginterferon alfa-2a and ribavirin for this subgroup was £23,772 per QALY gained (the manufacturer's base case ICER was £20,613 per QALY gained). The ERG also used an alternative sustained virological response rate of 92.3% for patients with cirrhosis for sofosbuvir in combination with peginterferon alfa-2a and ribavirin in this subgroup. This was the response rate used by the manufacturer for sofosbuvir and ribavirin (24 week) for patients in this subgroup with cirrhosis. The ERG noted that a higher response rate would better reflect a population which is not treatment-experienced. Applying this alternative response rate lowered the ICER to £18,187 per QALY gained. See ERG additional analyses, pages 2-3, table 1.

6.33 The ERG also explored the impact of alternative assumptions about the natural history of chronic hepatitis C infection on the manufacturer's

ICERs. In particular, they investigated the impact of assuming an alternative distribution of patients with cirrhosis. The ERG used a distribution for new and existing patients with cirrhosis obtained from Hartwell et al. (2011) based on data from a London teaching hospital where 32% of existing patients and 10% of new patients had cirrhosis. The results of the exploratory analysis suggested that using this distribution increased the manufacturer's base case ICERs for treatment naïve patients and reduced the ICERs for treatment experienced patients across all genotypes. In treatment naive people with genotype 3 who are interferon eligible, the ICER for sofosbuvir with peginterferon alfa-2a and ribavirin (12 weeks) compared with peginterferon alfa-2a and ribavirin (24 weeks) increased from £20,613 in the manufacturer's base case to £30,175 per QALY gained. The ICERs for treatment naïve people with genotype 1 HCV who cannot be treated with peginterferon alfa and for treatment naïve people with genotype 2 who are interferon eligible remained above £30,000 per QALY gained, while the remaining subgroups remained below £30,000 per QALY gained. See ERG additional analyses, pages 3-5, table 2.

6.34 The ERG explored the effect of using a lower transition probability from the non-cirrhotic state to the compensated cirrhosis state, at age 40 in the manufacturer's model. The resulting ICERs increased across all subgroups.

Indication	Comparison	Manufacturer's base case ICER (£/QALY)	Revised ICER (£/QALY)
Genotype 3, treatment naïve, interferon eligible	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. peginterferon and ribavirin(24 weeks)	20,613	22,862
Genotype 3, treatment naïve, interferon ineligible	sofosbuvir and ribavirin (24 weeks) vs. no treatment	21,478	24,984
Genotype 3, treatment experienced interferon eligible	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. no treatment	8,557	10,415
	sofosbuvir with peginterferon and ribavirin (12 weeks) vs.	12,246	14,368

Indication	Comparison	Manufacturer's base case ICER (£/QALY)	Revised ICER (£/QALY)
	peginterferon and ribavirin(48 weeks)		
Genotype 3, treatment experienced interferon ineligible	sofosbuvir and ribavirin (24 weeks) vs. no treatment	28,569	33,649
Genotype 1 treatment naïve, interferon eligible	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. telaprevir	11,836	14,338
	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. boceprevir	7,292	9,458
	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. peginterferon and ribavirin(48 weeks)	14,930	17,851
Genotype 1 treatment naïve, interferon ineligible	sofosbuvir and ribavirin (24 weeks) vs. no treatment	49,249	61,077

Source: ERG additional analyses, page 5-6, table 3.

6.35 The ERG explored the percentage of patients receiving 24 weeks of sofosbuvir treatment compared with 12 weeks and conducted sensitivity analyses around the effect of the length of treatment. The 3 groups which might receive 12 or 24 weeks of sofosbuvir treatment are:

- HCV genotype 1 receiving sofosbuvir with peginterferon alfa and ribavirin;
- HCV genotype 2, receiving sofosbuvir and ribavirin; and
- HCV genotype 3, receiving sofosbuvir with peginterferon alfa and ribavirin.

The ERG's clinical specialists differed in their opinions as to how long patients in these groups would be treated. One clinical specialist stated that it would be unlikely that more than 1-2% of patients would be considered better off with longer therapy and that these patients would be those identified in the summary of product characteristics in which consideration to longer treatment periods should be given. Another clinical specialist stated that approximately 20% of patients might require 24

weeks of therapy, especially those who are interferon intolerant and patients with more severe cirrhosis. The same specialist cautioned that it was difficult to predict what would happen when an all-oral regimen became available.

6.36 The ERG pointed out that the manufacturer's economic model only allows for 12 week regimens for sofosbuvir for treatment naïve people with genotype 1 HCV who are interferon eligible, and treatment naïve people with genotype 2 HCV (regardless of interferon eligibility). The economic model did have a 24 week regimen of sofosbuvir and ribavirin available for various genotype 3 HCV subgroups. Using this, the ERG compared treatment with sofosbuvir and ribavirin for 24 weeks with either peginterferon alfa and ribavirin treatment for 24 weeks in treatment naïve people with genotype 3 HCV and either no treatment or 48 weeks of peginterferon alfa and ribavirin treatment for treatment-experienced people with genotype 3 HCV. The resulting ICERs were more than double the manufacturer's base case results when selecting 12 weeks of sofosbuvir and ribavirin in the model (Table 23).

