

Sofosbuvir for treating chronic hepatitis C

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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1 Recommendations

1.1 Sofosbuvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1.

Table 1 Sofosbuvir for treating adults with chronic hepatitis C

Genotype	Sofosbuvir in combination with peginterferon alfa and ribavirin; Treatment history	Sofosbuvir in combination with peginterferon alfa and ribavirin; Recommendation	Sofosbuvir in combination with ribavirin; Treatment history	Sofosbuvir in combination with ribavirin; Recommendation
Adults with genotype 1 HCV	All	Recommended	All	Not recommended
Adults with genotype 2 HCV	All	Not licensed for this population	Treatment-naive	Only recommended for people who are intolerant to or ineligible for interferon
Adults with genotype 2 HCV	All	Not licensed for this population	Treatment-experienced	Recommended
Adults with genotype 3 HCV	Treatment-naive	Only recommended for people with cirrhosis	Treatment-naive	Only recommended for people with cirrhosis who are intolerant to or ineligible for interferon
Adults with genotype 3 HCV	Treatment-experienced	Recommended	Treatment-experienced	Only recommended for people with cirrhosis who are intolerant to or ineligible for interferon
Adults with genotype 4, 5 or 6 HCV	All	Only recommended for people with cirrhosis	All	Not recommended

HCV, hepatitis C virus; treatment-experienced, the person's hepatitis C has not adequately responded to interferon-based treatment; treatment-naïve, the person has not had treatment for chronic hepatitis C

- 1.2 People currently receiving treatment initiated within the NHS with sofosbuvir that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Sofosbuvir (Sovaldi, Gilead Sciences) is a uridine nucleotide analogue that inhibits hepatitis C virus (HCV) polymerase, preventing viral replication. Sofosbuvir has a UK marketing authorisation for use 'in combination with other medicinal products for treating chronic hepatitis C in adults'. The recommended dose is 1 daily 400 mg tablet, taken orally. It should be used in combination with peginterferon alfa and ribavirin, or ribavirin only, as stated in the summary of product characteristics. Monotherapy with sofosbuvir is not recommended. The average duration of treatment is 12 or 24 weeks depending on the person's HCV genotype and history of previous treatment with interferon. Combination treatment regimens without peginterferon alfa for people with genotype 1, 4, 5 or 6 HCV infection have not been investigated in phase 3 studies. According to the summary of product characteristics, treatment regimens without peginterferon alfa should be used for people with genotype 1, 4, 5 or 6 infection only if they are intolerant to or ineligible for peginterferon alfa therapy and are in urgent need of treatment. The summary of product characteristics states that, for all genotypes, consideration should be given to extending the duration of therapy from 12 to 24 weeks, especially for people who have 1 or more factors historically associated with lower response rates to interferon-based therapies. These include people with advanced liver fibrosis or cirrhosis, high baseline viral concentrations, previous unresponsiveness to peginterferon alfa and ribavirin combination therapy, or a single nucleotide polymorphism without 2 copies of the C allele near their IL28B gene (that is, non-CC genotype IL28B polymorphism); or for people of African and Caribbean family origin.
- 2.2 The summary of product characteristics lists the following most common adverse reactions for sofosbuvir plus ribavirin, with or without 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 tablet pack of 400 mg tablets (excluding VAT, BNF May 2014). The cost of a 12-week course of treatment is £34,982.94 and a 24-week course is £69,965.88 (both excluding VAT), not including the cost for ribavirin and peginterferon alfa. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee considered evidence submitted by Gilead Sciences and a review of the submissions by the Evidence Review Group (ERG).

3.1 The company provided clinical-effectiveness evidence, identified by systematic review, consisting of 13 studies investigating the effect of sofosbuvir plus ribavirin alone or ribavirin and peginterferon alfa in adults with chronic hepatitis C. These included:

- Studies in people who have not had treatment for hepatitis C virus (HCV) before (described as 'treatment-naive' in this document) with genotype 1, 4, 5 or 6 HCV:
 - 1 phase 3 open-label, single arm study (NEUTRINO, n=327)
 - 3 phase 2 randomised controlled trials (ATOMIC, n=332; QUANTUM, n=50; SPARE, genotype 1 only, n=60).
- Studies in people with treatment-naive HCV or in people who have had treatment before (described as 'treatment-experienced' in this document) with genotype 2 and 3 HCV:
 - 4 phase 3 randomised controlled trials (FISSION, n=499 treatment-naive; FUSION, n=201 treatment-experienced; POSITRON, n=278 treatment-naive and -experienced, people who had treatment before were considered to be intolerant to interferon, ineligible for interferon or unwilling to take it; VALENCE, n=419 treatment-naive and -experienced)
 - 1 phase 2 open-label, randomised controlled trial (ELECTRON, n=95 treatment-naive)
 - 1 phase 2 single-arm open-label study (LONESTAR-2, n=47 treatment-experienced)
 - 1 phase 2 2-arm open-label single cohort study (PROTON, n=25 treatment-naive).
- 1 phase 2 open-label 4 cohort study in people with genotype 1, 2 and 3 HCV

and HIV co-infection (PHOTON-1, n=223).

- 1 phase 2 open-label single-arm study in people with HCV waiting for a liver transplant (P7977-2025, n=61).

People in the sofosbuvir trials were tested for cirrhosis using Fibrotest (a biomarker test that uses the results of 6 blood serum tests to generate a score correlating to the degree of liver damage) and Fibroscan (a non-invasive scan allowing the measurement of liver fibrosis based on its elasticity). No liver biopsies were performed at study entry and therefore liver fibrosis according to METAVIR score (which is based on liver biopsy histology) was not available for the sofosbuvir trials.

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

Treatment-naïve population

- 3.2 NEUTRINO compared the efficacy and safety of sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks in people with genotype 1, 4, 5 or 6 treatment-naïve chronic HCV with a historical control. The primary outcome was sustained virological response 12 weeks after the end of treatment. The study did not include sites in the UK. A historical control rate of 60% for sustained virological response was used for peginterferon alfa-2a and ribavirin, taken from the phase 3 telaprevir (ADVANCE) and boceprevir (SPRINT-2) trials. The people in the study had a median age of 54 years (age range 19 to 70 years); 64% were men; 78% had baseline HCV RNA greater than 6 log₁₀ IU/ml (viral load, or the number of virus particles in the blood; a viral load less than 6 log₁₀ IU/ml has been linked to better response to treatment); 17% had cirrhosis; 89% had genotype 1 HCV and 11% had genotype 4, 5 or 6 HCV.
- 3.3 Results from the NEUTRINO study showed that 12 weeks after the end of treatment with sofosbuvir plus peginterferon alfa and ribavirin, 90% (95% confidence interval [CI] 87 to 93%, p<0.001) of people with genotype 1, 4, 5 or 6 treatment-naïve HCV had a sustained virological response. Cirrhosis and non-CC IL28B polymorphism were both associated with a reduced sustained

virological response at 12 weeks: 92% (95% CI 89 to 95%) for people without cirrhosis, 80% (95% CI 67 to 89%) for those with cirrhosis ($p=0.0018$), and 98% (95% CI 93 to 100%) for people with the IL28B CC genotype polymorphism compared with 87% (95% CI 82 to 91%) for those with the non-CC IL28B polymorphism ($p=0.006$). Sustained virological response at 12 weeks was 90% for people with genotype 1 HCV. Overall, the sustained virological response at 12 weeks was 97% for people with genotype 4, 5 or 6 HCV (100% in the 33 people without cirrhosis, and 50% in the 2 people with cirrhosis). No patient had a relapse during treatment. Relapse after virological response at the end of treatment occurred in 28 of 327 people after stopping treatment; 25 completed 12 weeks of treatment and 3 did not complete the treatment course. The company did not provide any information about the family origin of people in the NEUTRINO study.

- 3.4 ATOMIC compared the efficacy and safety of sofosbuvir plus peginterferon alfa and ribavirin in people with genotype 1, 4, 5 or 6 treatment-naïve chronic HCV. The study included 3 treatment arms: 1 arm had sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, the second arm had the same treatment for 24 weeks, and the third arm had the same treatment for 12 weeks, followed by 12 weeks of sofosbuvir monotherapy (sofosbuvir monotherapy is outside of the marketing authorisation for sofosbuvir, but the results were included by the company for information). The primary outcome was sustained virological response 24 weeks after the end of treatment. Most people had genotype 1 HCV, and no one with genotype 5 HCV was enrolled in the study. Results showed that after treatment with sofosbuvir, sustained virological responses of 96% to 98% were achieved in each treatment arm. This suggests that for sofosbuvir plus peginterferon alfa and ribavirin treatment there is no increase in sustained virological response when treatment is extended beyond 12 weeks.
- 3.5 QUANTUM compared the efficacy and safety of sofosbuvir plus ribavirin for 12 weeks with 24 weeks of treatment in people with genotype 1, 4, 5 or 6 treatment-naïve chronic HCV. The primary outcome was sustained virological response 12 weeks after the end of treatment, which was 56% ($n=25$) for people who had 12 weeks of sofosbuvir plus ribavirin and 52% ($n=25$) for people who had 24 weeks of sofosbuvir plus ribavirin. Results showed no statistically significant difference between treatment arms.

- 3.6 SPARE was a 2 part study that investigated the efficacy and safety of sofosbuvir plus ribavirin treatment for 24 weeks in people with genotype 1 treatment-naïve chronic HCV. The first part was a 1 arm open-label study of the efficacy and safety of sofosbuvir plus ribavirin treatment for 24 weeks. The second part investigated 24 weeks of sofosbuvir plus ribavirin (using the licensed weight-based dose) compared with sofosbuvir plus a low, unlicensed dose of ribavirin. The primary outcome was sustained virological response 24 weeks after the end of treatment. In part 1 of the study, sustained virological response was achieved in 90% (n=9) of people. In part 2, 24 people in each group (96%) had viral suppression by week 4 of treatment. However after completing treatment, 7 people in the weight-based ribavirin group and 10 people in the low-dose ribavirin group had a relapse. The sustained virological response 12 weeks after the end of treatment in the intention-to-treat population was 68% (n=25) for people having 24 weeks of sofosbuvir plus weight-based ribavirin and 48% (n=25) for people having 24 weeks of sofosbuvir plus low-dose ribavirin. The sustained virological response 24 weeks after the end of treatment was the same as the response 12 weeks after the end of treatment.

Treatment-experienced population

- 3.7 The company did not provide any evidence for the efficacy of sofosbuvir plus ribavirin, or sofosbuvir plus peginterferon alfa and ribavirin in people with genotype 1, 4, 5 or 6 treatment-experienced chronic HCV.

Evidence in people with genotype 2 or 3 HCV

Treatment-naïve population

- 3.8 FISSION compared sofosbuvir plus ribavirin for 12 weeks with peginterferon alfa-2a plus ribavirin treatment for 24 weeks in people with genotype 2 or 3 treatment-naïve chronic HCV. The primary outcome was sustained virological response 12 weeks after the end of treatment. The non-inferiority of sofosbuvir plus ribavirin compared with peginterferon alfa-2a plus ribavirin for sustained virological response at 12 weeks (primary end point) was tested. People in the

study were randomised in a 1:1 ratio and stratified by the presence or absence of cirrhosis, HCV genotype (2 or 3) and baseline HCV RNA level ($<6 \log_{10}$ IU/ml or $\geq 6 \log_{10}$ IU/ml). The people in the study had a median age of 50 years (range from 19 to 77 years); 66% were men; 57% had baseline HCV RNA levels greater than $6 \log_{10}$ IU/ml; 20% had cirrhosis; 72% had genotype 3 HCV.

- 3.9 Results from FISSION showed that at 12 weeks after the end of treatment, sustained virological response was 67% in both treatment groups. Sofosbuvir plus ribavirin was non-inferior to peginterferon alfa-2a plus ribavirin for the primary end point. The absolute difference between treatment groups after adjusting for stratification was 0.3% (95% CI -7.5% to 8.0%, non-inferiority $p < 0.001$). HCV genotype and cirrhosis were associated with differences in sustained virological response (see table 2).

Table 2 Sustained virological response 12 weeks after the end of treatment from FISSION

HCV genotype	Sofosbuvir plus ribavirin; Percentage of people with a sustained virological response 12 weeks after end of treatment (95% CI)	Peginterferon alfa-2a plus ribavirin; Percentage of people with a sustained virological response 12 weeks after end of treatment (95% CI)
2	97% (90 to 100%), (n=70)	78% (66 to 87%), (n=67)
3	56% (48 to 63%), (n=183)	63% (55 to 70%), (n=176)
2 or 3 without cirrhosis	72% (65 to 78%), (n=206)	74% (67 to 80%), (n=193)
2 or 3 with cirrhosis	47% (33 to 62%), (n=50)	38% (25 to 53%), (n=50)
2 without cirrhosis	98.3% CI not reported, (n=59)	81.5 % CI not reported, (n=54)
2 with cirrhosis	90.9% CI not reported, (n=11)	61.5 % CI not reported, (n=13)
3 without cirrhosis	61% CI not reported, (n=145)	71% CI not reported, (n=139)

HCV genotype	Sofosbuvir plus ribavirin; Percentage of people with a sustained virological response 12 weeks after end of treatment (95% CI)	Peginterferon alfa-2a plus ribavirin; Percentage of people with a sustained virological response 12 weeks after end of treatment (95% CI)
3, with cirrhosis	34% CI not reported, (n=38)	30% CI not reported, (n=37)

CI, confidence interval; HCV, hepatitis C virus

- 3.10 ELECTRON was carried out in 2 centres in New Zealand. The study included 8 treatment arms, only 5 of which were used by the company to inform its submission. The treatment arms presented included people with genotype 1, 2 and 3 treatment-naïve chronic HCV who had sofosbuvir plus ribavirin with or without peginterferon alfa-2a. In 4 of the treatment arms, people with genotype 2 or 3 HCV had sofosbuvir plus ribavirin for 12 weeks and either 0, 4, 8 or 12 weeks of peginterferon alfa-2a. In another treatment arm, added as a protocol amendment after the 4 previous dose-ranging treatment arms were completed, people with genotype 2 or 3 HCV had sofosbuvir plus peginterferon alfa-2a and ribavirin for 8 weeks. Across the 5 study arms that were included in the company's submission, 100% of people with genotype 2 or 3 HCV had a sustained virological response 12 weeks after the end of treatment.
- 3.11 PROTON was a study in 22 centres in the USA in which people with genotype 1, 2 and 3 treatment-naïve chronic HCV had sofosbuvir plus peginterferon alfa-2a and ribavirin. The company only presented results from the study arm that included people with genotype 2 or 3 HCV, who had sofosbuvir plus peginterferon alfa-2a and ribavirin for 12 weeks, because the other study arm was not used to inform its regulatory submission. Results from PROTON showed that sustained virological response 12 weeks after the end of treatment was 92% (no confidence interval reported in company's submission) across both genotypes, and 93% in people with genotype 2 HCV and 90% in people with genotype 3 HCV.

Treatment-experienced population

- 3.12 FUSION compared the efficacy and safety of sofosbuvir plus ribavirin for either 12 or 16 weeks in people with genotype 2 or 3 chronic HCV, whose disease had no response to previous HCV treatment (25%), or had lost its initial response during or after previous HCV treatment (75%). The study did not include sites in the UK.

The people in the study had a median age of 56 years (range 24 to 70 years); 70% were men; 73% had baseline HCV RNA levels greater than 6 log₁₀ IU/ml; 34% had cirrhosis; 63% had genotype 3 HCV.

- 3.13 Results from FUSION showed that HCV genotype and cirrhosis were associated with differences in sustained virological response (see table 3).

Table 3 Sustained virological response 12 weeks after the end of treatment from FUSION

HCV genotype	Sofosbuvir plus ribavirin for 12 weeks; Percentage of people with a sustained virological response 12 weeks after end of treatment	Sofosbuvir plus ribavirin for 16 weeks; Percentage of people with a sustained virological response 12 weeks after end of treatment
2 or 3	50% (95%CI 40 to 60%), (n=100)	73% (95% CI 63 to 81%), (n=95)
2	86% CI not reported, (n=36)	94% CI not reported, (n=32)
3	30% CI not reported, (n=64)	62% CI not reported, (n=63)
2 without cirrhosis	96% CI not reported, (n=26)	100% CI not reported, (n=23)
2 with cirrhosis	60% CI not reported, (n=10)	78% CI not reported, (n=9)
3 without cirrhosis	37% CI not reported, (n=38)	63% CI not reported, (n=40)
3 with cirrhosis	19% CI not reported, (n=26)	61% CI not reported, (n=23)

CI, confidence interval; HCV; hepatitis C virus

- 3.14 LONESTAR-2 evaluated the efficacy and safety of sofosbuvir plus peginterferon alfa-2a and ribavirin for 12 weeks in people with genotype 2 or 3 chronic HCV, whose disease had no response to previous HCV treatment (15%), or had lost its initial response during or after previous HCV treatment (85%). The study included 1 site in the USA. The people in the study had a median age of 56 years (age range 39 to 72 years); 68% were men; the mean baseline HCV RNA level was 6.2 log₁₀ IU/ml (range from 4.0 to 7.2 log₁₀ IU/ml); 55% had cirrhosis; 51% had

genotype 3 HCV.

- 3.15 Results from LONESTAR-2 showed that sustained virological response 12 weeks after the end of treatment was 89% (no confidence intervals were reported in the company's submission) in people with genotype 2 or 3 HCV. HCV genotype and cirrhosis were not associated with statistically significant differences in sustained virological response. At 12 weeks after the end of treatment, sustained virological response was 96% and 83% in people with genotype 2 and genotype 3 HCV respectively. In people with genotype 2 HCV without cirrhosis, sustained virological response at 12 weeks after the end of treatment was 100% and in people with cirrhosis it was 93%. In people with genotype 3 HCV, the sustained virological response was 83% for people with and without cirrhosis.

Treatment-naïve or treatment-experienced

- 3.16 VALENCE was an unblinded study in which all people with genotype 2 HCV had sofosbuvir plus ribavirin for 12 weeks, and those with genotype 3 HCV had sofosbuvir plus ribavirin for 24 weeks. Because of changes made during the study, 11 people with genotype 3 HCV had a 12 week course of therapy. As a result of emerging data showing that people with genotype 3 HCV had higher sustained virological responses when they were treated for longer, treatment for all people with genotype 3 in the study was extended to 24 weeks and the goals of the study were redefined to be descriptive and not include hypothesis testing. People in the study had a median age of 51 years (range 19 to 74 years); 60% were men; the mean baseline HCV RNA level was 6.4 log₁₀ IU/ml; 21% had cirrhosis; 78% had genotype 3 HCV. In around 65% of people with treatment-experienced HCV, initial response was lost during or after previous treatment, 30% had no response to interferon-based treatment, and 5% were intolerant to interferon.
- 3.17 Results from VALENCE showed that sustained virological response 12 weeks after the end of treatment for people with genotype 2 HCV having sofosbuvir plus ribavirin for 12 weeks was 93% (no confidence intervals were reported in company's submission). In people with genotype 3 HCV who were treated for 24 weeks, the sustained virological response 12 weeks after the end of treatment was 84% overall, 93% in people who had never been treated and 77% in people

who had been previously treated (no confidence intervals for this study were reported in the company's submission).

