# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Sofosbuvir for treating chronic hepatitis C

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using sofosbuvir in the NHS in England. The Appraisal Committee has considered the evidence submitted by the manufacturer and the views of non-manufacturer consultees and commentators, and clinical specialists and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the evaluation report).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
- Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply:
    - The health technology cannot be appropriately administered until training is in place?
    - The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?
    - The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?

If so, please specify the reasons and an estimate of the time period within which the recommendation can be complied with.

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation**

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using sofosbuvir in the NHS in England.

For further details, see the Guides to the technology appraisal process.

**The key dates for this appraisal are:**

Closing date for comments: 5 September 2014

Third Appraisal Committee meeting: 10 September 2014

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

# 1 Appraisal Committee's preliminary recommendations

### Sofosbuvir in combination with peginterferon alfa and ribavirin

1.1 Sofosbuvir, in combination with peginterferon alfa and ribavirin, is recommended as an option for treating genotype 1 chronic hepatitis C in adults.

1.2 Sofosbuvir, in combination with peginterferon and ribavirin, is recommended as an option for treating genotype 3 chronic hepatitis C in adults with cirrhosis.

1.3 Sofosbuvir, in combination with peginterferon alfa and ribavirin, is recommended as an option for treating genotype 3 chronic hepatitis C in adults without cirrhosis, only if they had treatment for hepatitis C before.

1.4 Sofosbuvir, in combination with peginterferon alfa and ribavirin, is not recommended for treating genotype 4, 5 and 6 chronic hepatitis C in adults.

### Sofosbuvir in combination with ribavirin alone

1.5 Sofosbuvir, in combination with ribavirin alone is not recommended for treating adults with genotype 1, 4, 5 and 6 chronic hepatitis C.

1.6 Sofosbuvir, in combination with ribavirin, is recommended as an option for treating genotype 2 chronic hepatitis C in adults only if they:

- have not had treatment for chronic hepatitis C before and are intolerant to or ineligible for interferon therapy or
- have had treatment for chronic hepatitis C before, regardless of interferon eligibility.

1.7 Sofosbuvir, in combination with ribavirin, is recommended as an option for treating genotype 3 chronic hepatitis C only in adults with cirrhosis.

1.8 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 (see summary table below).

## Table 1 Summary of preliminary recommendations

| Population | Treatment History | Interferon Eligibility | Recommendation |
|---|---|---|---|
| **Sofosbuvir in combination with peginterferon alfa and ribavirin** | | | |
| **Adults with genotype 1 HCV** | treatment naive | interferon eligible | **recommended** |
| | treatment experienced | interferon eligible | **recommended** |
| **Adults with genotype 3 HCV** | treatment naive | interferon eligible | not recommended in people without cirrhosis<br>**recommended in people with cirrhosis** |
| | treatment experienced | interferon eligible | **recommended** |
| **Adults with genotype 4, 5, and 6 HCV** | treatment naive | interferon eligible | not recommended |
| | treatment experienced | interferon eligible | not recommended |
| **Sofosbuvir in combination with ribavirin** | | | |
| **Adults with genotype 1 HCV** | treatment naive | interferon unsuitable | not recommended |
| | treatment experienced | interferon unsuitable | not recommended |
| **Adults with genotype 2 HCV** | treatment naive | interferon eligible | not recommended |
| | treatment naive | interferon unsuitable | **recommended** |
| | treatment experienced | interferon eligible | **recommended** |
| | treatment experienced | interferon unsuitable | **recommended** |
| **Adults with genotype 3 HCV** | treatment naive | interferon unsuitable | not recommended in people without cirrhosis<br>**recommended in people with cirrhosis** |
| | treatment experienced | interferon unsuitable | not recommended in people without cirrhosis<br>**recommended in people with cirrhosis** |
| **Adults with genotype 4, 5, and 6 HCV** | treatment naive | interferon unsuitable | not recommended |
| | treatment experienced | interferon unsuitable | not recommended |

HCV – hepatitis C virus;

treatment naïve – people who have not had prior treatment for chronic hepatitis C;

treatment experienced – people who have had prior treatment with interferon based therapy for chronic hepatitis C which did not have an adequate response to that treatment

interferon unsuitable – includes people who are intolerant to and ineligible for interferon.