Table 23 ERG's economic analyses for a 24 week sofosbuvir and ribavirin regimen in patients with genotype 3 HCV

Indication	Comparison	Manufacturer's base case ICER (£/QALY)	ICER with 24 week SOF and ribavirin (£/QALY)
GT3 treatment naïve, interferon eligible	sofosbuvir and ribavirin vs. peginterferon alfa and ribavirin (24 weeks)	20,613	46,713
GT3 treatment experienced, interferon eligible	sofosbuvir and ribavirin vs. no treatment	8,557	28,438
	sofosbuvir and ribavirin vs. peginterferon alfa and ribavirin (48 weeks)	12,246	48,687

Source: ERG additional analyses, page 8, table 4.

6.37 The ERG conducted sensitivity analyses to evaluate the impact of changing the average age of entry into the model. The resulting ICERs were generally lower when a lower average age of 35 years was selected for entry into the model and higher when the average age selected was 55

years. The ERG conducted sensitivity analyses using a utility increment after sustained virological response of 0 and 0.04, compared with the manufacturer's base case which used a utility increment of 0.05 after sustained virological response. The resulting ICERs in the ERG's analysis were consistently higher than the manufacturer's base case results. See ERG additional analysis, page 8, table 5.

6.38 The ERG conducted a sensitivity analysis in which it applied an alternative transition probability from the cirrhosis state to hepatocellular carcinoma state which it calculated from Cardoso et al (2010). The probability was calculated as 0.0123 (95% CI 0.028 to 0.0218) and upper and lower bounds of the confidence interval were included in the analysis. Only 3 of the ERG's comparisons using the revised transition probability results in ICERs over £30,000 per QALY gained. See ERG additional analysis, page 13, table 8.

6.39 The ERG also evaluated a scenario which combined a number of its alternative assumptions. This scenario analysis considered the combined impact on the manufacturer's ICERs of including a transition from the sustained virological response with cirrhosis stage to hepatocellular carcinoma (section 6.38), alternative utility increments after a sustained virological response (section 6.37), and an alternative estimate of efficacy for peginterferon alfa and ribavirin in the HCV genotype treatment naïve, interferon-eligible population (section 6.31). The resulting ICERs are shown in Table 24 ERG's combined scenario analyses compared with manufacturer's base case ICERsTable 24.

Table 24 ERG's combined scenario analyses compared with manufacturer's base case ICERs

Indication	Comparison	Manufacturer's base case ICER (£/QALY)	Revised ICER Incr = 0 (£/QALY)	Revised ICER Incr = 0.041 (£/QALY)
Genotype 2 treatment naïve, interferon eligible	sofosbuvir and ribavirin (12 weeks) vs. peginterferon and ribavirin(24 weeks)	46,324	86,589	58,383
Genotype 2 treatment naïve,	sofosbuvir and ribavirin (12 weeks) vs. no treatment	8,154	16,289	10,242

Indication	Comparison	Manufacturer's base case ICER (£/QALY)	Revised ICER Incr = 0 (£/QALY)	Revised ICER Incr = 0.041 (£/QALY)
interferon ineligible				
Genotype 2 treatment experienced, interferon eligible	sofosbuvir and ribavirin (12 weeks) vs. no treatment	9,274	18,383	11,484
	sofosbuvir and ribavirin (12 weeks) vs. peginterferon and ribavirin(48 weeks)	12,519	24,407	15,297
Genotype 2 treatment experienced, interferon ineligible	sofosbuvir and ribavirin (12 weeks) vs. no treatment	8,591	17,135	10,763
Genotype 3 treatment naïve, interferon eligible	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. peginterferon and ribavirin(24 weeks)	20,613	40,919	28,211
Genotype 3 treatment naïve, interferon ineligible	sofosbuvir and ribavirin (24 weeks) vs. no treatment	21,478	42,435	27,330
Genotype 3 treatment experienced, interferon eligible	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. no treatment	8,557	17,499	11,161
	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. peginterferon and ribavirin(48 weeks)	12,246	24,816	15,822
Genotype 3 treatment experienced, interferon ineligible	sofosbuvir and ribavirin (24 weeks) vs. no treatment	28,569	55,733	35,170
Genotype 1 treatment naïve, interferon eligible	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. telaprevir	11,836	26,377	15,376
	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. boceprevir	7,292	16,417	9,415
	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. peginterferon and ribavirin(48 weeks)	14,930	47,723	28,213
Genotype 1 treatment naïve, interferon ineligible	sofosbuvir and ribavirin (24 weeks) vs. no treatment	49,249	109,526	59,587
Genotype 4/5/6	sofosbuvir with peginterferon and ribavirin (12 weeks) vs. peginterferon and ribavirin(48 weeks)	26,797	58,568	31,271

Source: ERG additional analyses, page 14-15, table 9.