Population for whom interferon treatment was unsuitable (treatment-naïve and treatment-experienced)

- 3.18

POSITRON evaluated the efficacy and safety of sofosbuvir plus ribavirin compared with placebo for 12 weeks in people with genotype 2 or 3 HCV. People in the study had previously discontinued interferon therapy owing to unacceptable adverse events (the company referred to this group as interferon intolerant), or had a concurrent medical condition preventing therapy with an interferon-containing regimen (the company referred to this group as interferon ineligible), or were unwilling to have interferon treatment. Similar proportions of people with genotype 2 and 3 HCV were enrolled (51% and 49% respectively) in the study. People were randomised in a 3:1 ratio to receive sofosbuvir plus ribavirin or placebo, and were stratified (grouped) by the presence or absence of cirrhosis. The difference in sustained virological response 12 weeks after the end of treatment was assessed for superiority, which was demonstrated if the p-value was less than 0.05. People treated in the study had a median age of 54 years (range 21 to 75 years); 54% were men; 70% had baseline HCV RNA levels greater than 6 log₁₀ IU/ml; 16% had cirrhosis. The proportions of people who were intolerant to interferon, ineligible for interferon, or unwilling to have it were 9%, 44%, and 47% respectively. Most people had not had previous treatment for chronic hepatitis C (81.3%).
- 3.19

Results from POSITRON showed that HCV genotype and cirrhosis were associated with differences in sustained virological response in people treated with sofosbuvir plus ribavirin (see table 4). The difference in sustained virological response between the sofosbuvir plus ribavirin and the placebo group was statistically significant (p<0.001) for people with genotype 2 or 3 chronic HCV.

Table 4 Sustained virological response 12 weeks after the end of treatment from POSITRON

HCV genotype	Percentage of people with a sustained virological response 12 weeks after end of treatment; Sofosbuvir plus ribavirin for 12 weeks	Percentage of people with a sustained virological response 12 weeks after end of treatment; Placebo
2 or 3	78% (95%CI 72 to 83%), (n=207)	0%, (n=71)

HCV genotype	Percentage of people with a sustained virological response 12 weeks after end of treatment; Sofosbuvir plus ribavirin for 12 weeks	Percentage of people with a sustained virological response 12 weeks after end of treatment; Placebo
2	93% CI not reported, (n=109)	-
3	61% CI not reported, (n=98)	-
2 without cirrhosis	92% CI not reported, (n=92)	-
2 with cirrhosis	94% CI not reported, (n=17)	-
3 without cirrhosis	68% CI not reported, (n=84)	-
3 with cirrhosis	21% CI not reported, (n=14)	-

CI, confidence interval; HCV, hepatitis C virus

People with HIV and HCV co-infection

3.20 The safety and efficacy of 12 or 24 weeks of treatment with sofosbuvir plus ribavirin in people with genotype 1, 2 or 3 chronic hepatitis C who were co-infected with HIV was evaluated in an open-label clinical study (PHOTON-1). People in the study had genotype 2 or 3 treatment-naïve or treatment-experienced HCV or genotype 1 treatment-naïve HCV. People with genotype 2 or 3 treatment-naïve HCV had sofosbuvir plus ribavirin for 12 weeks. People with genotype 2 or 3 treatment-experienced HCV and people with genotype 1 treatment-naïve HCV had sofosbuvir plus ribavirin for 24 weeks. Participants were either not on antiretroviral therapy with a CD4+ cell count above 500 cells/mm³ or had virologically suppressed HIV-1 with a CD4+ cell count above 200 cells/mm³. At the time of enrolment, 95% of participants had antiretroviral therapy. Preliminary sustained virological response at 12 weeks was available for 210 people.

3.21 Results from PHOTON-1 showed that treatment with sofosbuvir plus ribavirin for

12 weeks in people with genotype 1, 2 or 3 HCV and HIV co-infection and 24 weeks in people with genotype 1, 2 or 3 HCV and HIV co-infection resulted in sustained virological response at 12 weeks after treatment irrespective of HCV genotype ($\geq 93\%$; interim analysis). Similar safety and tolerability profiles were reported in people with HIV and HCV co-infection and in people with HCV only.

People awaiting liver transplant

- 3.22 An open-label clinical study (P7977-2025) was carried out in people with chronic hepatitis C awaiting a liver transplant. It evaluated the safety and efficacy of sofosbuvir plus ribavirin administered before transplant to prevent post-transplant HCV reinfection. The primary end point of the study was post-transplant virological response (HCV RNA undetectable at 12 weeks after transplant). People with HCV regardless of genotype, with hepatocellular carcinoma suitable for liver transplant, had 400 mg sofosbuvir and 1,000 to 1,200 mg ribavirin daily for a maximum of 24 weeks. This was subsequently amended to 48 weeks or until the time of liver transplant, whichever was first. An interim analysis of results for 61 people who had sofosbuvir and ribavirin, most of whom had genotype 1 HCV, showed that 44 had a liver transplant up to 48 weeks after treatment with sofosbuvir and ribavirin and 41 had no detectable HCV RNA at the time of their transplant. Results suggested that treatment with sofosbuvir and ribavirin prevented HCV recurrence in 64% of people compared with a 100% historical risk of reinfection without prophylaxis. During treatment, HCV RNA suppression in people with well-compensated cirrhosis awaiting a liver transplant for hepatocellular carcinoma was rapid and similar to that seen in other patient populations treated with sofosbuvir regimens.

Adverse effects of treatment

- 3.23 The company presented data on adverse events for NEUTRINO, FISSION, FUSION, POSITRON and VALENCE. The most common adverse events among people 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. Of these events, fatigue and headache were usually the most frequent, affecting more than 40% of the people in some studies.

Health-related quality of life

- 3.24 The company assessed health-related quality of life during the phase 2 and III trials using the Chronic Liver Disease Questionnaire – Hepatitis C (CLDQ-HCV), the Functional Assessment of Chronic Illness Therapy-Fatigue measurement system (FACIT-F), the Work Productivity and Activity Impairment questionnaire (WPAI), or the Short Form-36 items survey (SF-36). People in the phase 3 trials were not aware of their sustained virological response when completing the quality-of-life questionnaires. The results from NEUTRINO showed that there were differences in health-related quality of life scores between baseline and the end-of-treatment and that scores returned to baseline values by the post-treatment week 12 visit. The results from the FISSION study indicated that health-related quality of life during treatment in people who had peginterferon alfa-2a plus ribavirin was statistically significantly lower than for people in the sofosbuvir plus ribavirin arm. No difference was seen between the arms 12 weeks after the end of each treatment. The CLDQ-HCV results from FUSION indicated that health-related quality of life scores did not decrease significantly in either treatment group and there were no statistically significant differences in overall scores between the groups. The health-related quality of life data obtained from POSITRON showed decreases (worsening) in all SF-36 scales and the Mental Component and Physical Component scores in both treatment groups during treatment (baseline through to week 12). In the sofosbuvir plus 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 statistically significant differences from placebo at any time point.

Mixed treatment comparison

- 3.25 The company carried out a mixed treatment comparison to explore the comparative data for sofosbuvir and other relevant comparators. Because of

limited data, a mixed treatment comparison network could not be formed for all the relevant populations in the decision problem and the comparison was done only for people with genotype 1, 2 or 3 treatment-naïve HCV for whom interferon therapy was suitable. In addition, the company's economic model required that efficacy data were split by cirrhosis status and these data were not available for all trials. In people with genotype 1 HCV, a network including sofosbuvir was possible only by linking 2 small phase 2 trials (ATOMIC and PROTON) which included only people without cirrhosis. In people with genotype 2 or 3 HCV, the mixed treatment comparison results were based on people with and without cirrhosis combined. The results of the mixed treatment comparison showed that for people with genotype 1 treatment-naïve HCV regardless of cirrhosis status, 84.9% of those who had sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks had a sustained virological response at 12 weeks after treatment, compared with 46.2% of people who had peginterferon alfa and ribavirin for 48 weeks, 76.5% of people who had telaprevir plus peginterferon alfa and ribavirin and 69.7% of people who had boceprevir plus peginterferon alfa and ribavirin. For people with genotype 2 treatment-naïve HCV without cirrhosis, 98.6% of those who had sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks had a sustained virological response at 12 weeks after treatment, compared with 85.6% of people who had peginterferon alfa and ribavirin for 24 weeks. For people with genotype 2 treatment-naïve HCV with cirrhosis, sustained virological response was achieved in 97.5% of people who had sofosbuvir and ribavirin for 12 weeks, and in 67.5% of those who had peginterferon alfa and ribavirin for 24 weeks. For people with genotype 3 treatment-naïve HCV without cirrhosis for whom interferon therapy was suitable, 62% of those who had sofosbuvir plus ribavirin for 12 weeks had a sustained virological response at 12 weeks after treatment, compared with 68.3% of people who had peginterferon alfa and ribavirin for 24 weeks. For people with genotype 3 treatment-naïve HCV with cirrhosis who had sofosbuvir plus ribavirin for 12 weeks or peginterferon alfa and ribavirin for 24 weeks, the sustained virological response was similar (47.8% and 42.8% respectively) between the 2 treatment groups. The company highlighted several limitations to its mixed treatment comparison including the fact that the 12-week sofosbuvir plus ribavirin regimen used to treat genotype 3 HCV is not licensed. Therefore, the company stated that the results of the mixed treatment comparison could not be considered robust.

Evidence Review Group comments

- 3.26 The ERG reviewed the clinical evidence in the company's submission. It considered that the company's interpretation of the clinical evidence was overall justified and unbiased. However, the ERG cautioned that most of the evidence provided did not directly address the decision problem, because of the lack of head-to-head studies against current standard of care comparators. In addition, it highlighted that no studies were included that examined the efficacy of sofosbuvir within its marketing authorisation for people with genotype 1 treatment-experienced HCV. The ERG also noted that some of the evidence from VALENCE supporting the treatment regimens licensed for use in people with genotype 3 HCV should be interpreted with caution because randomisation was broken during the study, and some people were switched from 12 to 24 weeks of treatment with sofosbuvir plus ribavirin.
- 3.27 The ERG noted that the company only included adverse events from the 5 phase 3 studies (NEUTRINO, FISSION, FUSION, POSITRON and VALENCE). However, the ERG confirmed that the adverse events in the phase 2 studies were similar to those in the phase 3 studies. Overall, the ERG was satisfied that the evidence showed that treatment with sofosbuvir-based regimens was generally well tolerated and led to fewer adverse events than treatment with peginterferon alfa and ribavirin.

Cost effectiveness

- 3.28 The company identified 112 cost-effectiveness studies of chronic hepatitis C treatments. No studies were identified that compared sofosbuvir with alternative treatments.
- 3.29 To assess the cost effectiveness of sofosbuvir the company submitted a multi-state Markov model, which compared sofosbuvir plus ribavirin and sofosbuvir plus peginterferon alfa and ribavirin with the comparators defined in the decision problem (that is, boceprevir or telaprevir plus peginterferon alfa and ribavirin for people with genotype 1 HCV, and peginterferon alfa and ribavirin or placebo for people with other HCV genotypes). The structure of the model was based on published health economic models, but was amended by the company

to reflect the data available from its pivotal clinical trials and only distinguished between people with and without cirrhosis. The company used patient characteristics from the HCV UK research database to inform the population entering the model, including mean age at start of treatment, disease severity distribution and weight. The model had a total of 9 health states according to disease stage and treatment response. People entered the model in either the non-cirrhotic or compensated cirrhosis stages of disease. People who had antiviral treatment could move into the non-cirrhotic or sustained virological response cirrhotic health states. Those who did not clear the virus after treatment remained in their respective health states, or progressed to more severe stages of chronic HCV. All patients in the decompensated cirrhosis health state were assumed to be candidates for liver transplant. The model assumed that people who have a sustained virological response will not progress to more severe health states during or after therapy. Reversion to less severe health states was not permitted if treatment was unsuccessful.

- 3.30 The company applied age-specific general population mortality rates to each health state in the model. The same model structure was 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 lasted 1 year. A half-cycle correction was applied, which is consistent with previous hepatitis C appraisals. An NHS and personal and social services perspective was taken and a lifetime horizon was used, with costs and outcomes discounted at 3.5%.
- 3.31 Data from clinical trials were used to inform model inputs for treatment effects, health-related quality of life and adverse events. Treatment effect data were based on the sustained virological responses taken from the sofosbuvir clinical trials. If data for comparators were not available in these trials, they were taken from other published studies identified by the company. The company collected quality-of-life scores at baseline, week 12 during treatment, and at 4, 12 and 24 weeks after treatment. The SF-36 quality of life data were converted to SF-6D utility data and used in the company's base case. The company also converted SF-36 data to the EQ-5D and incorporated these in a deterministic sensitivity analysis. Adverse event rates were obtained from the sofosbuvir clinical trials and published studies. The company incorporated the 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 included for interventions associated with managing these adverse events.

- 3.32 The company used transition probabilities for disease progression from 2 published UK health technology assessments and 1 UK study: Hartwell et al. (2011), Shepherd et al. (2007), and Grishchenko et al. (2009), which used estimates from the Trent database (a large sample of people with HCV who attended only non-tertiary centres in the UK).
- 3.33 Utility values estimated from the sofosbuvir clinical studies were not used to inform the model. Instead, the company used utility values from previous technology appraisals for hepatitis C treatments that were based on the UK trial of mild chronic hepatitis C by Wright et al. (2006). The company calculated treatment-related utilities by applying treatment-related utility decrements to the baseline utility estimates.
- 3.34 The company compared sofosbuvir plus ribavirin (with or without peginterferon alfa), telaprevir plus peginterferon alfa and ribavirin, boceprevir plus peginterferon alfa and ribavirin, peginterferon alfa plus ribavirin, and best supportive care. Sofosbuvir, telaprevir, boceprevir, peginterferon alfa-2a and ribavirin were used in the model according to their marketing authorisations. The company applied no stopping rules, lead-in phase, or option for sofosbuvir retreatment, in line with the sofosbuvir clinical trials.
- 3.35 The company used costs in 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). Costs for drugs used to treat adverse events in the model were taken from the BNF. The company used the BNF price of ribavirin (Copegus 400mg, 56 tablet packs) at a cost of £246.65 in the model. Costs for the health states in the model were identified using published sources taken from the resource and costs systematic review done by the company. The costs for the non-cirrhotic health state were based on a calculation of the costs associated with mild and moderate cirrhosis (Wright et al.) using an assumed 77%: 23% split between mild and moderate cirrhosis. Costs were inflated to 2011 to 2012 prices (using the Hospital and Community Health Service pay and prices index).

- 3.36 Monitoring costs 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, published studies or expert opinion.

Results

- 3.37 The company presented base-case analyses for sofosbuvir plus ribavirin with or without peginterferon alfa compared with current standard of care, based on HCV genotype, interferon eligibility and treatment history. The company's results show that sofosbuvir treatment regimens increased the cost of treatment, but were associated with more quality-adjusted life years (QALYs) gained, a greater probability of sustained virological response (cure), and a reduction in end-stage liver disease and death.

Genotype 1

- 3.38 For people with genotype 1 treatment-naïve HCV for whom interferon therapy was suitable, the company's base-case analysis showed that the incremental cost-effectiveness ratio (ICER) for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £14,930 per QALY gained (incremental cost £19,129; incremental QALYs 1.3). Boceprevir plus peginterferon alfa and ribavirin was dominated (that is, sofosbuvir plus peginterferon alfa and ribavirin was less expensive and more effective) and telaprevir plus peginterferon alfa and ribavirin was extendedly dominated (that is, its ICER is higher than that of the next, more effective option when compared with a common baseline). For people with genotype 1 treatment-naïve HCV for whom interferon therapy was not suitable, the company's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £49,249 per QALY gained (incremental cost £63,903; incremental QALYs 1.3).
- 3.39 The company did not do an economic analysis for genotype 1 treatment-experienced HCV because there was no clinical evidence available to

populate the economic model for this population. However, an economic analysis for genotype 1 treatment-experienced HCV was later provided by the company (see section 3.69).

Genotype 2

- 3.40 In people with genotype 2 treatment-naïve HCV for whom interferon therapy was suitable, the company's base-case ICER for sofosbuvir plus ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 24 weeks was £46,324 per QALY gained (incremental cost £27,779; incremental QALYs 0.6). In people with genotype 2 treatment-naïve HCV for whom interferon therapy was not suitable, the company's base-case ICER for sofosbuvir plus ribavirin for 12 weeks compared with no treatment was £8,154 per QALY gained (incremental cost £20,051; incremental QALYs 2.5).
- 3.41 In people with genotype 2 treatment-experienced HCV for whom interferon therapy was suitable, the company's base-case ICER for sofosbuvir plus ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £9,274 per QALY gained (incremental cost £21,498; incremental QALYs 2.3). In people with genotype 2 treatment-experienced HCV for whom interferon therapy was not suitable, the company's base-case ICER for sofosbuvir and ribavirin treatment for 12 weeks compared with no treatment was £8,591 per QALY gained (incremental cost £20,697; incremental QALYs 2.4).

Genotype 3

- 3.42 In people with genotype 3 treatment-naïve HCV for whom interferon therapy was suitable, the company's base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 24 weeks was £20,613 per QALY gained (incremental cost £24,970; incremental QALYs 1.2). In people with genotype 3 treatment-naïve HCV for whom interferon therapy was not suitable, the company's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £21,478 per QALY gained (incremental cost £55,137; incremental QALYs 2.6).

- 3.43 In people with genotype 3 treatment-experienced HCV for whom interferon therapy was suitable, the company's base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £8,557 per QALY gained (incremental cost £19,634; incremental QALYs 2.3). In people with genotype 3 treatment-experienced HCV for whom interferon therapy was not suitable, the company's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £28,569 per QALY gained (incremental cost £58,828; incremental QALYs 2.1).