# 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 and 6 HCV infection have not been investigated in phase III studies. According to the summary of product characteristics, treatment regimens without peginterferon alfa should be used for people with genotype 1, 4, 5 and 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, 'British national formulary' [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 manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of sofosbuvir and a review of this submission by the Evidence Review Group (ERG; section 4).

3.1 The manufacturer 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:
  - 3 phase II randomised controlled trials (QUANTUM, n=50; SPARE, genotype 1 only, n=60; ATOMIC, n=332)
  - 1 open label, single arm study (NEUTRINO, n=327).
- 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 III 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 II randomised controlled trial (ELECTRON, n=95 treatment-naive)
  - 1 phase II open-label study (LONESTAR-2, n=47 treatment-experienced)
  - 1 open-label single cohort study (PROTON, n=25 treatment-naive).
- 1 open-label 4-cohort study in people with genotype 1, 2 and 3 HCV and HIV co-infection (PHOTON-1, n=223).
- 1 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-naive 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-naive chronic HCV with a historical control rate of 60% using peginterferon alfa-2a and ribavirin derived from phase III telaprevir (ADVANCE) and boceprevir trials (SPRINT2). The primary outcome was sustained virological response 12 weeks after the end of treatment. The study did not include sites in the UK. Superiority to the historical control was established if the p-value from a 2-sided 1-sample exact test was less than 0.05. 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 $\log_{10}$ IU/ml (viral load, or the number of virus particles in the blood; a viral load less than 6 $\log_{10}$ IU/ml has been linked to better

response to treatment); 17% had cirrhosis; 89% had 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-naive 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 and 97% for people with genotype 4, 5 or 6 HCV. No patients experienced 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.

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-naive 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 treatment for 12 weeks, followed by 12 weeks of sofosbuvir monotherapy (outside of the marketing authorisation for sofosbuvir, but included by the manufacturer 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 96–98% 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-naive chronic HCV. The primary outcome was sustained virological response 12 weeks after the end of treatment. Results were provided by the manufacturer as academic-in-confidence and therefore cannot be reported here.

3.6 SPARE was a 2-part study which investigated the efficacy and safety of sofosbuvir plus ribavirin treatment for 24 weeks in people with genotype 1 treatment-naive chronic HCV. The first part was a proof of concept, 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, disease relapsed in 7 people in the weight-based ribavirin group, and in 10 people in the low-dose ribavirin group.

### Treatment-experienced population

3.7 The manufacturer 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-naive 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-naive 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. Non-inferiority was demonstrated if the lower bound of the 2-sided 95% confidence interval on the difference in sustained virological response (sofosbuvir and ribavirin group minus the peginterferon alfa-2a and ribavirin group) was less than or equal to 15%. If non-inferiority was demonstrated, then the superiority of sofosbuvir plus ribavirin compared with peginterferon alfa-2a and ribavirin could also be demonstrated if the 2-sided p-value associated with the test of superiority was less than 0.05. 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 ≥6 $\log_{10}$ IU/ml). People with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio. 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 1).

**Table 1 Sustained virological response 12 weeks after the end of treatment from FISSION**

| | **Percentage of people with a sustained virological response 12 weeks after end of treatment (95% CI)** | |
|---|---|---|
| **Genotype** | **Sofosbuvir plus ribavirin** | **Peginterferon alfa-2a plus ribavirin** |
| 2 | 97% (90 to 100%) (n=73) | 78% (66 to 87%) (n=67) |
| 3 | 56% (48 to 63%) | 63% (55 to 70%) |

| | | |
|---|---|---|
| | (n=183) | (n=176) |
| 2 or 3, without cirrhosis | 72% (65 to 78%)<br>(n=206) | 74% (67 to 80%)<br>(n=193) |
| 2 or 3, with cirrhosis | 47% (33 to 62%)<br>(n=50) | 38% (25 to 53%)<br>(n=50) |
| 2, without cirrhosis | Academic in confidence | Academic in confidence |
| 2, with cirrhosis | Academic in confidence | Academic in confidence |
| 3, without cirrhosis | 61% (CIs academic in confidence)<br>(n=145) | 71% (CIs academic in confidence)<br>(n=139) |
| 3, with cirrhosis | 34% (CIs academic in confidence)<br>(n=38) | 30% (CIs academic in confidence)<br>(n=37) |

3.10 ELECTRON was a randomised, open-label study in 2 centres in New Zealand which included 8 treatment arms, only 5 of which were used by the manufacturer to inform its submission. The treatment arms presented included people with genotype 1, 2 and 3 treatment-naive 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 manufacturer'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 2-arm open-label study in 22 centres in the USA in which people with genotype 1, 2 and 3 treatment-naive chronic HCV had sofosbuvir plus peginterferon alfa-2a and ribavirin. The manufacturer 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 manufacturer'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 $\log_{10}$ 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 2).