Comments from other consultees

6.40 The clinical specialists stated that curing people of HCV has the possibility of reducing onward transmission and thereby would lower the cost per QALY of sofosbuvir. Since the public health impact of reduced onward transmission is not accounted for in the economic model, the clinical specialists considered that the estimated ICERs may be over-estimated.

7 Equality issues

7.1 It was raised during consultation that hepatitis C adversely affects certain populations, who could be considered at risk of being disadvantaged in terms of accessing the healthcare system and therefore at risk of inequity of access to innovative new treatments (such as certain immigrant populations, prison populations and people who inject drugs). Attendees at the scoping workshop agreed that this issue related to implementation and could not be addressed through technology appraisal recommendations.

8 Innovation

8.1 The manufacturer considers that sofosbuvir offers a step-change in the efficacy, safety and tolerability for the treatment of chronic hepatitis C making successful HCV cure a realistic probability for a high proportion of patients including those who currently have no other treatment options. The manufacturer states that sofosbuvir meets the five criteria for step-change innovation as laid out in the Kennedy Report 2009 in that it:

- significantly and substantially improves the way that a current need is met
- meets a need which the NHS has identified as being important
- has a robust evidence base providing research on the populations in which the product is effective
- has demonstrated an appropriate level of effectiveness, and
- the product has marketing authorisation for the particular indication.

As further evidence of the innovativeness of sofosbuvir, the manufacturer highlighted that European Medicines Association accepted an accelerated regulatory approval process for sofosbuvir which is a designation only granted to those medicines of major public health interest.

8.2 The manufacturer also states in its submission that there are a number of health related benefits that are not included in the QALY calculation, including the reduction in onward transmission of HCV through rapid clearance of the virus from the body due to effective treatment, together with the potential for reversal of liver fibrosis once cured of HCV, and the reduction in risk of hepatocellular carcinoma and mortality from HCV. According to the manufacturer, improved cure rates together with increased number of patients eligible for treatment sofosbuvir could have a positive impact on public health therefore reducing long-term burden to the NHS.

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Boceprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal No. 253, Apr 2012, Review Proposal Date April 2015.
- Telaprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal No. 252, Apr 2012, Review Proposal Date April 2015.
- Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal No. 200, Sep 2010. Guidance on static list.
- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. NICE technology appraisal No. 106, Aug 2006 (partially updated in TA200). Guidance on static list.
- Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C (partially updated in TA200). NICE technology appraisal No. 75, Jan 2004. Guidance on static list.
- Needle and syringe programmes (replaces NICE public health guidance 18), NICE public health guidance 52 (2014).

Under development

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

- Hepatitis C: diagnosis and management of hepatitis C. NICE clinical guideline. Publication date to be confirmed.
- Simeprevir for treating genotype 1 or 4 chronic hepatitis C'. NICE technology appraisal. Earliest anticipated date of publication January 2015.
- Faldaprevir for treating genotype 1 chronic hepatitis C. NICE technology appraisal. Publication date to be confirmed.
- Sofosbuvir-lidepasvir for treating genotype 1 chronic hepatitis C. NICE technology appraisal. Publication date to be confirmed.

NICE pathways

- There is a NICE pathway on Hepatitis B and C testing, which is available from http://pathways.nice.org.uk/pathways/hepatitis-b-and-c-testing.

Appendix B:

Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002798/WC500160600.pdf

Interim NHS clinical commissioning policy statement: Sofosbuvir+Daclatasvir/Ledipasvir +/- Ribavirin for defined patients with Hepatitis C (April 2014).

http://www.england.nhs.uk/wp-content/uploads/2014/04/sofosbuvir-pol-stat.pdf

Commissioning position:

Patients eligible for treatment are those with significant risk of death or irreversible damage within the next 12 months, irrespective of genotype. For example, there are patients listed for liver transplantation and others who are either approaching but not yet on a liver transplant waiting list, or who may not fulfil other criteria to allow liver transplantation to be performed.

Such patients would be defined as follows:

1) Evidence of present or previous decompensated cirrhosis with an episode of ascites, variceal bleeding, or encephalopathy.

2) Child Pugh Score > or = 7

3) Non-hepatic manifestation of HCV infection likely to lead to irreversible damage within 12 months AND intolerant of or failed to respond to pegylated interferon-based treatment

4) Exceptional cases: Only patients at high risk of death, needing a liver transplant, or likely to suffer irreversible harm in the next 12 months, who are not suitable for treatment with pegylated interferon-based treatment, will be eligible.

The scheme will treat ~500 patients who fulfil the criteria for a total treatment duration of 12 weeks.

Treatment will be delivered through specialized centres (circa 15) that will be selected for this role and which can meet the stated criteria and offer reasonable geographic access.

In creating this policy statement NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of these treatments in current clinical practice, whether the scientific research has shown the treatments to be of benefit to patients (including how any benefit is balanced against possible risks), and whether its use represents the best use of NHS resources.