Genotypes 4, 5 or 6

- 3.44 In people with genotype 4, 5 or 6 treatment-naive HCV for whom interferon therapy was suitable, the company's original base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £26,797 per QALY gained (incremental cost £23,942; incremental QALYs 0.9). In sensitivity analyses, the sustained virological response for peginterferon alfa plus ribavirin for 48 weeks (which varied between 26.6% and 73.4%) had a large impact on the cost-effectiveness results.
- 3.45 The company tested the robustness of the model using deterministic sensitivity analyses. Results showed that the ICERs were most sensitive to changes in the discount rate (varied between 0% and 6% for costs and outcomes simultaneously) and the utility increment after achieving a sustained virological response. The company concluded that the results of the deterministic sensitivity analyses showed that the ICERs for sofosbuvir remained below £20,000 per QALY gained in the following subgroups:
- people with genotype 2 treatment-naive and treatment-experienced HCV, for whom interferon treatment is unsuitable, compared with no treatment
 - people with genotype 2 and 3 treatment-experienced HCV, for whom interferon therapy is suitable, compared with no treatment.

The results of the deterministic sensitivity analyses showed that the ICERs for sofosbuvir were between £20,000 and £30,000 per QALY gained in the

following subgroups:

- people with genotype 1 treatment-naïve HCV, for whom interferon therapy is suitable, compared with peginterferon alfa and ribavirin and boceprevir plus peginterferon alfa and ribavirin
- people with genotype 2 treatment-experienced HCV, for whom interferon therapy is suitable, compared with peginterferon alfa and ribavirin
- people with genotype 3 treatment-experienced HCV, for whom interferon therapy is suitable, compared with peginterferon alfa and ribavirin.

The results of the deterministic sensitivity analyses showed that the ICERs for sofosbuvir were above £30,000 per QALY gained in the following subgroups:

- people with genotype 1 treatment-naïve HCV, for whom interferon therapy is suitable, compared with telaprevir plus peginterferon alfa and ribavirin
- people with genotype 3 treatment-naïve HCV, for whom interferon is unsuitable, compared with no treatment
- people with genotype 3 treatment-naïve HCV, for whom interferon therapy is suitable, compared with peginterferon alfa and ribavirin.

3.46 The company also carried out probabilistic sensitivity analyses to explore parameter uncertainty. Although it did not draw any specific conclusions from the analyses, results suggested that sofosbuvir had less than a 50% probability of being cost effective in 6 of the base-case comparisons (if the maximum acceptable ICER was £20,000 per QALY gained) and greater than a 50% probability of being cost effective in 9 of the base-case comparisons (if the maximum acceptable ICER was £30,000 per QALY gained).

3.47 During clarification, the company explored the effect of including a transition probability from Cardoso et al. (2010; 0.005; 95% CI 0.013 to 0.002) from the sustained virological response cirrhotic health state to the hepatocellular carcinoma health state in the economic model, and varied the probability in line with the upper and lower limits of the 95% confidence interval (see section 3.52). The ICERs from the company's exploratory analyses were slightly higher than

those estimated in the company's base case (ranging from £7,507 per QALY gained [for sofosbuvir plus peginterferon alfa and ribavirin compared with boceprevir plus peginterferon alfa and ribavirin in people who are eligible for interferon, with genotype 1 treatment-naïve HCV] to £54,957 per QALY gained [for sofosbuvir plus ribavirin compared with 24 weeks of peginterferon alfa-2a and ribavirin treatment in people with genotype 2 treatment-naïve HCV, for whom interferon therapy is suitable]).

HCV and HIV co-infected populations

- 3.48 The company provided a separate economic analysis for people co-infected with HIV and HCV. In people with HIV and genotype 1 treatment-naïve HCV for whom interferon therapy is suitable, the company's base-case ICER for sofosbuvir plus ribavirin treatment for 24 weeks compared with no treatment was £28,504 per QALY gained, or £43,836 per QALY gained compared with peginterferon alfa-2a and ribavirin treatment for 48 weeks. The company's base-case ICER for sofosbuvir plus ribavirin for 12 weeks compared with peginterferon alfa 2a and ribavirin treatment for 48 weeks in people with genotype 2 treatment-naïve HCV and HIV-co-infection was £55,867 per QALY gained. The company's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment in people with genotype 2 treatment-experienced HCV and HIV co-infection was £10,572 per QALY gained, or £128,248 per QALY gained compared with peginterferon alfa-2a and ribavirin treatment for 48 weeks. For people with genotype 3 treatment-naïve HCV and HIV co-infection, 12 weeks of sofosbuvir plus ribavirin dominated treatment with peginterferon alfa and ribavirin. The ICERs for 24 weeks of sofosbuvir plus ribavirin were £10,646 per QALY gained compared with no treatment and £90,822 per QALY gained compared with peginterferon alfa-2a and ribavirin for 48 weeks in people with genotype 3 treatment-experienced HCV and HIV co-infection. The company did not provide an economic analysis for people co-infected with HIV and genotype 4, 5 or 6 HCV.

Evidence Review Group comments

- 3.49 The ERG reviewed the company's model and economic systematic review. The

ERG considered that the company's methods of economic evaluation and the model produced were acceptable. It validated the company's model by comparing the total costs and QALYs predicted by the model for the treatment-naïve interferon-eligible genotype 1 HCV population with the corresponding figures for treatment with peginterferon alfa plus ribavirin with and without boceprevir or telaprevir obtained from the previous NICE technology appraisal guidance for boceprevir for the treatment of genotype 1 chronic hepatitis C and telaprevir for the treatment of genotype 1 chronic hepatitis C. The ERG found that the company's model for sofosbuvir was broadly consistent with previous models considered in NICE technology appraisals for hepatitis C, in terms of total costs and QALYs assumed for peginterferon alfa and ribavirin, and for telaprevir. However, the ERG noted that there was a discrepancy between models in the total costs estimated for boceprevir, but it was not able to account for the differences without reviewing the data used in the boceprevir submission. The ERG also considered that the company's economic model captured most of the important aspects of the disease pathway, but noted that it did not include a transition from the sustained virological response cirrhotic health state to the hepatocellular carcinoma health state, which had been previously included in other hepatitis C models. Despite this omission from the company's model, the ERG showed that it did not affect the base-case ICERs substantially. The ERG considered that the company's model extrapolated intermediate outcomes to final outcomes in a consistent way, drawing on standard sources from the literature.

- 3.50 The ERG noted that the transition probabilities used by the company in its economic model for the HCV and HIV co-infected population from the non-cirrhotic to compensated cirrhosis health states were higher than those assumed for the mono-infected population. The ERG further noted that people with HCV and HIV co-infection are likely to have a higher mortality than the population with HCV only, regardless of sustained virological response, and this was not taken into account in the company's model. The ERG noted that a study by Van Der Helm et al. (2013) concluded that the effects of HCV treatment on HIV progression needed to be evaluated further. Therefore, in the ERG's opinion, the evidence needed to accurately evaluate the cost effectiveness of sofosbuvir in the HCV and HIV co-infected population was not currently available.

Additional exploratory ERG analyses

3.51 The ERG carried out several exploratory analyses, which included:

- adding a transition probability from the sustained virological response cirrhotic health state to the hepatocellular carcinoma health state and exploring the effect of using different transition probabilities between these 2 health states
- assessing the effect on the ICERs of variations to all-cause mortality probabilities
- evaluating the effect of changing the average age of entry into the model
- using a range of alternative sustained virological response estimates from studies of comparator treatments
- assessing the effect of an alternative distribution of people with cirrhosis
- exploring the effect of the number of people having 24 weeks of sofosbuvir compared with those having 12 weeks of sofosbuvir
- assessing the effect of using alternative utility increments after sustained virological response.

3.52 The ERG heard from its clinical advisers that a transition from the sustained virological response cirrhotic health state to the hepatocellular carcinoma health state should be included in models for chronic hepatitis C to reflect the clinical course of the disease. The ERG noted that this transition was not included in the company's economic model. In addition, the ERG was unable to calculate the transition probability between these 2 health states used by the company (0.005) in its response to clarification based on the study by Cardoso et al. (see section 3.47). The ERG recalculated the transition probability using the Cardoso et al. study, to produce a value of 0.0123 (95% CI 0.028 to 0.0218). The effect of including this value (and also the upper and lower confidence interval values) was explored by the ERG in a sensitivity analysis that produced ICERs ranging from £7,593 per QALY gained [for sofosbuvir plus peginterferon alfa and ribavirin compared with boceprevir plus peginterferon alfa and ribavirin in people with genotype 1 treatment-naïve HCV, for whom interferon therapy is suitable] to

£60,887 per QALY gained [for sofosbuvir plus ribavirin compared with 24 weeks of peginterferon alfa and ribavirin treatment in people with genotype 2 treatment-naïve HCV for whom interferon therapy is suitable]).

- 3.53 The ERG noted that the company used the simple average of mortality from men and women to calculate the age-specific mortality used in the model. The ERG commented that more men are treated for HCV in clinical practice in England, therefore a weighted average should have been used. During clarification, the company re-ran their economic model with weighted average mortality probabilities, but did not indicate what weights were used to obtain its results. The ERG carried out an exploratory analysis using a weighting of 61% men and 39% women as used in Wright et al. The ICERs from the ERG's exploratory analyses were slightly higher than those estimated in the company's base case (ranging from £7,453 per QALY gained [for sofosbuvir compared with boceprevir plus peginterferon alfa and ribavirin in people with genotype 1 treatment-naïve HCV, for whom interferon therapy is suitable] to £50,083 per QALY gained [for sofosbuvir compared with no treatment in people with genotype 1 treatment-naïve HCV, for whom interferon is unsuitable]).
- 3.54 The ERG noted that the company's model used an efficacy estimate drawn from a single source when multiple efficacy estimates were available for the same treatment and indication. NICE asked the ERG to carry out further exploratory analyses to inform the Committee's understanding of the effect on the company's ICERs of using a range of alternative sustained virological response estimates from studies of comparator treatments. For people with genotype 1 treatment-naïve HCV, the ERG used alternative estimates of sustained virological response for boceprevir plus peginterferon alfa-2b and ribavirin from the SPRINT-2 study, in line with estimates used in the NICE technology appraisal of boceprevir (that is, 68.2% for people with no cirrhosis and 41.7% for people with cirrhosis, compared with the company's base-case values of 64.1% for people with no cirrhosis and 55.0% for people with cirrhosis). Applying the alternative sustained virological response estimates for boceprevir gave a lower ICER than the company's base case (the ICER was not reported by the ERG in its additional analyses).
- 3.55 The ERG also used alternative sustained virological response estimates for people with genotype 3 treatment-naïve HCV, who are eligible for interferon.

First, the ERG modelled the effect of an alternative sustained virological response of 90.7% for sofosbuvir plus peginterferon alfa-2a and ribavirin. This response was at the lower end of the 95% confidence interval for the population with no cirrhosis from the sofosbuvir trials (an estimate of 97.4% was used in the company's base case, an average of the sustained virological response from ELECTRON and PROTON). The resulting ICER for sofosbuvir plus peginterferon alfa-2a and ribavirin compared with peginterferon alfa-2a and ribavirin for this subgroup was £23,772 per QALY gained (compared with the company's base-case ICER of £20,613 per QALY gained). The ERG also explored the effect of an alternative sustained virological response of 92.3% for sofosbuvir plus peginterferon alfa-2a and ribavirin in people with genotype 3 treatment-naïve HCV and cirrhosis. Applying this alternative response lowered the ICER to £18,187 per QALY gained.

3.56 The ERG also explored the effect of alternative assumptions about the natural history of chronic hepatitis C infection on the company's ICERs. In particular, it investigated the effect of assuming an alternative distribution of cirrhosis. The ERG used a distribution for new and existing cirrhosis obtained from Hartwell et al. (2011) based on data from a London teaching hospital where 32% of existing patients with HCV and 10% of new patients with HCV had cirrhosis. The results of the exploratory analysis suggested that using this distribution increased the company's base-case ICERs for people with treatment-naïve HCV and reduced the ICERs for people with treatment-experienced HCV across all genotypes. In people with genotype 3 treatment-naïve HCV for whom interferon therapy was suitable, the ICER for sofosbuvir plus peginterferon alfa-2a and ribavirin (12 weeks) compared with peginterferon alfa and ribavirin (24 weeks) increased from £20,613 per QALY gained in the company's base case to £30,175 per QALY gained. The ICERs for treatment for people with genotype 1 treatment-naïve HCV remained above £30,000 per QALY gained (irrespective of interferon eligibility). Results for all other subgroups remained below £30,000 per QALY gained.

3.57 The ERG explored the effect of using a lower transition probability from the non-cirrhotic health state to the compensated cirrhosis health state, at age 40 years in the company's model. The resulting ICERs increased across all subgroups and were higher than those estimated in the company's base case (ranging from £9,458 per QALY gained [for sofosbuvir compared with boceprevir

plus peginterferon alfa and ribavirin in people with genotype 1 treatment-naïve HCV, for whom interferon therapy is suitable] to £61,077 per QALY gained [for sofosbuvir compared with no treatment in people with genotype 1 treatment-naïve HCV, for whom interferon treatment is unsuitable]).

3.58 The ERG explored the effect on the company's base-case ICERs of varying the percentage of people having 24 weeks of sofosbuvir treatment compared with those having 12 weeks of treatment. The 3 subgroups who might have 12 or 24 weeks of sofosbuvir treatment according to the marketing authorisation are people with:

- genotype 1 HCV, having sofosbuvir plus peginterferon alfa and ribavirin
- genotype 2 HCV, having sofosbuvir and ribavirin
- genotype 3 HCV, having sofosbuvir plus peginterferon alfa and ribavirin.

The ERG's clinical advisers differed in their opinions about how long these groups would have treatment. One clinical expert stated that it would be unlikely that more than 1% to 2% of people would be considered better off with longer therapy and that this group are identified in the summary of product characteristics as needing consideration for longer treatment periods. Another clinical expert stated that at least 20% of people might need 24 weeks of therapy, especially those who are intolerant to interferon or have severe cirrhosis.

3.59 The ERG pointed out that the company's economic model allows for a 12 week regimen of sofosbuvir plus peginterferon alfa and ribavirin for people with genotype 1 treatment-naïve HCV for whom interferon therapy is suitable and a 12 week regimen of sofosbuvir and ribavirin for people with genotype 2 treatment-naïve HCV (regardless of interferon eligibility). The economic model did allow for a 24 week regimen of sofosbuvir and ribavirin for various genotype 3 HCV subgroups. The ERG therefore compared sofosbuvir plus ribavirin for 24 weeks with either peginterferon alfa and ribavirin treatment for 24 weeks in people with genotype 3 treatment-naïve HCV and either no treatment or 48 weeks of peginterferon alfa and ribavirin treatment for people with genotype 3 treatment-experienced HCV. The resulting ICERs were more than double the company's base-case results (which assumed that these patient groups only

have 12 weeks of sofosbuvir and ribavirin).

- 3.60 The ERG carried out sensitivity analyses to evaluate the effect of changing the average age of entry into the model. The resulting ICERs generally decreased when a lower average age of 35 years was selected for entry into the model, and were higher when the average age selected was 55 years. The lowest ICERs ranged from £6,717 per QALY gained (using 35 years) to £9,170 per QALY gained (using 55 years) for sofosbuvir compared with boceprevir plus peginterferon alfa and ribavirin in people with genotype 1 treatment-naïve HCV, for whom interferon therapy is suitable. The highest ICERs ranged from £47,254 per QALY gained (using 35 years) to £60,976 per QALY gained (using 55 years) for sofosbuvir compared with 24 weeks of peginterferon alfa-2a and ribavirin treatment in people with genotype 2 treatment-naïve HCV, for whom interferon therapy is suitable.
- 3.61 The ERG also carried out sensitivity analyses to explore the effect on the company's ICERs of using different utility increments (0 and 0.04 [taken from Vera-Llonch et al. 2013], compared with the company's estimate of 0.05) after sustained virological response. The resulting ICERs in the ERG's sensitivity analysis were consistently higher than the company's base-case results. When using a utility increment of 0.04, the ICERs ranged from £7,899 per QALY gained for sofosbuvir plus peginterferon alfa and ribavirin compared with boceprevir plus peginterferon alfa and ribavirin in people with genotype 1 treatment-naïve HCV, for whom interferon therapy is suitable, to £53,793 per QALY gained for sofosbuvir plus peginterferon alfa and ribavirin compared with no treatment in people with genotype 1 treatment-naïve HCV, for whom interferon treatment is unsuitable. When using a utility increment of 0, the ICERs ranged from £12,732 per QALY gained for sofosbuvir plus peginterferon alfa and ribavirin compared with boceprevir plus peginterferon alfa and ribavirin in people with genotype 1 treatment-naïve HCV, for whom interferon therapy is suitable, to £92,795 per QALY gained for sofosbuvir plus peginterferon alfa and ribavirin compared with no treatment in people with genotype 1 treatment-naïve HCV, for whom interferon treatment is unsuitable.
- 3.62 The ERG also explored the effect on the company's base-case ICERs when alternative estimates of sustained virological response for peginterferon alfa plus ribavirin to those used by the company (from McHutchison et al. 2009) were

applied, for people with genotype 1 treatment-naïve HCV for whom interferon therapy is suitable. The ERG used estimates from Roberts et al. (2009), which reported a sustained virological response of 51% for people without cirrhosis and 6% for people with cirrhosis, and estimates from Hadziyannis et al. (2004), which were 56% and 38% respectively. Using the estimates from Roberts et al. the company's ICER for sofosbuvir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin increased to £18,209 per QALY gained. Similarly, the base-case ICER increased to £21,848 per QALY gained for the same comparison when estimates from Hadziyannis et al. were used.

- 3.63 The ERG also carried out a scenario analysis that considered the combined impact on the company's ICERs of including a transition from the sustained virological response cirrhotic health state to the hepatocellular carcinoma health state, alternative utility increments after a sustained virological response, and an alternative estimate of efficacy for peginterferon alfa and ribavirin in the population with genotype 1 treatment-naïve HCV who are eligible for interferon (using values described in sections 3.52, 3.61 and 3.62). The ICERs from the ERG's exploratory analyses were higher than those estimated in the company's base case (ranging from £9,415 per QALY gained [for sofosbuvir plus peginterferon alfa and ribavirin compared with boceprevir plus peginterferon alfa and ribavirin in people with genotype 1 treatment-naïve HCV, for whom interferon therapy is suitable] to £109,526 per QALY gained [for sofosbuvir plus ribavirin compared with no treatment in people with genotype 1 treatment-naïve HCV, for whom interferon is unsuitable]).