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

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

3.14 LONESTAR-2 was a single-arm open-label study that 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 $\log_{10}$ IU/ml (range from 4.0 to 7.2 $\log_{10}$ 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 reported in manufacturer'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-naive 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 indicating that people with genotype 3 HCV had higher sustained virological response rates 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 $\log_{10}$ IU/ml; 21% had cirrhosis; 78% had genotype 3 HCV. In around 65% of people with treatment-experienced HCV, initial response was lost during previous treatment or post treatment, 30% had no response to interferon-based treatment, and 5% were interferon intolerant.

3.17 Results from VALENCE showed that sustained virological response 12 weeks after the end of treatment for people with genotype 2 HCV receiving sofosbuvir plus ribavirin for 12 weeks was 93% (no confidence intervals were reported in manufacturer'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% (no confidence intervals were reported in the manufacturer's submission).

**Population for whom interferon treatment was unsuitable (treatment-naive 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 who had previously discontinued interferon therapy owing to unacceptable adverse events (the manufacturer referred to this group as interferon intolerant), who had a concurrent medical condition precluding therapy with an interferon-containing regimen (the manufacturer referred to this group as interferon ineligible), or who were unwilling to have interferon treatment. Collectively, these 3 groups are described as 'interferon unsuitable' throughout this document. 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 by the presence or absence of cirrhosis. The difference in sustained virological response at 12 weeks 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 $\log_{10}$ IU/ml; 16% had cirrhosis. The proportions of

people who were interferon intolerant, ineligible, or unwilling 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 3). 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 3 Sustained virological response 12 weeks after the end of treatment from POSITRON**

| | **Percentage of people with a sustained virological response 12 weeks after end of treatment** | |
|---|---|---|
| **Genotype** | **Sofosbuvir plus ribavirin for 12 weeks** | **Placebo** |
| 2 or 3 | 78% (95%CI 72 to 83%)<br>(n=207) | 0%<br>(n=71) |
| 2 | 93%*<br>(n=109) | - |
| 3 | 61%*<br>(n=98) | - |
| 2, without cirrhosis | 92%*<br>(n=92) | - |
| 2, with cirrhosis | 94%*<br>(n=17) | - |
| 3, without cirrhosis | 68%*<br>(n=84) | - |
| 3, with cirrhosis | 21%*<br>(n=14) | - |
| *Confidence intervals not reported. | | |

## *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-naive or

treatment-experienced HCV or genotype 1 treatment-naive HCV. People with genotype 2 or 3 treatment-naive HCV had sofosbuvir plus ribavirin for 12 weeks. People with genotype 2 or 3 treatment-experienced HCV and people with genotype 1 treatment-naive HCV had sofosbuvir plus ribavirin for 24 weeks. Participants were either not on antiretroviral therapy with a CD4+ cell count above 500 cells/$mm^3$ or had virologically suppressed HIV-1 with a CD4+ cell count above 200 cells/$mm^3$. 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 2 or 3 HCV and HIV co-infection and 24 weeks in people with genotype 1 HCV and HIV co-infection resulted in sustained virological response at 12 weeks after treatment irrespective of HCV genotype (≥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) in people with chronic hepatitis C awaiting a liver transplant, 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 1000–1200 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 manufacturer 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. In the studies comparing sofosbuvir plus ribavirin with placebo, common adverse events occurred more frequently or at similar frequencies in both groups, whereas in studies comparing sofosbuvir plus ribavirin with peginterferon alfa and ribavirin, the common adverse events that occurred in 10% or more of people in at least 1 group were consistently more frequent in the peginterferon alfa and ribavirin arms.