Additional analyses for genotypes 1 and 3 HCV

- 3.64 During consultation the Committee asked that the company provide additional evidence, which the Committee believed would permit it to come to a better informed conclusion. Specifically, the Committee requested that the company carry out several exploratory analyses for sofosbuvir plus ribavirin, with or without peginterferon alfa, compared with peginterferon alfa and ribavirin in people with genotype 1 and genotype 3 chronic hepatitis C, because these genotypes represent 89% of HCV infections in England. This included revised cost-effectiveness analyses presented separately for people with and without cirrhosis, with and without HIV-co-infection, and by treatment history. The

Committee asked that the analyses should incorporate:

- the transition from the sustained virological response cirrhotic health state to the hepatocellular carcinoma health state, using the transition probability estimates from Cardoso et al.
- alternative sustained virological response estimates for peginterferon alfa and ribavirin (for example from Hadziyannis et al.)
- alternative utility increments after sustained virological response (for example SF-36 values from the trials collected at 24 weeks post-treatment, and Vera-Llonch et al.) and
- alternative costs for ribavirin (for example, the cost of generic ribavirin as calculated by the [Commercial Medicines Unit](#) Electronic Market Information Tool) in the model.

The Committee also asked that sensitivity analyses, including the Committee's assumptions, should be explored:

- assuming that up to 100% of people with genotype 3 HCV have sofosbuvir plus ribavirin for 24 weeks
- assuming that an increased proportion of people for whom interferon therapy is suitable may be unwilling to have interferon treatment and therefore have sofosbuvir plus ribavirin for 24 weeks
- varying the age of entry into the model from 35 and 55 years
- varying all-cause mortality by assuming the population entering the model comprises 61% men and 39% women, in line with estimates from Wright et al.

3.65 The company provided the additional analyses requested, although the revised base-case assumptions were slightly different to those requested by the Committee. The company justified each change to the revised base-case assumptions, which included a transition from the sustained virological response cirrhotic health state and the non-sustained virological response cirrhotic health state to the hepatocellular carcinoma health state, using the transition probability estimates from Cardoso et al. (2010); alternative utility increments from Vera-Llonch et al., alternative costs for ribavirin and all-cause mortality assuming

the population entering the model comprises 61% men and 39% women, in line with estimates from Wright et al. The company chose to use the sustained virological response rates for peginterferon alfa and ribavirin from McHutchison et al. for its revised base case, and provided a sensitivity analysis incorporating the sustained virological response rates from Hadziyannis et al. (see section 3.74).

- 3.66 The company presented ICERs to the Committee for subgroups stratified by genotype, treatment history, interferon eligibility and cirrhosis status. The company provided the Committee with a 'global' ICER based on all patients mono-infected with HCV for genotypes 1 to 6, which was £16,199 per QALY gained. The company also provided the Committee with 'global' ICERs by genotype, weighted by treatment history and cirrhosis status, which ranged from £10,753 per QALY gained in people with genotype 1 HCV to £31,361 per QALY gained in people with genotype 2 HCV.

Genotype 1

- 3.67 For people with treatment-naïve genotype 1HCV, for whom interferon therapy is suitable, the company's revised base-case analysis showed that the ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £17,476 per QALY gained. The ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with boceprevir plus peginterferon alfa and ribavirin was £10,335 per QALY gained and £15,396 per QALY gained compared with telaprevir plus peginterferon alfa and ribavirin. For people with genotype 1 treatment-naïve HCV, for whom interferon therapy is not suitable, the company's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £47,611 per QALY gained.
- 3.68 When stratified by the presence or absence of cirrhosis, the company's revised base-case analysis showed that the ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks in people with treatment-naïve HCV who are eligible for interferon was £25,237 per QALY gained for people without cirrhosis, and £5,352 for people with cirrhosis. The stratified ICER for sofosbuvir plus peginterferon alfa

and ribavirin treatment for 12 weeks compared with boceprevir plus peginterferon alfa and ribavirin was £14,280 per QALY gained for people without cirrhosis and £2,819 per QALY gained for people with cirrhosis. The stratified ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with telaprevir plus peginterferon alfa and ribavirin was £22,304 per QALY gained for people without cirrhosis and £4,253 per QALY gained for people with cirrhosis. For people with genotype 1 treatment-naïve HCV for whom interferon therapy is not suitable, the company's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment, stratified by cirrhosis status, was £51,478 per QALY gained for people without cirrhosis and £35,754 per QALY gained for people with cirrhosis.

- 3.69 Because of the lack of clinical trial evidence in people with genotype 1 treatment-experienced HCV, the company provided the Committee with an estimated cost-effectiveness calculation for this subgroup. The company explained that historically, approximately 50% of people with genotype 1 treatment-naïve HCV had disease that responded to treatment with peginterferon alfa and ribavirin, but in the interim analysis provided to the US Food and Drug Administration (FDA), 89% of people with genotype 1 treatment-naïve HCV in NEUTRINO had disease that responded to sofosbuvir plus peginterferon alfa and ribavirin. The FDA accepted that the higher rate of overall sustained virological response seen in NEUTRINO was likely driven by those patients who were virus-free 12 weeks after the end of treatment, but who would not have had this response if treated with peginterferon alfa and ribavirin alone. Assuming that people who would have had a sustained virological response with peginterferon alfa and ribavirin alone had a sustained virological response with sofosbuvir plus peginterferon alfa and ribavirin, the FDA assumed that the increase in sustained virological response from 50% to 89% represented the efficacy of sofosbuvir plus peginterferon alfa and ribavirin. The FDA calculated that given the high sustained virological responses in NEUTRINO, an approximate sustained virological response was 78% for people with treatment-experienced genotype 1 HCV. Additionally, the company presented interim evidence from Pol et al. (2013), a study of the efficacy of sofosbuvir in people with genotype 1 treatment-experienced HCV, which suggested that sustained virological responses in this group were 74% after treatment with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. Using the estimated sustained virological response of 78% calculated by the FDA, the company's ICER

for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin alone for 48 weeks was £12,641 per QALY gained. The company's ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with boceprevir plus peginterferon alfa and ribavirin was £683 per QALY gained and £8,203 per QALY gained when compared with telaprevir plus peginterferon alfa and ribavirin in people with genotype 1 treatment-experienced HCV.

Genotype 3

- 3.70 In people with genotype 3 treatment-naïve HCV for whom interferon therapy is suitable, the company's revised base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 24 weeks was £21,860 per QALY gained. In people with genotype 3 treatment-naïve HCV for whom interferon therapy is unsuitable, the company's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £21,049 per QALY gained.
- 3.71 In people with genotype 3 treatment-experienced HCV for whom interferon therapy is suitable, the company's base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £13,883 per QALY gained. In people with genotype 3 treatment-experienced HCV, for whom interferon therapy is unsuitable, the company's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £27,483 per QALY gained.
- 3.72 When stratified by the absence or presence of cirrhosis, in people with genotype 3 treatment-naïve HCV for whom interferon therapy is suitable, the company's revised base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 24 weeks was £40,623 per QALY gained for people without cirrhosis and £6,556 per QALY gained for people with cirrhosis. In people with genotype 3 treatment-naïve HCV for whom interferon therapy is unsuitable, the company's revised base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £28,044 per QALY gained in people with no

cirrhosis, and £10,505 per QALY gained in people with cirrhosis. In people with treatment-experienced genotype 3 HCV for whom interferon therapy is suitable, the company's revised base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £18,592 per QALY gained in people without cirrhosis and £6,260 per QALY gained in people with cirrhosis. In people with genotype 3 treatment-experienced HCV for whom interferon therapy is unsuitable, the company's revised base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £31,416 per QALY gained in people without cirrhosis and £19,179 per QALY gained in people with cirrhosis.

HCV and HIV co-infected populations

- 3.73 The company provided a separate economic analysis for people co-infected with HIV and HCV. The company reported results from the 1910 study (Rodriguez-Torres et al. [2013]), which included (F0-F3) patients with HCV and HIV co-infection and no cirrhosis. The sustained virological response of 90% seen in the 1910 study was also seen in people with HCV mono-infection and no cirrhosis in NEUTRINO, which suggested that similar response rates are seen in people with genotype 1 HCV having sofosbuvir plus peginterferon and ribavirin for 12 weeks, regardless of HCV and HIV co-infection status. The company presented revised base-case ICERs in people co-infected with HIV and genotype 1 or 3 HCV, which ranged from £10,376 per QALY gained in people with genotype 3 treatment-experienced HCV and HIV having sofosbuvir and ribavirin for 24 weeks compared with no treatment, to £27,059 per QALY gained in people with genotype 1 treatment-naïve HCV having sofosbuvir and ribavirin for 24 weeks compared with no treatment.

Additional sensitivity analyses

- 3.74 The Committee asked that the revised base case include the sustained virological responses from Hadziyannis et al. rather than from McHutchison et al. for peginterferon alfa and ribavirin in people with genotype 1 treatment-naïve HCV. The company expressed concern about this approach because the sustained virological response in Hadziyannis et al. assumed that a METAVIR score from F0

to F2 represented people without cirrhosis and a score from F3 to F4 represented people with cirrhosis, whereas in NEUTRINO, METAVIR scores of F4 for cirrhosis and F0-F3 for non-cirrhosis were defined. The company also commented that people in the McHutchison et al. study were more representative of people in the NEUTRINO study. Therefore, the company used the sustained virological responses from McHutchison et al. in its revised base-case analysis. However, it provided the Committee with the results of a scenario analysis in which it used the sustained virological responses for peginterferon alfa and ribavirin from Hadziyannis et al., which suggested that for people with genotype 1 treatment-naïve HCV, the ICER for sofosbuvir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone was £25,014 per QALY gained, whereas its revised base-case ICER using the sustained virological responses for peginterferon alfa and ribavirin from McHutchison et al. was £17,476 per QALY gained.

- 3.75 The company presented a scenario analysis assuming that 100% of people with genotype 3 HCV for whom interferon therapy is suitable would have 24 weeks of sofosbuvir and ribavirin. In people with genotype 3 treatment-naïve HCV for whom interferon therapy is suitable, assuming that 100% of people would have 24 weeks of sofosbuvir and ribavirin treatment compared with 24 weeks of peginterferon alfa and ribavirin treatment, the ICER was £46,956 per QALY gained. In people with genotype 3 treatment-experienced HCV for whom interferon therapy is suitable, assuming that 100% of people would have 24 weeks of sofosbuvir and ribavirin treatment compared with 48 weeks of peginterferon alfa and ribavirin treatment, the ICER was £48,306 per QALY gained. The company also presented the results of a scenario analysis using the upper (20%) and lower (2%) proportion of people with genotype 3 HCV for whom interferon therapy is suitable and who were expected to have sofosbuvir and ribavirin for 24 weeks as suggested by the ERG's clinical advisers. In people with genotype 3 treatment-naïve HCV for whom interferon therapy is suitable, assuming that 2% of people would have 24 weeks of sofosbuvir and ribavirin treatment compared with 24 weeks of peginterferon alfa and ribavirin treatment, the ICER was £22,385 per QALY gained, and £27,062 per QALY gained when 20% was used. In people with genotype 3 treatment-experienced HCV for whom interferon therapy is suitable, assuming that 2% of people would have 24 weeks of sofosbuvir and ribavirin treatment compared with 24 weeks of peginterferon alfa and ribavirin treatment, the ICER was £14,467 per QALY gained and £19,890

per QALY gained when 20% was used.

- 3.76 The ERG reviewed the company's additional evidence. The ERG noted that the company had used most of the Committee's preferred base-case assumptions (see section 3.64). It further noted that the company did not provide a sensitivity analysis exploring the impact on the ICER of using utility data collected in the clinical trials. The ERG carried out an exploratory analysis in which it used all of the Committee's preferred assumptions to calculate the ICERs for treatment for people with genotype 1 and 3 HCV and also carried out the exploratory scenario analyses requested by the Committee (see section 3.64). The ERG's exploratory analyses resulted in an ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks of £30,993 per QALY gained for people with treatment-naïve genotype 1 HCV, for whom interferon therapy is suitable. The ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with boceprevir plus peginterferon alfa and ribavirin was £12,172 per QALY gained and £18,704 per QALY gained compared with telaprevir plus peginterferon alfa and ribavirin. For people with genotype 1 treatment-naïve HCV, for whom interferon therapy is unsuitable, the base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £58,113 per QALY gained.
- 3.77 The ERG stratified the exploratory ICERs by the presence or absence of cirrhosis. The ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £38,460 per QALY gained for people without cirrhosis, and £12,891 for people with cirrhosis. The ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with boceprevir plus peginterferon alfa and ribavirin was £15,653 per QALY gained for people without cirrhosis and £2,274 per QALY gained for people with cirrhosis. The ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with telaprevir plus peginterferon alfa and ribavirin was £24,509 per QALY gained for people without cirrhosis and £4,680 per QALY gained for people with cirrhosis compared with telaprevir plus peginterferon alfa and ribavirin. For people with genotype 1 treatment-naïve HCV for whom interferon therapy is unsuitable, the base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £58,118 per QALY gained for people without cirrhosis and £58,093 per QALY gained for people with cirrhosis.

- 3.78 In people for whom interferon therapy is suitable, with genotype 3 treatment-naïve HCV, the ERG's exploratory analyses resulted in an ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 24 weeks of £28,666 per QALY gained. In people with genotype 3 treatment-naïve HCV for whom interferon therapy is unsuitable, the base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £26,611 per QALY gained. In people with genotype 3 treatment-experienced HCV for whom interferon therapy is suitable, the ERG's exploratory analyses showed that the ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £16,979 per QALY gained. In people with genotype 3 treatment-experienced HCV, for whom interferon therapy is unsuitable, the company's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £34,261 per QALY gained.
- 3.79 When stratified by the presence or absence of cirrhosis, in people with genotype 3 treatment-naïve HCV for whom interferon therapy is suitable, the ERG's exploratory analyses resulted in an ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 24 weeks that was £46,036 per QALY gained for people without cirrhosis and £8,318 per QALY gained for people with cirrhosis. In people with genotype 3 treatment-naïve HCV for whom interferon therapy is suitable, the ERG's exploratory analyses showed that the ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £31,851 per QALY gained in people with no cirrhosis, and £15,133 per QALY gained in people with cirrhosis. In people with treatment-experienced genotype 3 HCV for whom interferon therapy is suitable, the ERG's exploratory analyses showed that the ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £20,694 per QALY gained in people without cirrhosis and £8,093 per QALY gained in people with cirrhosis. In people with genotype 3 treatment-experienced HCV for whom interferon therapy is unsuitable, the ERG's exploratory analyses showed that the ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment was £35,744 per QALY gained in people without cirrhosis and £29,704 per QALY gained in people with cirrhosis.

Additional analyses in genotype 4, 5 and 6 HCV

- 3.80 During consultation several consultees, including the company, asked that the Committee reconsider the clinical and cost-effectiveness evidence for people with genotype 4 HCV. The consultees indicated that people with genotype 4 HCV represent a group with a particularly high unmet need and minority ethnic groups represent a higher proportion of people who have genotype 4 HCV in the UK. Whereas genotype 4 HCV accounts for 5% of all HCV genotypes in the UK (but is more prevalent in the Middle East and Africa), the prevalence of genotype 4 in the UK is increasing because of migration, HIV co-infection and intravenous drug use. Additionally, a consultee stated that the proportion of people with genotype 4 HCV who have haemophilia is higher than in other genotypes because of infection with blood products imported from abroad.
- 3.81 In order to fully explore the potential equality issues raised during consultation, additional evidence was requested from the company, which included HCV prevalence data by genotype and family origin, HIV co-infection and haemophilia in the UK. The company provided NICE with evidence from a HCV genotype surveillance report commissioned by the company to be produced by Public Health England, which showed the proportion of people with genotype 1 or 3 HCV who were of white or white British family origin was 81% and 72% respectively, whereas minority ethnic groups represented 8% and 18% respectively. The proportion of people with genotypes 4, 5 and 6 HCV who were of white or white British family origin was 44%, 53% and 19%, respectively, whereas minority ethnic groups represented 39%, 28% and 74%, respectively (see table 5).

Table 5 Genotype by family origin

HCV genotype	White or white British (%)	Asian or Asian British (%)	Black or black British (%)	Other or mixed origin (%)	Unknown (%)
1	13,675 (81)	875 (5)	116 (1)	265 (2)	2,023 (12)
2	1,883 (84)	75 (3)	12 (1)	35 (2)	239 (11)
3	12,001 (72)	2,894 (17)	37 (0.22)	146 (0.88)	1,532 (9)
4	593 (44)	378 (28)	48 (4)	90 (7)	239 (18)
5	25 (53)	7 (15)	6 (13)	0 (0)	9 (19)

HCV genotype	White or white British (%)	Asian or Asian British (%)	Black or black British (%)	Other or mixed origin (%)	Unknown (%)
6	12 (19)	4 (6)	1 (2)	42 (66)	5 (8)
Non-1	46 (70)	3 (5)	0 (0)	1 (2)	16 (24)
Dual	13 (59)	6 (27)	0 (0)	0 (0)	3 (14)

HCV, hepatitis C virus

- 3.82 The company also provided genotype distribution data from the 2012 United Kingdom Haemophilia Centre Doctors' Organisation look-back exercise, which reported a prevalence of 3% and 1% of HCV genotypes 4 and 5 respectively among UK HCV-infected people with haemophilia. The proportion of people with haemophilia with genotypes 1, 2 and 3 HCV is 96%. Additionally, the company presented commercial-in-confidence evidence that a disproportionate number of people with HIV co-infection have genotype 4 HCV compared with people without HIV co-infection.
- 3.83 The Committee requested that the company submit a literature review of a range of sustained virological responses for peginterferon alfa and ribavirin to address uncertainty in the sustained virological responses in the comparator arm of the economic model. The company identified 7 studies reporting efficacy data for patients with genotype 4, 5 or 6 HCV in its systematic literature review. The company excluded all studies that recruited solely from Egypt, Africa, Asia or the Middle East because of documented differences in baseline characteristics and response to treatment. According to the company, only Manns et al. (2001) and Lindsay et al. (2001) provided combined data on genotypes 4, 5 and 6 HCV. Of these studies, Manns et al. included more patients (n=16) compared with Lindsay et al. (n=8). The company supported the use of Manns et al. with unpublished data from Imperial College London, which provides treatment for the largest numbers of people with genotype 4 HCV in England, suggesting that the sustained virological response of 50% from Manns et al. in people without cirrhosis was similar to the rate observed at Imperial College (49.5% in patients with genotype 4 having peginterferon alfa and ribavirin for 48 weeks). The company also calculated the sustained virological response for people with genotype 4, 5 or 6 HCV with cirrhosis to be 38.6% based on the relative difference in sustained virological response between people without cirrhosis and people with cirrhosis in the studies in genotype 1, 2 and 3 HCV.

3.84 The ERG did not agree that only studies that included combined genotypes 4, 5 and 6 HCV should be analysed, because this approach excluded some trials of genotype 4 HCV that have larger sample sizes. The ERG did its own rapid systematic literature review that identified 17 studies with sample sizes of 10 or more people with genotype 4 HCV. Ten of the studies took place in the Middle East (particularly Egypt) and 7 were from Europe (3 were randomised controlled studies, 4 were non-randomised studies). The ERG calculated the overall weighted mean sustained virological response for the 4 well-reported Middle Eastern studies out of the 10 and the 3 randomised controlled studies from the 7 European studies separately, resulting in a sustained virological response of 65.6% and 55.7%, respectively. When all 17 studies were combined with Manns et al. and Lindsay et al., the resulting weighted sustained virological response was 54.8%. The ERG's clinical advisers provided comment on the relevance of the Middle Eastern studies to NHS practice, stating that there is a significant difference between patients of Egyptian family origin in Europe and those in Egypt, because the average age and number of comorbidities is higher in most European studies, which translates into a reduced response rate.

3.85 The Committee also asked the company to provide a revised base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks for people with genotype 4, 5 or 6 treatment-naïve HCV, using the Committee's preferred assumptions, which were using:

- the Cardoso et al. transition probabilities from the sustained virological response with cirrhosis health state and the cirrhosis health state without a sustained virological response to the hepatocellular carcinoma health state
- the utility increment after a sustained virological response from Vera-Llonch et al. and
- a men:women distribution ratio from Wright et al.

The Committee also requested that the company show the impact of alternative sustained virological responses for peginterferon alfa and ribavirin alone for 48 weeks from the systematic review of published sources included in its initial submission to the Committee, together with a rationale for the preference of Manns et al. in the revised base-case model over other

sources.

- 3.86 The company used the sustained virological responses observed in NEUTRINO for the sofosbuvir plus peginterferon alfa and ribavirin arm of the model. The revised base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks (using the sustained virological response of 50% for peginterferon alfa and ribavirin from Manns et al.) increased from £26,797 per QALY gained in the original model to £27,505 per QALY gained in the revised base-case model. The company had identified 7 studies, which included peginterferon alfa and ribavirin for 48 weeks in a treatment arm with sustained virological responses ranging from 33% (Zeuzem et al. 2005) to 77% (Fried et al. 2002). These sustained virological responses were not stratified by cirrhosis status, therefore the company applied the same sustained virological response for people without cirrhosis as for people with cirrhosis in the model. Sustained virological responses for sofosbuvir plus peginterferon alfa and ribavirin from the NEUTRINO study were stratified by cirrhosis status (100% for people without cirrhosis and 50% for people with cirrhosis). The resulting ICERs for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks using the sustained virological response from Zeuzem et al. (33%) was £19,148 per QALY gained, and £244,387 per QALY gained when Fried et al. (77%) was used. The company also calculated the ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks using the sustained virological response of 97% for the combined cohort of people with and without cirrhosis in NEUTRINO. The resulting ICER was £47,394 per QALY gained.
- 3.87 The company provided a sensitivity analysis that used the transition probability from the compensated cirrhosis without a sustained virological response health state to hepatocellular carcinoma from Fattovich et al. (1997) rather than Cardoso et al., which increased the ICERs from £27,505 to £31,713 per QALY gained in the revised base case. When the sustained virological response for peginterferon alfa and ribavirin for 48 weeks from Zeuzem et al. and Fried et al. were used, the ICERs were £22,096 and £151,837 per QALY gained, respectively.
- 3.88 The ERG used the same revised base-case assumptions as the company and applied the weighted sustained virological response from the 17 studies it

identified, which resulted in a ICER of £37,820 per QALY gained and increased to £40,761 per QALY gained when the transition probability from Fattovich et al. was used for the transition from compensated cirrhosis without a sustained virological response to hepatocellular carcinoma. When the ERG used the weighted sustained virological response from the 10 Middle Eastern studies, the ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks was £69,181 per QALY gained, whereas the ICER using the 7 European studies in people with genotype 4 HCV only was £40,664 per QALY gained, and £39,109 per QALY gained when the 7 European studies were supplemented with the results from Manns et al. and Lindsay et al.

3.89 Full details of all the evidence are in the [committee papers](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of sofosbuvir, having considered evidence on the nature of chronic hepatitis C and the value placed on the benefits of sofosbuvir by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.1 The Committee heard from the clinical experts that chronic hepatitis C is often clinically asymptomatic, and that it is estimated to be undiagnosed in approximately 50% of people with the condition in England. However, when the condition progresses and cirrhosis occurs, it has a significant daily effect on the person with the virus and their carers. The Committee acknowledged the concerns of the patient experts that there is a stigma attached to having chronic hepatitis C, because of its link to injectable drug use. In addition, there is a reluctance to treat chronic hepatitis C in people who use injectable drugs, partly because of mistaken beliefs that they do not adhere to treatment and often become re-infected. The Committee heard from the patient experts that the availability of sofosbuvir and other new treatments that are expected to become available over the next 5 years will encourage more people with chronic hepatitis C to seek diagnosis and treatment. In addition, people who use injectable drugs whose chronic hepatitis C is successfully treated may go on to address their drug use, leading to broader societal benefits that are not captured in the company's evidence submission. The Committee recognised the effect of chronic hepatitis C on the lives of people with the virus. It concluded that treatments that give a sustained virological response (which is considered equivalent to a cure), and that consequently help reduce the rate of HCV transmission and the stigma associated with having chronic hepatitis C, are of significant importance.
- 4.2 The Committee discussed the clinical management of chronic hepatitis C in adults. It heard from the clinical experts that different treatment options can have varied results, depending on the person's HCV genotype, level of liver damage, comorbidities and previous treatment history. For people with genotype 1 chronic hepatitis C, the Committee heard that boceprevir plus peginterferon alfa and ribavirin or telaprevir plus peginterferon alfa and ribavirin (see the NICE

technology appraisal guidance on boceprevir for the treatment of genotype 1 chronic hepatitis C and telaprevir for the treatment of genotype 1 chronic hepatitis C) are commonly used, and that for people with genotypes 2 to 6 HCV, peginterferon alfa plus ribavirin or watchful waiting (closely monitoring the condition but not giving any treatment) are currently the main treatment options. The clinical experts highlighted that interferon-based treatment can be associated with side effects such as chronic fatigue, neuropsychological effects and flu-like symptoms, which can be a barrier to people wanting to start treatment, or taking their treatment for the recommended duration. The Committee also heard from the patient experts that interferon-based treatment may cause chronic side effects, such as autoimmune responses and thyroid problems, which need additional long-term management and therefore pose another barrier to people starting and completing treatment. The Committee acknowledged that the marketing authorisation for sofosbuvir offers people the option to have shortened courses of peginterferon alfa and ribavirin, or in some circumstances to have treatment without peginterferon alfa, thereby reducing potential adverse effects associated with interferon-based therapy. The Committee agreed with the clinical experts and patient experts that the option to have a shortened course of interferon-based therapy with sofosbuvir, or the possibility of sofosbuvir being used without peginterferon alfa in some circumstances, would make it a valuable treatment option for people with chronic hepatitis C.

- 4.3 The Committee acknowledged that the marketing authorisation in the UK for sofosbuvir licenses it to be used in adults with chronic hepatitis C in all genotypes. It heard from the clinical experts that in England, most people with chronic hepatitis C have genotypes 1 or 3 HCV (46% and 43% respectively), with genotype 1 HCV being associated with a poor response to antiviral therapy and an increased rate of progression to severe chronic liver disease. The Committee noted that the marketing authorisation also allows sofosbuvir to be used in people who have or have not had previous treatment for chronic hepatitis C. The Committee also noted that the marketing authorisation allows sofosbuvir in combination with ribavirin to be used in people with genotypes 1, 4, 5 or 6 HCV who could be considered interferon intolerant or ineligible and who are in urgent need of treatment. It heard from company representatives that people would be considered interferon intolerant or ineligible if interferon treatment was contraindicated (as described in the summary of product characteristics for

peginterferon) or in people whose disease did not have an adequate response to previous interferon treatment. The Committee asked the clinicians and commissioners for a definition of who would be considered interferon intolerant or ineligible, but did not receive a clear response. The Committee heard from the clinical experts that sofosbuvir is an important new treatment that will address an unmet need, particularly in people who have previously been treated but did not have a sustained virological response, in people whose condition has relapsed, or in people who have become re-infected after treatment. The Committee was aware that the marketing authorisation specifies that sofosbuvir treatment should be 'initiated and monitored by a physician experienced in the management of patients with chronic hepatitis C'. It agreed with comments received during consultation that treatment should be focused in specialist centres and that treatment decisions, such as determining whether someone is interferon intolerant or ineligible for interferon treatment, should be made preferably by a multidisciplinary team. The Committee concluded that most people with chronic hepatitis C are likely to have at least some benefit from adding sofosbuvir to their treatment regimen and that the condition should be treated in an appropriate setting, as specified in the sofosbuvir marketing authorisation.

Clinical effectiveness

- 4.4 The Committee considered the clinical effectiveness of sofosbuvir plus ribavirin, with or without peginterferon alfa, for people with genotypes 1 to 6 chronic hepatitis C. It noted the concerns of the Evidence Review Group (ERG) that because of the lack of head-to-head studies comparing sofosbuvir with current standard of care treatments, most of the evidence provided by the company did not directly address the decision problem. The Committee acknowledged that the company was able to provide evidence from only 1 head-to-head trial (FISSION, in people with genotype 2 or 3 treatment-naïve HCV, for whom interferon therapy is suitable; see sections 3.8 and 3.9) that was consistent with the decision problem. The Committee was aware that the direct comparison with standard of care treatment was further limited to people with genotype 2 HCV only because the marketing authorisation recommends 24 weeks of sofosbuvir and ribavirin treatment for people with genotype 3 HCV, but people with genotype 3 HCV in the FISSION study had 12 weeks of sofosbuvir and ribavirin. In addition, the Committee expressed concern about the robustness of the estimates of the

clinical effectiveness of sofosbuvir across the different subgroups for whom it is licensed when stratified (grouped) by treatment history, presence or absence of cirrhosis, and interferon eligibility, given that most trials were single-arm and open-label with historical controls that only included relatively small patient numbers and provided short-term data. The Committee heard from the clinical experts that the current standard of care has been used for many years in the UK, and has been supported by numerous trials; therefore it was not unreasonable to use historical controls. The clinical experts also commented that hepatitis C trials are often open label because some people realise they are taking an interferon-based regimen, potentially making blinding difficult. The Committee was aware that the number of people with cirrhosis in the clinical trials was relatively small, although it reflected the proportion of people with cirrhosis seen in clinical practice, and the exclusion criteria meant that people who use injectable drugs were not included in any studies. The Committee acknowledged the limitations of carrying out trials for hepatitis C, and concluded that there was considerable uncertainty surrounding the evidence base presented by the company. Therefore the true magnitude of the effect of sofosbuvir in each subgroup could not be robustly estimated.

- 4.5 The Committee acknowledged that in the NEUTRINO trial, people with genotype 1 (89% of people in the trial), 4, 5 or 6 treatment-naïve HCV who had sofosbuvir plus peginterferon alfa and ribavirin had a high sustained virological response (91%) 12 weeks after treatment compared with the historical control of 60% that was presented by the company. The Committee concluded that sofosbuvir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in people with treatment-naïve genotype 1, 4, 5 or 6 HCV.
- 4.6 The Committee considered the clinical effectiveness of sofosbuvir plus peginterferon alfa and ribavirin in people with treatment-experienced genotype 1, 4, 5 or 6 HCV. No trial data were available on the clinical effectiveness of sofosbuvir in people with these genotypes who had previously had treatment for HCV. The Committee heard from the clinical experts that there was no reason to expect a different response in treatment-experienced HCV than in treatment-naïve HCV. The Committee also heard from clinical experts that it was unlikely that further studies of sofosbuvir plus peginterferon alfa and ribavirin in people with treatment-experienced HCV would be started because new

interferon-free regimens are rapidly replacing older interferon-based regimens. The Committee was aware of the evidence from the company that the US Food and Drug Administration had accepted that the increase in sustained virological response in people with genotype 1 treatment-naïve HCV from 50% to 89% in NEUTRINO (subsequently recalculated as 91%) represented an efficacy of 78% for sofosbuvir plus peginterferon alfa and ribavirin in those people who would not have a sustained virological response with peginterferon alfa and ribavirin alone (see section 3.69). The Committee also considered interim results from an ongoing open-label, single-arm study by Pol et al. (2013) on the efficacy of sofosbuvir plus peginterferon alfa and ribavirin in people with genotype 1 treatment-experienced HCV, which the company provided during consultation. These interim data suggested that 74% of patients who did not previously have a sustained virological response with peginterferon alfa plus ribavirin plus another direct-acting antiviral (ledipasvir or tegobuvir) had a sustained virological response 12 weeks after treatment with sofosbuvir plus peginterferon alfa and ribavirin. The Committee also considered that in the small numbers of people with genotype 4, 5 or 6 HCV in the NEUTRINO study (in people with treatment-naïve genotype 1, 4, 5 and 6 HCV), the sustained virological responses 12 weeks after sofosbuvir treatment were approximately 97%, which was similar to those in people with genotype 1 HCV (see section 3.3). The Committee concluded that although there was uncertainty about the robustness of the evidence base in people with HCV genotype 1, 4, 5 or 6 who have had HCV treatment before, there was sufficient evidence for the Committee to make a recommendation on the use of sofosbuvir in people with genotype 1, 4, 5 or 6 treatment-experienced HCV.

- 4.7 The Committee discussed the design of the clinical trials for sofosbuvir plus ribavirin in people with genotype 2 and 3 HCV. It noted that the main evidence came from 4 trials (FISSION, [treatment-naïve HCV, interferon-eligible], FUSION, [treatment-experienced HCV], POSITRON [treatment-naïve and treatment-experienced HCV, people who were ineligible for interferon or intolerant to it or unwilling to have it] and VALENCE [treatment-naïve and treatment-experienced]). The Committee acknowledged that FISSION was the only trial with an active comparator (peginterferon alfa-2a and ribavirin treatment for 24 weeks) but noted that it was an open-label study, which was susceptible to the introduction of selection bias and that when broken down by genotype, treatment history, interferon eligibility and cirrhosis status, the results were based on small patient numbers. The Committee was also aware that sustained

virological response in the combined study population (FISSION) was 67% in both the sofosbuvir plus ribavirin 12 week treatment arm and in the peginterferon alfa-2a and ribavirin 24 week treatment arm. The Committee noted that when stratified by genotype, people with genotype 2 HCV had a higher sustained virological response with 12 weeks of sofosbuvir plus ribavirin (97%) than people having peginterferon alfa and ribavirin alone (78%). The Committee noted that people with genotype 3 HCV having 12 weeks of sofosbuvir plus ribavirin had a lower sustained virological response rate 12 weeks after treatment (56%) than people receiving peginterferon alfa and ribavirin alone for 24 weeks (63%). The Committee was aware that all 4 trials in people with genotype 2 and 3 HCV had small patient numbers in each stratified subgroup (by genotype, treatment history, interferon eligibility and cirrhosis) and different designs, and concluded that these factors introduced uncertainty around the clinical effectiveness of sofosbuvir. On balance, the Committee concluded that sofosbuvir plus ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response at 12 weeks after treatment in people with genotype 2 HCV.

- 4.8 The Committee further considered the results of the VALENCE study, which showed that longer treatment with sofosbuvir plus ribavirin was needed for people with genotype 3 treatment-naïve HCV (24 weeks rather than 12 weeks) to obtain a comparable sustained virological response at 12 weeks after treatment to that seen in people with genotype 2 HCV (data not reported here; academic-in-confidence). This was also supported by the results of FISSION, which showed that the sustained virological response for 12 weeks treatment with sofosbuvir and ribavirin in people with genotype 3 HCV was consistently lower than that seen in people with genotype 3 HCV who had peginterferon alfa-2a and ribavirin for 24 weeks (see section 3.9). The Committee also discussed the clinical effectiveness of sofosbuvir in people with genotype 2 and 3 treatment-experienced HCV, noting that the evidence for this subgroup came from FUSION (which compared sofosbuvir plus ribavirin for 12 weeks [plus placebo for an extra 4 weeks] with sofosbuvir and ribavirin for 16 weeks), and from subpopulations in VALENCE. The Committee noted that sustained virological response was consistently higher for people with genotype 2 HCV (86% and 94% in the 12 week and 16 week treatment groups in FUSION; 93% after 12 weeks treatment in VALENCE) than for people with genotype 3 HCV, who needed longer treatment with sofosbuvir and ribavirin (16 weeks and 24 weeks) for a similar

response to be shown. The Committee noted that in the studies people with cirrhosis also generally had a lower response than those without cirrhosis (irrespective of genotype). The Committee considered that treatment with sofosbuvir plus ribavirin was likely to lead to a better sustained virological response in people with genotype 3 HCV compared with the current standard of care (24 weeks of peginterferon alfa and ribavirin treatment), but only when sofosbuvir plus ribavirin treatment was extended to 24 weeks. The Committee concluded that taking into account the limitations of the trial designs and the use of historical controls there was considerable uncertainty around the true magnitude of benefit of sofosbuvir plus ribavirin compared with peginterferon alfa and ribavirin for 24 weeks in people with genotype 3 HCV.

- 4.9 The Committee considered the available evidence for sofosbuvir plus peginterferon alfa and ribavirin in people with genotype 3 HCV. The Committee was aware that the European public assessment report for sofosbuvir stated that because peginterferon alfa and ribavirin alone had a higher historical efficacy in people with genotype 3 HCV than in people with genotype 1 HCV, it could be inferred that a similar improvement in efficacy seen in people with genotype 1 HCV would be expected in people with genotype 3 HCV when sofosbuvir was added to peginterferon alfa and ribavirin. This was supported by the relevant results from PROTON and ELECTRON, which showed that the sustained virological responses 12 weeks after the end of treatment were 90% and 100%, respectively in people with genotype 3 HCV. The Committee was aware that these results were from open-label studies in small numbers of people, and that there was considerable uncertainty around the true magnitude of benefit of sofosbuvir plus peginterferon alfa and ribavirin in people with genotype 3 HCV. On balance, however, the Committee concluded that 12 weeks of sofosbuvir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone for 24 weeks in inducing a sustained virological response in people with genotype 3 treatment-naïve HCV.
- 4.10 The Committee considered the available evidence for sofosbuvir plus ribavirin in people co-infected with chronic hepatitis C and HIV. It noted that the interim analysis presented in the company's original submission and the regulatory submission was from an ongoing open-label study with sofosbuvir and ribavirin (PHOTON-1), which included people with genotype 1, 2 or 3 HCV and HIV who had not had treatment for hepatitis C, and people with genotype 2 or 3 HCV and

HIV who had been treated before. The Committee subsequently considered the evidence provided by the company during consultation from the 1910 study (Rodriguez-Torres et al. [2013]), which compared sofosbuvir plus peginterferon alfa and ribavirin treatment with peginterferon alfa and ribavirin alone in people with genotype 1 HCV and HIV. The Committee was aware that the interim results of both studies suggested that sustained virological responses in people with HCV and HIV-co-infection were similar to those seen in people with HCV mono-infection. The Committee understood that the summary of product characteristics states that people with HCV and HIV co-infection should have the same sofosbuvir treatment schedule as people with HCV mono-infection, and concluded that this was appropriate.