### *Health-related quality of life*

3.24 The manufacturer assessed health-related quality of life during the phase II 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 III trials were not aware of their sustained virological response status 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 manufacturer conducted 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-naive HCV in whom interferon therapy was suitable. In addition, the manufacturer'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 II 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-naive 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, 69.7% of people who had boceprevir plus peginterferon alfa and ribavirin. For people with genotype 2 treatment-naive 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-naive 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-naive 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-naive 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 manufacturer highlighted several limitations to its mixed treatment comparison including the fact that the 12 week sofosbuvir plus ribavirin regimen used to treat genotype HCV is not licenced. Therefore, the manufacturer 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 manufacturer's submission. It considered that the manufacturer'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 manufacturer only included adverse events from the 5 phase III studies (NEUTRINO, FISSION, FUSION, POSITRON and VALENCE). However, the ERG confirmed that the adverse events in the phase II studies were similar to those in the phase III 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 manufacturer 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 manufacturer 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 manufacturer to reflect the data available from its pivotal clinical trials and only distinguished between people with and without cirrhosis. The manufacturer 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 transplantation. 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 manufacturer 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 manufacturer. The manufacturer 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 manufacturer's base case. The manufacturer also converted SF-36 to EQ-5D and incorporated these in a deterministic sensitivity analysis. Adverse event rates were obtained from the sofosbuvir clinical trials and published studies. The manufacturer 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 (from the BNF 2014) could be assigned for interventions associated with managing these adverse events.

3.32 The manufacturer 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 manufacturer 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 manufacturer calculated treatment-related utilities by applying treatment-related utility decrements to the baseline utility estimates.

3.34 The manufacturer 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 manufacturer applied no stopping rules, lead-in phase, or option for sofosbuvir retreatment, in line with the sofosbuvir clinical trials.

3.35 The manufacturer 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). The manufacturer used the BNF price of ribavirin (Copegus 400 mg, 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 manufacturer. The costs of various drugs used to treat adverse events included in the model were sourced from the BNF 2014. 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. [2006]) using an assumed 77%: 23% split between mild and moderate cirrhosis. Costs were inflated to 2011/12 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 manufacturer 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 manufacturer's results show that sofosbuvir treatment regimens increased the cost of treatment, but were associated with more quality-adjusted life years 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-naive HCV in whom interferon therapy was suitable, the manufacturer's 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 £14,930 per QALY gained (incremental cost £19,129; incremental QALYs 1.3). Boceprevir plus peginterferon alfa and ribavirin was dominated (that is, 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-naive HCV for whom interferon therapy was not suitable, the manufacturer'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 manufacturer 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 manufacturer (see section 3.69).

**Genotype 2**

3.40 In people with genotype 2 treatment-naive HCV for whom interferon therapy was suitable, the manufacturer'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-naive HCV for whom interferon therapy was not suitable, the manufacturer's base-case ICER for sofosbuvir plus ribavirin for 12 weeks compared with no treatment was £8154 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 manufacturer's base-case ICER for sofosbuvir plus ribavirin treatment for 12 weeks compared with peginterferon alfa and ribavirin treatment for 48 weeks was £9274 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 manufacturer's base-case ICER for sofosbuvir and ribavirin treatment for 12 weeks compared with no treatment was £8591 per QALY gained (incremental cost £20,697; incremental QALYs 2.4).

### Genotype 3

3.42 In people with genotype 3 treatment-naive HCV for whom interferon therapy was suitable, the manufacturer'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-naive HCV for whom interferon therapy was not suitable, the manufacturer'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 manufacturer'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 £8557 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 manufacturer'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 manufacturer'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 £26,797 per QALY gained (incremental cost £23,942; incremental QALYs 0.9).

3.45 The manufacturer 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 manufacturer 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 who with genotype 2 and 3 treatment-experienced HCV for whom interferon therapy was 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-naive HCV for whom interferon therapy was 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 was suitable compared with peginterferon alfa and ribavirin
- people with genotype 3 treatment-experienced HCV for whom interferon therapy was 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-naive HCV for whom interferon therapy was suitable compared with telaprevir plus peginterferon alfa and ribavirin
- people for whom interferon is unsuitable with genotype 3 treatment-naive HCV compared with no treatment

- people with genotype 3 treatment-naive HCV for whom interferon therapy was suitable compared with peginterferon alfa and ribavirin.