- 4.11 The Committee considered the adverse reactions associated with sofosbuvir plus ribavirin with and without peginterferon alfa. It noted that the adverse events reported in the main sofosbuvir clinical studies (NEUTRINO, FISSION, FUSION, POSITRON and VALENCE) were generally consistent with those reported in other studies for hepatitis C treatments. It heard from the clinical experts that sofosbuvir is considered to have a better safety profile than peginterferon alfa and ribavirin, and most adverse events reported in the trials were likely to be related to treatment with peginterferon alfa and ribavirin rather than sofosbuvir. The Committee concluded that the adverse reactions associated with sofosbuvir plus ribavirin with or without peginterferon alfa were generally tolerable and that sofosbuvir was not likely to cause additional adverse reactions compared with existing treatment regimens.
- 4.12 The Committee discussed the company's mixed treatment comparison. It heard from the company that a network could not be formed for all the relevant populations and a comparison could be performed only for genotypes 1, 2 and 3 treatment-naïve HCV because of data limitations. Therefore, results from the mixed treatment comparison were not used to inform the economic model. The Committee noted that instead, the company adopted what they described as a conservative approach and used trial data that reported the highest sustained virological response for the comparators, including naïve comparisons with boceprevir and telaprevir plus peginterferon alfa and ribavirin for people with genotype 1 HCV. The Committee agreed with the ERG's view that the company's mixed treatment comparison was not robust. Therefore the Committee concluded that it was reasonable for the company not to use the mixed treatment

comparison to inform its cost-effectiveness analyses.

Cost effectiveness

- 4.13 The Committee considered the company's original economic model provided in the company's submission, the assumptions underlying the values of the parameters, and the critique and exploratory analyses carried out by the ERG. The Committee also considered the revised base-case model submitted by the company in response to the additional analyses requested by the Committee. The Committee noted that the company's model structure differed slightly from that used in previous technology appraisals for hepatitis C, in that people with mild and moderate chronic hepatitis C were considered collectively as a population without cirrhosis, and therefore the model distinguished only between people with and without cirrhosis. The Committee heard from the clinical experts that this approach was reasonable and consistent with how people are currently diagnosed in clinical practice. It heard from the clinical experts that previously, people had invasive liver biopsies and as a result their disease was classified as mild, moderate or severe. However, current practice involves the use of less invasive diagnostic tests that do not differentiate between mild and moderate disease and can distinguish only between cirrhosis and non-cirrhosis. The Committee also noted that the company's model incorporated the assumption that all people who had cirrhosis were candidates for liver transplant, and that pre-transplant patients were therefore included in the modelling presented. The Committee concluded the approach taken by the company was appropriate.
- 4.14 The Committee acknowledged that the ICERs from the company's original economic model were for treatment for a combined cohort of people with and without cirrhosis (hereafter referred to as the 'combined cohort'). The Committee heard from clinical experts that it was standard clinical practice for people with and without cirrhosis to be considered as separate subgroups, because cirrhosis affects a person's likelihood of a sustained virological response. The Committee considered individual ICERs presented by the company for each genotype by treatment history, interferon eligibility and cirrhosis status (where available) and noted that the ICERs were consistently much lower in the subgroups of people with cirrhosis than in the subgroups of people without cirrhosis. The Committee also noted that patient numbers underpinning the clinical evidence used in the

economic model were very small for the groups of people with cirrhosis, and that the sustained virological responses were in some cases as high as in people without cirrhosis. The Committee heard from clinical experts that sustained virological responses were historically lower in people with cirrhosis across all HCV genotypes than in people without cirrhosis. In addition, the Committee was aware that the summary of product characteristics states that consideration should be given to extending sofosbuvir treatment from 12 to 24 weeks in people who have 1 or more factors historically associated with lower response rates to interferon-based therapies and that 1 of the factors listed is cirrhosis. The Committee considered that the high sustained virological responses that were generated from the small numbers of patients in the subgroup of people with cirrhosis (which resulted in very low ICERs) in each stratified subgroup should be interpreted with caution. The Committee noted that the ICERs from the combined cohort appeared artificially low, considering that most of the group would not have cirrhosis. The Committee concluded that the consideration of the cost effectiveness of sofosbuvir for each genotype should take into consideration both the combined cohort ICER and also the estimated ICERs for treatment in people with and without cirrhosis.

4.15 The Committee acknowledged that, in response to consultation, the company presented a revised base-case model for HCV genotypes 1, 3, 4, 5 and 6 that incorporated most of its preferred assumptions (see section 3.64). The company explained and justified deviations from the Committee's preferred assumptions, which were included in the revised model.

4.16 The Committee noted that the revised model included a transition probability from the sustained virological response cirrhotic health state to the hepatocellular carcinoma health state (0.0128) using data from Cardoso et al. as requested by the Committee. In addition, the company also updated the transition probability from the health state for people with cirrhosis who have not had a sustained virological response to the hepatocellular carcinoma health state (0.0631; also from Cardoso et al.) rather than using the transition probability estimate (0.014) from Fattovich et al. (1997) that was used in the original model. The Committee heard from the clinical experts that using both transition probabilities from the Cardoso et al. study also had face validity because it would allow the modelling of a relative reduction in the probability that a patient would progress to hepatocellular carcinoma after having a sustained virological

response. The Committee also heard from the clinical experts that the Cardoso et al. evidence that a person with cirrhosis who has a sustained virological response is 4 to 5 times less likely to later have hepatocellular carcinoma is consistent with the progression to hepatocellular carcinoma seen in clinical practice. The Committee noted that the Cardoso et al. transition probabilities were based on a population whose baseline characteristics were closer to the population seen in clinical practice in England. However, the Committee also heard from clinical experts that exploring alternative sources for transition probabilities, such as Fattovich et al. was appropriate. The Committee concluded that although there is significant uncertainty about the absolute reduction in the probability of progression to hepatocellular carcinoma between the sustained virological response with cirrhosis health state and the health state of cirrhosis without a sustained virological response, Cardoso et al. was an acceptable source for transition probabilities for the company's revised base-case model. However, the Committee also concluded that it was plausible that the transition probability for people without a sustained virological response may lie somewhere between the Cardoso et al. and Fattovich et al. estimates.

- 4.17 The Committee considered the impact of using alternative sustained virological responses for peginterferon alfa and ribavirin in genotype 1 HCV on the results from the revised economic model. The Committee noted that the company preferred the sustained virological responses for peginterferon alfa and ribavirin treatment in people with genotype 1 HCV from McHutchison et al. because it was a larger study and the baseline characteristics of patients were better matched to the patients in the pivotal NEUTRINO trial. It also noted that the ERG considered the estimates from Hadziyannis et al. (2004) to be more relevant because they were most generalisable to patients with HCV in England. This was because the study included people with the genotypes most relevant to the UK population, that is, genotypes 1 and 3 HCV. The Committee heard from the clinical experts that there is a wide variation in sustained virological response in clinical practice and that the baseline characteristics of patients included in each study differed. This had an impact on the absolute sustained virological responses in these studies. The clinical experts noted that it was important to consider a range of alternative sustained virological responses from the evidence base rather than arbitrarily choosing a single rate from a particular study. The Committee noted that the sensitivity analyses subsequently presented by the company showed that the ICERs for sofosbuvir plus peginterferon alfa and ribavirin compared with

peginterferon alfa and ribavirin alone in people with genotype 1 treatment-naïve HCV were £25,000 per QALY gained using the estimates from Hadziyannis et al. compared with £17,500 per QALY gained using the estimates from McHutchison et al. On balance, the Committee concluded that the sustained virological responses from McHutchison et al. were an acceptable source for including in its base-case model, but noted that the sustained virological responses could lie between those provided by the McHutchison and Hadziyannis data sets.

- 4.18 The Committee considered the cost of ribavirin used in the company's model. The Committee noted that the company used the cost of ribavirin from the BNF (June 2013) in the original model (Copegus; £246.65) and asked that the company explore the impact of using the price of generic ribavirin paid by the NHS (£42.05 based on the Department of Health [Commercial Medicines Unit](#) Electronic market information tool) which is available nationally through contracts negotiated by the NHS Commercial Medicines Unit. In response to consultation the company included the generic cost of ribavirin in its revised base-case analysis, but noted that the Medicines and Healthcare products Regulatory Agency stated that generic ribavirin should only be used in combination with interferon alfa-2b, which only has 3% of the market share in the UK. The Committee concluded that the generic cost of ribavirin had a small effect on the ICER as demonstrated by the ERG analysis, but that sensitivity analyses around the generic costs of comparator treatment were appropriate.
- 4.19 The Committee discussed the utility values used in the company's model. It acknowledged that health-related quality of life was largely assessed in the clinical trials for sofosbuvir using the SF-36 questionnaire and that none of the clinical trials collected data using the EQ-5D quality-of-life measure. The Committee understood that the company obtained SF-36 health-related quality-of-life data at various time points, including 24 weeks after the end of treatment in some trials. The Committee appreciated that the company tried to be pragmatic in its approach to modelling the effects of treatment by applying a utility increment of 0.05 (from Wright et al.) after sustained virological response in the company's base-case analysis. However, it asked that the company present a revised base-case model that explored the use of different utility estimates including more up-to-date estimates from the literature such as Vera-Llonch et al. (2013) and estimates from the pivotal clinical trials. The Committee noted that the company stated it was unable to incorporate the estimates from the pivotal

clinical trials because the data were not available, but provided a revised base-case model incorporating an alternative utility increment (0.041; Vera-Llonch et al.) after a sustained virological response. The Committee noted that using this utility increment increased the company's base-case ICERs slightly. The Committee concluded that although alternative utility estimates from the pivotal studies would have been preferred, using the utility increment from Vera-Llonch et al. in its revised base case was acceptable.

- 4.20 The Committee discussed the discount rate used in the company's model and considered whether this appraisal met the criteria for using a non-reference case discount rate for costs and health benefits that can be applied in situations 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), as described in [NICE's guide to the methods of technology appraisal](#). The Committee noted that the company's base-case analysis used a discount rate of 3.5% for costs and health benefits in line with the NICE reference case and that the deterministic sensitivity analysis presented by the company suggested that the ICERs were particularly sensitive to the discount rate used. The Committee heard from the clinical experts that a person who does not have cirrhosis and has a sustained virological response could be considered cured. However, the Committee was aware that no data are available beyond the follow-up period from the trials; therefore evidence supporting the long-term durability of a sustained virological response is lacking. The Committee also noted that people with cirrhosis who experience a sustained virological response would not have their health fully restored. Therefore, the Committee concluded that sofosbuvir did not meet the criteria for using non-reference case discount rates, and agreed that the company's approach to using the standard discount rate of 3.5% was appropriate.
- 4.21 The Committee considered whether the cost effectiveness of sofosbuvir for treating hepatitis C was better assessed for the population as a whole (that is, using the 'global' ICERs presented by the company in response to consultation, which are weighted by genotype, treatment history and the presence or absence of cirrhosis, see section 3.66) or separately for each genotype. The Committee was unconvinced by the global ICER approach put forward by the company because the evidence from the clinical experts suggested that in clinical practice treatment is stratified by genotype, treatment history and other characteristics,

including cirrhosis status. This is because the capacity to benefit from treatment for chronic hepatitis C differs depending on the patient's characteristics. The Committee therefore concluded that it was more appropriate to consider the clinical and cost effectiveness for each relevant subgroup of patients separately in the company's base-case analyses.

Genotype 1

Treatment-naïve, interferon eligible

4.22 The Committee considered the cost effectiveness of sofosbuvir plus peginterferon alfa and ribavirin for people with genotype 1 treatment-naïve HCV who are eligible for interferon treatment. The Committee noted that the ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin alone for 48 weeks was less than £17,500 per QALY gained. The Committee noted that the ICERs for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with response-guided treatment with boceprevir plus peginterferon alfa and ribavirin and telaprevir plus peginterferon alfa and ribavirin were £10,300 and £15,400 per QALY gained, respectively. The Committee noted that when stratified by the presence or absence of cirrhosis, the ICERs for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks were £5,400 and £25,200 per QALY gained, respectively. The ICERs for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with boceprevir plus peginterferon alfa, when stratified by the presence or absence of cirrhosis, were £2,800 and £14,300 per QALY gained, respectively. The ICERs for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with telaprevir plus peginterferon alfa, when stratified by the presence or absence of cirrhosis, were £4,200 and £22,300 per QALY gained, respectively. The Committee also considered the ERG's exploratory analyses (see section 3.76). The ERG's resulting ICER for the combined cohort for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin alone for 48 weeks was just over £30,000 per QALY gained. The Committee believed that this ICER represented the upper limit of what could be considered to be plausible, but that the ICERs for sofosbuvir plus peginterferon alfa and ribavirin for

12 weeks compared with response-guided boceprevir and telaprevir plus peginterferon alfa and ribavirin treatment, which are the standard of care in the NHS, were £12,200 and £18,700 per QALY gained. The Committee concluded that sofosbuvir plus peginterferon alfa and ribavirin was cost effective for people with treatment-naïve genotype 1 HCV.

Treatment-experienced, interferon eligible

- 4.23 The Committee considered the cost effectiveness of sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with standard of care in people with genotype 1 treatment-experienced HCV for whom interferon is suitable. The Committee acknowledged the uncertainty in the ICER for the population who have treatment-experienced HCV in the light of the lack of clinical evidence, but noted that there are very few treatment options for these patients, who have a high unmet need. The Committee noted that the estimate of sustained virological response in the treatment-experienced population provided by the company was accepted by the European Medicines Agency and clinical experts. The Committee noted that the ICERs for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks (£12,600 per QALY gained), boceprevir plus peginterferon alfa and ribavirin (£700 per QALY gained), and telaprevir plus peginterferon alfa and ribavirin (£8,200 per QALY gained) for the combined cohort of people with and without cirrhosis could be considered cost effective although ICERs stratified by cirrhosis status were not available. The Committee considered that if the relative proportion of people with and without cirrhosis was similar to that observed in the group with treatment-naïve HCV, then it would be likely that the stratified ICERs for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin alone for 48 weeks would be cost effective for people with and without cirrhosis even when taking into account the assumptions in the ERG's exploratory analyses, which would increase the ICERs further. The Committee also noted that the stratified ICERs for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with response-guided boceprevir and telaprevir plus peginterferon alfa and ribavirin treatment would be even lower for these groups, and that these 2 treatment regimens are the standard of care in the NHS. The Committee concluded that sofosbuvir plus peginterferon alfa and ribavirin is a cost-effective treatment option for people

with genotype 1 treatment-experienced HCV who are eligible for interferon treatment.

Treatment-naïve, interferon ineligible

4.24 The Committee considered the cost effectiveness of sofosbuvir plus ribavirin for 24 weeks compared with standard of care (no treatment) in people with genotype 1 treatment-naïve HCV for whom interferon is unsuitable. It noted that the ICER for sofosbuvir and ribavirin compared with no treatment for this population was £47,600 per QALY gained. In response to consultation, the company stated that although it is necessary to have options for this subgroup of patients for whom interferon treatment is unsuitable and who have a high unmet need, it is anticipated that the number of people in this group having 24 weeks of sofosbuvir plus ribavirin would be extremely low. The Committee also heard from the company that it was not expecting people with genotype 1 HCV who are interferon eligible to be given the option of the 24 week interferon-free sofosbuvir regimen. The Committee concluded that although the number of people with genotype 1 treatment-naïve HCV for whom interferon is unsuitable is potentially small, the high ICER for sofosbuvir plus ribavirin alone compared with no treatment for this population does not represent a cost-effective use of NHS resources and could not be recommended.

Treatment-experienced, intolerant to or ineligible for interferon treatment

4.25 The Committee considered the lack of evidence for sofosbuvir plus ribavirin for 24 weeks compared with the standard of care (no treatment) in the subgroup of people with genotype 1 treatment-experienced HCV who are intolerant to or ineligible for interferon treatment. However, considering the Committee had accepted the ICERs generated using the sustained virological responses recognised by the US Food and Drug Administration (FDA) for the genotype 1 treatment-experienced HCV population who are eligible for interferon, the Committee took a pragmatic view on how to establish an estimated ICER for this population. The starting point for the Committee was the ICER of £47,600 per QALY gained (that is the ICER for people with genotype 1 treatment-naïve HCV,

for whom interferon is unsuitable). Assuming that the relative difference between the ICERs in the treatment-naïve and treatment-experienced HCV groups seen in other genotypes also applies to genotype 1 HCV, the Committee would expect that the ICERs for the genotype 1 treatment-experienced HCV group would likely be slightly lower than the ICER for people in the genotype 1 treatment-naïve HCV group. When stratified by the presence or absence of cirrhosis, the ICERs would be likely to increase in the subgroup without cirrhosis and decrease in the subgroup with cirrhosis, in a similar proportion to that seen in the subgroup of people with treatment-naïve genotype 1 HCV for whom interferon is unsuitable. However, the ICERs would still remain high. The Committee noted that if the assumptions used in the ERG's exploratory analyses were applied, the ICERs would increase in the combined cohort as well as in the subgroups with and without cirrhosis. The Committee was aware that people with genotype 1 treatment-experienced HCV for whom interferon is unsuitable are a group with a high unmet need. However, the Committee concluded that based on the very uncertain evidence presented and the high ICERs, treatment with sofosbuvir plus ribavirin for 24 weeks does not represent a cost-effective use of NHS resources for people with genotype 1 treatment-experienced HCV who are intolerant to or ineligible for interferon treatment and therefore could not be recommended in this group.

Genotype 2

- 4.26 The Committee considered the cost effectiveness of sofosbuvir plus ribavirin compared with peginterferon alfa and ribavirin for 24 weeks in people with genotype 2 HCV who are eligible for interferon treatment, or no treatment in people who are intolerant or ineligible for treatment with interferon. The Committee noted that sofosbuvir plus peginterferon alfa and ribavirin does not have a marketing authorisation for treating genotype 2 HCV. The Committee noted that the ICER from the company's original base-case model for sofosbuvir and ribavirin compared with peginterferon alfa and ribavirin alone was approximately £46,300 per QALY gained in people who are eligible for treatment with interferon and who have treatment-naïve HCV, and £12,500 per QALY gained in people who have treatment-experienced HCV and are eligible for treatment with interferon. The ICER for sofosbuvir and ribavirin compared with no treatment for people who are intolerant to or ineligible for interferon was £8,200 per QALY

gained for people with treatment-naïve HCV, and £8,600 per QALY gained for people with treatment-experienced HCV. The Committee concluded that sofosbuvir plus ribavirin was not a cost-effective use of NHS resources in adults with genotype 2 treatment-naïve HCV who are eligible for treatment with interferon. However, the Committee concluded that sofosbuvir plus ribavirin was a cost-effective use of NHS resources for adults with genotype 2 HCV who are eligible for treatment with interferon and who have had treatment for HCV, and for adults with genotype 2 HCV who are intolerant or ineligible for interferon treatment, regardless of their treatment history.

Genotype 3

Treatment-naïve, interferon eligible

4.27 The Committee considered the cost effectiveness of sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks in people with genotype 3 treatment-naïve HCV who are eligible for treatment with interferon. The Committee noted from the company's revised base case that the combined cohort ICER (with and without cirrhosis) for sofosbuvir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone for this population was approximately £21,900 per QALY gained. The Committee noted that when stratified by cirrhosis status, the ICER for people with treatment-naïve HCV without cirrhosis who are eligible for treatment with interferon was approximately £40,600 per QALY gained, whereas the ICER for people with cirrhosis was approximately £6,600 per QALY gained. The Committee noted that the ICERs for the subgroups of patients with or without cirrhosis were highly uncertain due to the small patient numbers included in the studies. The Committee noted that the effect of using the combined cohort analysis, which includes a larger subgroup without cirrhosis and a small subgroup with cirrhosis, resulted in a combined cohort ICER that was artificially low (£21,900 per QALY gained). The Committee considered that despite this uncertainty there was more confidence around the ICER for the subgroup with cirrhosis because the treatment remained cost effective despite using a variety of assumptions including those suggested by the ERG in its exploratory analyses. The Committee also acknowledged that people with

cirrhosis are in greater need of treatment than those without cirrhosis. Therefore, the Committee concluded that sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks could be considered a cost-effective use of NHS resources in people with genotype 3 treatment-naïve HCV who are eligible for interferon treatment and who have cirrhosis, but it was not a cost-effective use of NHS resources in people who do not have cirrhosis.

- 4.28 The Committee noted that the marketing authorisation for sofosbuvir allows 24 weeks dual therapy with sofosbuvir plus ribavirin as an alternative to 12 weeks with sofosbuvir plus peginterferon alfa and ribavirin for people with genotype 3 HCV who are eligible for treatment with interferon. The Committee considered the exploratory analyses carried out by the company, modelling the effect on the revised base-case ICERs of varying the proportion of people with genotype 3 HCV receiving sofosbuvir plus ribavirin for 24 weeks in people eligible for treatment with interferon (see section 3.75). The Committee noted that the scenario analysis presented by the company, in which 100% of people with treatment-naïve genotype 3 HCV received sofosbuvir plus ribavirin for 24 weeks compared with peginterferon plus ribavirin for 24 weeks, resulted in an ICER of £47,000 per QALY gained. The ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks treatment compared with peginterferon and ribavirin treatment for 24 weeks increased from approximately £21,900 per QALY gained to approximately £22,400 and £27,100 per QALY gained when it was assumed that 2% and 20% had sofosbuvir and ribavirin for 24 weeks treatment in the population with treatment-naïve HCV who are eligible for interferon. The Committee noted that when stratified by cirrhosis status, the revised base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks treatment compared with peginterferon and ribavirin treatment for 24 weeks increased in the subgroup without cirrhosis to £41,700 and £51,300 per QALY gained when it was assumed that 2% and 20% had sofosbuvir and ribavirin in the treatment-naïve population. In the subgroup with cirrhosis, the ICER increased to £6,800 and £8,400 per QALY gained using the same assumptions. The Committee concluded that the duration of treatment with sofosbuvir had a considerable effect on the ICERs in people with genotype 3 HCV, although it heard from the company, clinical experts and commissioners that sofosbuvir and ribavirin treatment for 24 weeks would only be appropriate for people ineligible for interferon therapy.

Treatment-experienced, interferon eligible

- 4.29 The Committee considered the cost effectiveness of sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks in people with genotype 3 treatment-experienced HCV who are eligible for treatment with interferon. The Committee noted that the company's revised base-case ICER for the combined cohort was £13,900 per QALY gained. When stratified by cirrhosis status, the ICER for people without cirrhosis was £18,600 per QALY gained, whereas the ICER for people with cirrhosis was £6,300 per QALY gained. The Committee was aware that these ICERs were also uncertain, due to small patient numbers included in the studies, and that sustained virological responses were identical for people in the subgroups with and without cirrhosis, which is clinically unlikely due to the poorer sustained virological responses usually seen in people with cirrhosis. The Committee was willing to accept this uncertainty because the ICERs were within the range it could consider a technology might be cost-effective in the group without cirrhosis and even lower in the group with cirrhosis. The ICERs remained in this range when the ERG's exploratory assumptions were used. The Committee acknowledged that this subgroup also has no further treatment options and can be considered to have a high unmet need. The Committee therefore concluded that sofosbuvir plus peginterferon alfa and ribavirin was a cost-effective use of NHS resources in people with genotype 3 treatment-experienced HCV who were eligible for interferon treatment.
- 4.30 As with the treatment-naïve, interferon-eligible group with genotype 3 HCV, the Committee considered the exploratory analyses carried out by the company that modelled the effect on the revised base-case ICERs of increasing the proportion of people with treatment-experienced genotype 3 HCV receiving sofosbuvir plus ribavirin for 24 weeks (see section 3.75). The ICER for sofosbuvir plus ribavirin for 24 weeks compared with peginterferon plus ribavirin for 48 weeks in people with treatment-experienced genotype 3 HCV who are eligible for interferon treatment increased to £48,300 per QALY gained. The ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks also increased for the population for whom interferon therapy is suitable and who had treatment-experienced HCV, from approximately £13,900 per QALY gained to approximately £14,500 and £19,900 per QALY gained when it was assumed that 2% and 20% had sofosbuvir and ribavirin. The

Committee concluded that the duration of treatment with sofosbuvir had a considerable effect on the ICERs in people with genotype 3 HCV, and it agreed with the company, clinical experts and commissioners that sofosbuvir and ribavirin treatment for 24 weeks would only be appropriate for people ineligible for interferon therapy.

Treatment-naïve, interferon ineligible

- 4.31 The Committee considered the cost effectiveness of sofosbuvir and ribavirin for 24 weeks compared with no treatment in people with genotype 3 treatment-naïve HCV who are ineligible for treatment with interferon. The Committee noted that the company's revised base-case ICER for this population was £21,000 per QALY gained, which was calculated based on sustained virological responses seen in VALENCE. The Committee noted that the VALENCE study was unblinded when treatment was extended for all people with genotype 3 HCV. Therefore it was of poor quality and open to potential bias. The Committee noted that when the population was stratified by cirrhosis status, the ICER for sofosbuvir plus ribavirin was £28,000 per QALY gained for people without cirrhosis (which increased to £32,000 per QALY gained using the ERG assumptions) and £10,500 per QALY gained for people with cirrhosis. The Committee concluded that given the uncertainty around the ICER in the group without cirrhosis and the possibility that the ICER may be over £32,000 per QALY gained, it could not recommend sofosbuvir plus ribavirin treatment in people with genotype 3 treatment-naïve HCV without cirrhosis who are ineligible for interferon treatment. Because the ICER in the subgroup of people with cirrhosis remained low (£15,100 per QALY gained), even when using the ERG's exploratory assumptions, the Committee concluded that sofosbuvir plus ribavirin is cost effective for people with genotype 3 treatment-naïve HCV who have cirrhosis.

Treatment-experienced, interferon ineligible

- 4.32 The Committee considered the cost effectiveness of sofosbuvir and ribavirin for 24 weeks compared with no treatment in people with treatment-experienced genotype 3 HCV who are intolerant to or ineligible for treatment with interferon. The Committee considered that this group would represent a very small number

of patients in the NHS. The Committee considered the company's revised base-case ICER of approximately £27,500 per QALY gained for the combined cohort of people with and without cirrhosis. The Committee noted that this ICER was also based on the sustained virological response rates observed in VALENCE, a study that the Committee considered to be of low quality and open to potential bias (see sections 3.16 and 4.32). When the ICERs were stratified by cirrhosis status, the company's revised base-case ICER for the subgroup without cirrhosis was £31,400 per QALY gained (£35,000 per QALY gained using the assumptions from the ERG exploratory analyses). Due to the uncertainty around the ICER and the possibility that the ICER was over £35,000 per QALY gained, the Committee concluded that sofosbuvir plus ribavirin was not a cost-effective use of NHS resources in people with treatment-experienced genotype 3 HCV without cirrhosis who are intolerant to or ineligible for interferon treatment. The Committee noted that the company's revised base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment for people with cirrhosis was £19,200 per QALY gained (£29,700 per QALY gained when using the assumptions from the ERG exploratory analyses). The Committee considered the high unmet need of this subgroup for whom there are currently no other licensed treatment options. The Committee recognised the uncertainty in the evidence base for people with treatment-experienced genotype 3 HCV who have cirrhosis and are intolerant to or ineligible for interferon. However, on balance, it concluded that it would be consistent with its other recommendations for people with genotype 3 HCV to recommend sofosbuvir plus ribavirin for 24 weeks for people with cirrhosis and that this could be considered a cost-effective use of NHS resources, because the true ICER was likely to be between the company's revised base case and the ERG's exploratory estimates.

Genotypes 4, 5 and 6

Treatment-naïve, interferon eligible

- 4.33 The Committee considered the company's original base-case ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa and ribavirin for 48 weeks of approximately £26,800 per QALY gained in people with genotype 4, 5 or 6 treatment-naïve HCV, for whom interferon is

suitable. The Committee noted that the ICER was based on a naive comparison of the sustained virological responses 12 weeks after the end of treatment for sofosbuvir plus peginterferon alfa-2a and ribavirin observed in NEUTRINO and the sustained virological responses 24 weeks after the end of treatment with peginterferon alfa-2b and ribavirin observed in Manns et al. (2001). The Committee heard from clinical experts and the company that peginterferon alfa 2a and peginterferon alfa-2b were assumed to be equally efficacious and that sustained virological response 24 weeks after the end of treatment was essentially equivalent to sustained virological response 12 weeks after the end of treatment. The Committee noted that of the 35 people with genotype 4, 5 or 6 in the NEUTRINO study, 100% of the 33 people without cirrhosis achieved a sustained virological response compared with 50% of the 2 people with cirrhosis. However in Manns et al., the subgroup without cirrhosis had a sustained virological response of 50% (as calculated by the company, based on the relative difference in sustained virological response between people without cirrhosis and people with cirrhosis in the studies in genotype 1, 2 and 3 HCV) and the subgroup with cirrhosis had a sustained virological response of 38.6%. The Committee noted that the difference in sustained virological responses between the sofosbuvir plus peginterferon alfa and ribavirin arm and the peginterferon alfa plus ribavirin alone arm of the model was a key driver of the ICER.

- 4.34 During consultation, the company presented the Committee with additional analyses for people with genotype 4, 5 or 6 HCV, which included alternative sustained virological responses for peginterferon alfa plus ribavirin from studies identified in a systematic review of studies in genotypes 4, 5 and 6 HCV and the impact of using different sustained virological responses on the ICER. The Committee noted that the studies were exclusively European (because the company considered the patient characteristics to be more relevant to patients in the UK) whereas the ERG had considered studies from the Middle East and Egypt to be an important source of data because these studies included larger numbers of patients. The Committee noted that the sustained virological responses for peginterferon alfa plus ribavirin in the European studies ranged from 33% (Zeuzem et al. [2005]) to 77% (Fried et al. [2002]), which spanned the range of sustained virological responses seen in the studies identified by the ERG. The Committee considered the revised base-case ICER of £27,500 per QALY gained presented by the company for sofosbuvir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin (using the sustained virological

responses from Manns et al. [2001] for the latter) in people with genotype 4, 5 or 6 HCV. The Committee noted that the company varied the sustained virological response for peginterferon alfa and ribavirin using Zeuzem et al. and Fried et al. but noted that sustained virological responses were not available by cirrhosis status. Therefore the company applied the same sustained virological response for people with and without cirrhosis. The ICERs for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa plus ribavirin for 48 weeks using Zeuzem et al. and Fried et al. were £19,148 and £244,387 per QALY gained, respectively. The Committee considered that a sustained virological response of 77% for 48 weeks of treatment with peginterferon alfa and ribavirin was improbable. The Committee considered the ERG's exploratory analyses, in which the sustained virological responses in the peginterferon alfa and ribavirin arm were based on a weighted average of the responses reported in the individual studies. The ERG used a sustained virological response of 54.8% from the European studies (which included the studies by Manns et al. and Lindsay et al.) which led to an ICER of approximately £39,100 per QALY gained. The Committee considered this to be the most relevant ICER because it was based on studies with populations that were most similar to patients in England and was generated using the Committee's preferred assumptions (see section 4.15). The Committee noted that the sustained virological responses for peginterferon alfa plus ribavirin for 48 weeks in people with genotype 4, 5 or 6 HCV were higher than those reported for people with genotype 1 HCV, providing indirect evidence that people with genotype 4 HCV are not more difficult to treat. The Committee concluded that the ICER of £39,100 per QALY gained for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks compared with peginterferon alfa plus ribavirin for 48 weeks using the ERG's calculated sustained virological response was the most plausible, although there remained considerable uncertainty about the ICER, because of the small number of people included in the NEUTRINO study.

- 4.35 The Committee considered comments received during consultation that recommending sofosbuvir plus peginterferon alfa and ribavirin only for a proportion of people with genotype 1, 2 or 3 HCV, but not for anyone with genotype 4, 5 or 6 HCV could potentially be interpreted as indirect discrimination. It heard from consultees that this was because a larger proportion of minority ethnic groups, people with HIV co-infection and haemophilia are represented in the genotype 4, 5 and 6 HCV population. In light of NICE's legal obligation to

promote equality, the Committee considered the additional evidence provided by the company that included family origin by HCV genotype, and the prevalence of HIV and HCV co-infection and HCV infection in people with haemophilia. The Committee noted that the family origin evidence was self-reported (and could therefore not be verified), and used broad categories. The Committee therefore considered this evidence to be uncertain, although it noted the anecdotal evidence provided by other consultees that minority ethnic groups are more highly represented in the genotype 4, 5 and 6 HCV population. The Committee considered the commercial-in-confidence evidence presented by the company about the genotype distribution of HCV in people with HCV and HIV co-infection and agreed that a disproportionate number of people had genotype 4 HCV and HIV co-infection compared with the overall population of people with HCV in England. The Committee noted that the evidence presented by the company suggested that 96% of people with haemophilia and HCV had genotype 1, 2 or 3 HCV, and 4% had genotype 4 or 5 because no patients were identified with genotype 6 HCV and haemophilia. The Committee noted that the distribution of HCV genotypes in people with haemophilia presented by the company was actually similar to the overall population of people with HCV in England. The Committee concluded that there did not appear to be a disproportionate percentage of people with haemophilia who had genotype 4 HCV in England. The Committee noted that the ICERs for sofosbuvir for people with genotype 4, 5 or 6 HCV for the combined cohort (people with and without cirrhosis) were very high. However, it agreed that, in the light of evidence on the higher representation of minority ethnic groups and HIV co-infection in these genotypes, further consideration should be given to whether anything could be done to remove or reduce the disproportionate impact for the protected groups.

- 4.36 The Committee noted that unlike genotype 1 HCV, people with genotype 4, 5 or 6 HCV currently only have peginterferon alfa and ribavirin for 48 weeks as a treatment option. The Committee considered that the people with the highest unmet need within this population are those with cirrhosis, because their disease is less likely to respond to treatment with peginterferon alfa and ribavirin for 48 weeks. Although the sustained virological response seen in people with genotype 4, 5 or 6 HCV with cirrhosis was 50% in NEUTRINO, the Committee noted that this was based on 2 patients; 1 who had a sustained virological response and 1 who did not. As with some of the other genotypes, the Committee used a pragmatic approach in estimating an ICER for sofosbuvir for

the group of people with genotype 4, 5 or 6 with cirrhosis. Using the starting point for the ICER (calculated by the ERG) as £39,100 per QALY gained, the Committee considered whether the ICER for genotypes 4, 5 and 6 responded in a similar manner as for other genotypes, that is, whether it would be significantly lower for treatment in people with cirrhosis than in people without cirrhosis. The Committee considered that it is plausible that the ICER for treatment in people with genotypes 4, 5 or 6 treatment-naïve HCV with cirrhosis could be within the range that is normally accepted as being cost effective, that is between £20,000 and £30,000 per QALY gained, and that the ICER for treatment in people with genotypes 4, 5 or 6 treatment-naïve HCV without cirrhosis is likely to be greatly in excess of the £39,100 per QALY gained estimated by the ERG for the combined cohort. Therefore, taking into consideration the potential equality issues raised about genotypes 4, 5 and 6 HCV, the high unmet need and the lack of treatment options for people with cirrhosis, the Committee considered it was reasonable to conclude that sofosbuvir plus peginterferon alfa and ribavirin for treating people with genotype 4, 5 or 6 treatment-naïve HCV who have cirrhosis was a cost-effective use of NHS resources.

Treatment-experienced, interferon eligible

- 4.37 The Committee considered cost-effectiveness evidence presented for people with genotypes 4, 5 or 6 treatment-experienced HCV, for whom interferon is suitable. The Committee noted that the company did not provide an ICER for treatment in this group and that an estimate for this ICER could only be based on the ICER in people who are eligible for interferon who have not had treatment before. The Committee acknowledged that there is even more uncertainty in the ICER for treatment in the population who have treatment-experienced HCV in the light of the lack of clinical evidence, but noted that there are very few treatment options for these patients, who have an even higher unmet need than people who have never been treated before. Considering the uncertainty in the evidence, but also taking into consideration the potential equality issues raised for people with genotype 4, 5 or 6 HCV, the Committee took a pragmatic view on how to establish an estimated ICER for this population. The Committee noted that sofosbuvir plus peginterferon alfa and ribavirin was recommended for genotype 1 treatment-experienced HCV on the basis of unmet need and approval from the FDA based on a sustained virological response that was calculated from the

population who had not had treatment before. Therefore, the Committee concluded that a similar approach could be used for people with genotype 4, 5 and 6 treatment-experienced HCV. Although sustained virological responses are typically lower in the treatment-experienced populations, the costs associated with disease progression and a comparison with no treatment mean that the ICERs for sofosbuvir in treatment-experienced people are consistently lower than the ICERs for sofosbuvir in people who have not had treatment. Using the starting point for the ICER (calculated by the ERG) as £39,100 per QALY gained for people with genotype 4, 5 or 6 treatment-naïve HCV, the Committee considered that it was plausible that the ICER in genotypes 4, 5 or 6 treatment-experienced HCV with cirrhosis could also be within the range that is normally accepted as being cost effective, that is between £20,000 and £30,000 per QALY gained. The Committee concluded that for all these reasons, sofosbuvir plus peginterferon alfa and ribavirin for treating people with genotype 4, 5 or 6 treatment-experienced HCV who have cirrhosis could be considered a cost-effective use of NHS resources.

Interferon unsuitable

- 4.38 The Committee considered the group of people with genotype 4, 5 or 6 HCV, for whom interferon therapy is unsuitable. The Committee noted that the company did not provide an ICER for sofosbuvir plus ribavirin in this population. The starting point for the Committee was the only cost-effectiveness evidence provided for this population, namely the ICER of £39,100 per QALY gained for people with genotype 4, 5 or 6 HCV, for whom interferon therapy is suitable. The Committee noted that the ICER for sofosbuvir plus ribavirin compared with no treatment in people with treatment-naïve genotype 1 HCV who were not eligible for interferon was more than double the ICER for sofosbuvir plus peginterferon and ribavirin compared with peginterferon and ribavirin in people who were interferon eligible. The Committee anticipated that the ICERs for sofosbuvir plus ribavirin in people with genotype 4, 5 or 6 HCV, for whom interferon therapy is unsuitable, would increase significantly due to the fact that treatment would be offered for 24 weeks instead of 12 weeks and this was likely to increase further using the ERG's exploratory assumptions. The Committee considered that, based on the lack of evidence provided for these genotypes, it was necessary to make a value judgment. Although people with genotype 4, 5 or 6 HCV represent a small

proportion of the total HCV population in England, it is still an important group with a high unmet need. The Committee reflected on the quality of evidence and the level of uncertainty, in addition to the very high costs associated with sofosbuvir plus ribavirin treatment for 24 weeks. The Committee concluded that treatment with sofosbuvir plus ribavirin for 24 weeks was not a cost-effective use of NHS resources and could not be recommended for adults with genotype 4, 5 or 6 HCV, for whom interferon therapy is not suitable.

4.39 The Committee noted the company presented separate economic analyses for people co-infected with HCV and HIV based on interim results from the PHOTON-1 study and the 1910 study. The Committee was aware the PHOTON-1 study provided results for people with genotypes 1, 2 or 3 HCV treated for 12 or 24 weeks with sofosbuvir and ribavirin and the 1910 study provided results for people with genotypes 1 or 3 HCV treated with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. The Committee was aware that, other than incorporating higher transition probabilities from the non-cirrhotic to the compensated cirrhosis state, the modelling did not differ for the mono-infected and co-infected populations. The Committee noted the ERG comment that there were differences in patient characteristics and outcomes that were not taken into account in the company's model. On balance, the Committee concluded that, based on the evidence presented and considered for this population, it was reasonable to include the group of people co-infected with HCV and HIV in the recommendations for the mono-infected group. However, the Committee agreed with the ERG that there were legitimate concerns about the modelling for the HIV and HCV co-infected group, and that future economic analyses should be presented separately for this population.

4.40 The Committee considered the concern expressed in comments received during consultation that some inexperienced clinicians may want to offer sofosbuvir and ribavirin for 24 weeks to people with genotypes 1, 4, 5 or 6 HCV who are interferon eligible in order to avoid the possible adverse effects associated with interferon treatment. The Committee heard from the company that the sustained virological responses with sofosbuvir plus peginterferon alfa and ribavirin in these genotypes are superior to those achieved using sofosbuvir and ribavirin alone. It also heard from company representatives that sofosbuvir plus ribavirin alone was only licensed for people in urgent need of care with genotype 1, 4, 5 or 6 HCV in whom interferon was contraindicated (as described in the summary of product

characteristics) or whose disease did not have an adequate response to interferon treatment. The company representatives agreed that sofosbuvir and ribavirin would be regarded as a second-line option and the decision to use dual therapy should only be made by clinicians experienced in treating hepatitis C, preferably after discussion by a multidisciplinary team. However, the Committee concluded that the concerns expressed during consultation were no longer relevant in light of the Committee's decision that sofosbuvir, in combination with ribavirin, should not be recommended for treating adults with genotype 1, 4, 5 or 6 chronic hepatitis C who are interferon intolerant or ineligible (see sections 1.1 and 4.25, 4.26 and 4.39).

- 4.41 The Committee noted a comment received from a member of the public during the second consultation stating that it was potentially more cost effective to treat hepatitis C in people with haemophilia than people without haemophilia due to the large expense associated with treating haemophilia and the additional expenses due to monitoring liver damage in that group. The Committee noted that the clinical trials excluded patients with haemophilia and no clinical evidence or cost-effectiveness analysis had been presented specifically for people with haemophilia and HCV. Therefore the Committee concluded that no evidence-based decision or modelling would be possible, and therefore no separate recommendation could be made specifically for this patient group.
- 4.42 The Committee discussed comments from the patient experts indicating that in practice the availability of treatment for people with chronic hepatitis C who use injectable drugs was limited, which could represent a potential equality consideration. The Committee heard from the clinical experts that treatment for these people is considered on an individual basis because of concerns about safety and treatment adherence, but that clinicians would like to offer sofosbuvir to people using injectable drugs, taking into account any precautions in the summary of product characteristics. The Committee acknowledged that access to treatment for this patient group was an issue related to implementation and could not be addressed through technology appraisal recommendations. However, the Committee concluded that although people who use injectable drugs were not represented in the pivotal clinical trials for sofosbuvir, based on the current evidence available, there was no reason to deny them access to treatment; therefore any recommendations on the use of sofosbuvir would be irrespective of injectable drug use.

- 4.43 The Committee discussed whether sofosbuvir could be considered an innovative treatment, providing a step change in the treatment of chronic hepatitis C. The Committee agreed that sofosbuvir offers the possibility of shortened interferon-based treatment regimens, or treatment without interferon therapy in some circumstances, which is particularly important and a major development in the current clinical management of chronic hepatitis C. The Committee therefore accepted that sofosbuvir is a valuable new therapy for treating chronic hepatitis C. The Committee agreed with the clinical experts and patient experts that there were other benefits to patients (such as relief of loss of cognitive ability in people with HCV) and public health benefits (such as reduced transmission of HCV) that were not captured in the QALY calculation and that, if taken into account, would decrease the ICERs.
- 4.44 During consultation, although a number of consultees noted the urgent need for guidance on the use of sofosbuvir, a comment was also received from NHS England, who is currently responsible for the commissioning of hepatitis C treatment, that it would not be possible to implement the recommendations in this guidance within 3 months. The Committee were in agreement that there may be increased demand for treatment following positive recommendations, but were not presented with evidence on the likely magnitude of this and considered that some patients may prefer to wait for NICE guidance on other interferon-free treatments for chronic hepatitis C before they seek treatment. The Committee highlighted that it would be reasonable for NICE to reflect on whether the standard 3-month implementation period is appropriate. The Committee noted that consultees were interested in the relative cost effectiveness of sofosbuvir compared with other agents in guidance development (although this did not fall within the scope of this appraisal). It therefore concluded that a 1 year review date for the guidance would be appropriate.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication. However, in this appraisal, following a request made by NHS England and a consultation with stakeholders, the period during which NHS England has to comply with the recommendations has been **extended to 31 July 2015**.
- 5.2 NHS England set out 4 principal reasons why it considered a variation to the deferred funding period is justified:
- The need to complete the work of the 'task and finish' service redesign group.
 - A substantial demand for treatment with sofosbuvir, which it anticipates will increase further, because patients who have not sought active treatment in the past will come forward, and which will be increased further by new patients identified through public awareness campaigns and screening of high-risk groups, which have either been initiated or which are planned.
 - The need to establish a hepatitis C network, which will involve setting up a series of centres with the staff and the other resources and systems necessary to provide a multidisciplinary team approach to care.
 - The establishment of a national database and dashboard to monitor and support individual care.
- 5.3 NHS England is clearly concerned about its ability to make sofosbuvir available in the way it considers necessary for planned, efficient and properly audited care. It advised NICE that it would be better able to do so if an extension to the deferred funding period to the end of July 2015 were to be made available.
- 5.4 The argument for an extension, based on the need to establish a national database and dashboard was not supported by a timescale from NHS England. In

addition, it appears that the dashboard component is, in any event, already being put in place. The consequences of not having the database at the same time as the dashboard were not made clear.

- 5.5 The work of the task and finish group is likely to be completed within the normal deferred funding period.
- 5.6 The question as to whether an extension to the deferred funding period is warranted appears to turn on whether either, or a combination of a substantial volume of patients seeking access to sofosbuvir, and the need to establish the hepatitis C network (with or without the database and monitoring function) amount to a substantive argument. Patients who consider that they can benefit from treatment now, supported as they may well be by their clinicians, may not wish to wait for treatment even though they may recognise the benefits of their care being part of a nationally-networked service. NHS England, on the other hand, argues that it has a responsibility to manage its resources efficiently in the interests of both current and future patients.
- 5.7 It is clear that sofosbuvir marks a step change in the treatment available to patients with hepatitis C. NICE has recommended its use, with some restrictions because it is clinically and cost effective. Having done so, NICE should be cautious about introducing any delay in patients gaining access to treatments from which they may benefit. However, it should also avoid placing the NHS in a position of confronting a significant tide of expectation from patients for access to care which they do not feel equipped to provide. To do so would risk sub-optimal treatment decisions and may subject the current service provision to undue stress.
- 5.8 The responsibility for securing care for the NHS in England rests with NHS England. NICE should be cautious and sure of its judgement before requiring NHS England to provide services that it does not consider that it can provide, or provide safely and efficiently. In effect, NICE would have to conclude that NHS England was mistaken. NHS England has indicated that it does not yet have in place the arrangements that it considers necessary for sofosbuvir to be provided, to the full extent recommended in this guidance. Its position, in setting out what it believes it needs to do to put the necessary arrangements in place, has credibility. NICE needs to be wary of substituting its judgement for NHS England's

in this respect.

- 5.9 In its response to consultation on the proposal to extend the deferred funding period, NHS England reiterated the need for clinical networks to support the use of new interventions for the treatment of chronic hepatitis C, which would allow the best quality of clinical care, and allow the most clinically and cost effective prescribing of high cost drug treatments. It further suggested that the network model will ensure better equity of access, noting that many patients with chronic hepatitis C infection come from marginalised groups who do not engage well with health services, and that there is a risk that without proper structures in place a significant proportion of patients in need will not get access to care. It argues that there is a substantial group of patients (mainly but not exclusively those with cirrhosis) who run the risk of serious harm if treatment is delayed, and that it will 'fast track' for consideration, by April 2015, an interim policy to provide oral antiviral therapy to all patients with cirrhosis (plus a small number with severe non-hepatic complications of HCV).
- 5.10 The consultation proposal was supported by the Department of Health on the condition that arrangements are put in place to provide access to treatment for the most seriously ill patients.
- 5.11 NICE heard from patient and professional groups that all the centres likely to be using these drugs have been treating patients with pegylated interferon in combination with ribavirin, boceprevir, and telaprevir for some considerable time, and that they already have staff trained and experienced in the use and monitoring of interferon and ribavirin. These consultees further stated that both simeprevir and sofosbuvir have very few significant side effects or drug-drug interactions (certainly fewer than the first generation protease inhibitors), and many of the centres will already be using sofosbuvir under NHS England's early access programme. NICE was advised that multidisciplinary team approaches to approving treatment are already in place in most treatment providers, as a consequence of the early access programme, and where not, that it would not take long to establish them. It heard that when the reduced treatment duration for the combination regimen of interferon with sofosbuvir is taken into account (12 weeks instead of 30 weeks) it would not be unreasonable to expect the existing capacity to be capable of treating a higher volume of patients.

- 5.12 Consultees pointed out that although many patients are expected to wait until all-oral regimens are available, those with stable cirrhosis at risk of decompensation or hepatocellular carcinoma, will decide that it is better to have treatment now than to delay. These people will not be served by NHS England's early access programme which is restricted to people with decompensated liver disease. NICE noted stakeholders' suggestions for specific groups that might need special consideration if funding for all is not immediately required; that is, those co-infected with HIV, gay men, drug users, and those for whom current treatment is having a detrimental effect on physical or mental wellbeing. NICE accepts these concerns but is satisfied that NHS England will now be putting in place measures to accommodate these patients as well.
- 5.13 NICE heard from Gilead that although it welcomed any opportunity to improve the current hepatitis C service model that may further enhance patient access and outcomes, the submission by NHS England provides no evidence that the proposed hepatitis C network is required for the implementation of the recommendations in this guidance. In particular, while a more sophisticated approach may be preferred in the context of the increase in the number of patients with chronic hepatitis C infection who would be expected to present for testing and treatment after implementation of fully oral interferon-free regimens for the non-cirrhotic group, Gilead believes there is no requirement for this approach for the implementation of this guidance – and NHS England has provided no evidence indicating that this would be the case. NICE understands that Gilead takes the position that in contrast to NHS England's assertions, the available evidence points to the fact that implementation of this guidance is very unlikely to result in substantial numbers of additional patients and indeed, will relieve rather than add to the existing burden on hepatitis C services.
- 5.14 NICE fully understands the concerns put forward by consultees who object to the proposed extension to the period of deferred funding. Any additional delay in accessing recommended treatments is, of course, undesirable. However, NHS England's plans to put in place an enhanced infrastructure reflect a real concern that the current arrangements expose the service and its patients to the risks associated with poor care coordination and inadequate resources. These concerns, though they may be disputed and must be balanced against the disadvantages of delayed access, are based on an arguable case. In addition, it is clear from its initial proposal and from its response to consultation that NHS

England is making a considerable effort to ensure that patients for whom a delay in access to sofosbuvir represents a serious medical risk will have access to it under the existing and planned interim commissioning policies.

- 5.15 An extension to the deferred funding period, to 31 July 2015, is therefore granted under section 7(5a)[ii and iii] of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013; the health technology cannot be appropriately administered until 'certain health service infrastructure requirements including goods, materials or other facilities, or other appropriate health services resources, including staff are in place'.
- 5.16 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in paragraph 5.1 above. This means that, if a patient has chronic hepatitis C and the healthcare professional responsible for their care thinks that sofosbuvir is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

- 6.1 The Committee heard from the NHS commissioning expert that NHS England is intending to collect clinical data from people treated with the new generation of HCV treatments. The Committee agreed that such efforts should be supported so that clinical data collected in routine clinical practice can be used in any review of guidance on these treatments. It recommended that clinical data, including genotype and sustained virological response at 12 weeks, is collected for all people treated with sofosbuvir in the NHS.

7 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3 year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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

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

Professor Gary McVeigh (Chair)

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)

GP, West Coker Surgery, Somerset

Dr Aomesh Bhatt

Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black

GP, Kingsland, Herefordshire

Professor David Bowen

Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley

Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Gerardine Bryant

GP, Swadlincote, Derbyshire

John Cairns

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

Dr Ian Campbell

Honorary Consultant Physician, Llandough Hospital, Cardiff

Ms Tracey Cole

Lay member

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Dr Martin Duerden

Assistant Medical Director, Betsi Cadwaladr University Health Board, North Wales

Mrs Susan Dutton

Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Alexander Dyker

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

Mr Christopher Earl

Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

Mrs Gillian Ells

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Professor Paula Ghaneh

Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Professor John Henderson

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Dr Paul Hepple

GP, Edinburgh

Professor John Hutton

Professor of Health Economics, University of York

Professor Steven Julious

Professor in Medical Statistics, University of Sheffield

Dr Tim Kinnaird

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Mr Warren Linley

Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

Dr Malcolm Oswald

Lay member

Professor Femi Oyebode

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

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust and Metropolitan Borough Council

Dr Mohit Sharma

Consultant in Public Health, Public Health England

Dr Murray Smith

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

Guideline representatives

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

Professor Matthew Hickman

Professor of Public Health and Epidemiology

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Richard Diaz and Christian Griffiths

Technical Leads

Fiona Pearce and Eleanor Donegan

Technical Advisers

Kate Moore

Project Manager

8 Sources of evidence considered by the Committee

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

- Copley V, Frampton G, Pickett K, et al. Sofosbuvir for treating chronic hepatitis C, April 2014

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Companies were also invited to make written submissions. Professional or expert and patient or carer group, and other consultees, had the opportunity to make written submissions. Companies, professional or expert and patient or carer group, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Company:

- Gilead Sciences

Professional or expert and patient or carer groups:

- British Liver Trust
- Liver4Life
- The Hepatitis C Trust
- HIV i-Base
- British Association for Sexual Health and HIV
- British Association for Study of the Liver
- British Association for the Study of the Liver Nurses Forum
- British HIV Association

- British Society of Gastroenterology
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health
- NHS Bromley CCG
- NHS England
- Welsh Government

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

- Department of Health, Social Services and Public Safety, Northern Ireland
- Healthcare Improvement Scotland
- Janssen
- Merck Sharp & Dohme
- Roche Products
- Centre for Sexual Health & HIV Research
- Foundation for Liver Research
- MRC Clinical Trials Unit
- National Institute for Health Research Health Technology Assessment Programme
- Southampton Health Assessment Centre

- National Clinical Guideline Centre
- Public Health England

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on sofosbuvir by attending the initial Committee discussion and providing a written statement to the Committee. They were invited to comment on the ACD.

- Dr Richard Aspinall, Consultant Hepatologist, nominated by the British Society of Gastroenterology – clinical expert
- Dr Michael Jacobs, Consultant in Infectious Diseases, nominated by the Royal College of Physicians – clinical expert
- Mr Charles Gore, Chief Executive of the Hepatitis C Trust, nominated by the Hepatitis C Trust – patient expert
- Mr Andrew Zapletal, nominated by the Hepatitis C Trust – patient expert

The following individuals were nominated as NHS commissioning experts by NHS England. They gave their expert and NHS commissioning personal view on sofosbuvir by attending the initial Committee discussion and providing a written statement to the Committee. They were invited to comment on the ACD.

- Ms Adele Torkington, selected by NHS England – NHS Commissioning expert

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

- Gilead Sciences

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