3.46 The manufacturer 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.

3.47 During clarification, the manufacturer 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 manufacturer's exploratory analyses were slightly higher than those estimated in the manufacturer's base case (ranging from £7507 per QALY gained [in people who were eligible for interferon with genotype 1 treatment-naive HCV for sofosbuvir plus peginterferon alfa and ribavirin compared with boceprevir plus peginterferon alfa and ribavirin] to £54,957 per QALY gained [in people with genotype 2 treatment-naive HCV for whom interferon therapy was suitable for sofosbuvir plus ribavirin compared with 24 weeks of peginterferon alfa-2a and ribavirin treatment]).

**HCV and HIV co-infected populations**

3.48 The manufacturer provided a separate economic analysis for people co-infected with HIV and HCV. In people with HIV and genotype 1 treatment-naive HCV for whom interferon therapy was suitable, the manufacturer'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 manufacturer's base-case ICER for people

with genotype 2 treatment-naive HCV and HIV-co-infection who had sofosbuvir plus ribavirin for 12 weeks compared with peginterferon alfa-2a and ribavirin treatment for 48 weeks was £55,867 per QALY gained. The manufacturer's base-case ICER for people with genotype 2 treatment-experienced HCV and HIV co-infection, who had sofosbuvir plus ribavirin for 24 weeks compared with no treatment 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-naive HCV and HIV co-infection, 12 weeks of sofosbuvir plus ribavirin dominated treatment with peginterferon alfa and ribavirin. In people with genotype 3 treatment-experienced HCV and HIV co-infection 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. The manufacturer 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 manufacturer's model and economic systematic review. The ERG considered that the manufacturer's methods of economic evaluation and the model produced were acceptable. It validated the manufacturer's model by comparing the total costs and QALYs predicted by the model for the treatment-naive 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 appraisals for boceprevir for the treatment of genotype 1 chronic hepatitis C (NICE technology appraisal guidance 253) and telaprevir for the treatment of genotype 1 chronic hepatitis C (NICE technology appraisal guidance 252). The ERG found that the manufacturer'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 manufacturer'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 manufacturer's model, the ERG showed that it did not affect the base-case ICERs substantially. The ERG considered that the manufacturer's model extrapolates 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 manufacturer 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 rate than the population with HCV only, regardless of sustained virological response, and this is not taken into account in the manufacturer'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 manufacturer's economic model. In addition, the ERG was unable to calculate the transition probability between these 2 health states used by the manufacturer (0.005) in its response to clarification based on a study by Cardoso et al. (2010) (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 £7593 per QALY gained [in people with genotype 1 treatment-naive HCV for whom interferon therapy was suitable for sofosbuvir plus peginterferon alfa and ribavirin compared with boceprevir plus peginterferon alfa and ribavirin] to £60,887 per QALY gained [in people with genotype 2 treatment-naive

HCV for whom interferon therapy was suitable for sofosbuvir plus ribavirin compared with 24 weeks of peginterferon alfa and ribavirin treatment]).

3.53 The ERG noted that the manufacturer used the simple average of mortality from men and women to calculate the age-specific mortality used in the model. The ERG commented that men are more likely to be treated in clinical practice in England, therefore a weighted average should have been used. During clarification, the manufacturer re-ran their economic model with weighted average mortality probabilities, but did not indicate what weights were used to obtain its results. The ERG conducted an exploratory analysis using a weighting of 61% men and 39% women as used in Wright et al. (2006). The ICERs from the ERG's exploratory analyses were slightly higher than those estimated in the manufacturer's base case (ranging from £7453 per QALY gained [in people with genotype 1 treatment-naive HCV for whom interferon therapy was suitable for sofosbuvir compared with boceprevir plus peginterferon alfa and ribavirin] to £50,083 per QALY gained [in people for whom interferon is unsuitable with genotype 1 treatment-naive HCV for sofosbuvir compared with no treatment]).

3.54 The ERG noted that the manufacturer's model used an efficacy estimate drawn from a single source in instances 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 manufacturer's ICERs of using a range of alternative sustained virological response estimates from studies of comparator treatments. For people with genotype 1 treatment-naive 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 manufacturer'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 manufacturer'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 the interferon-eligible genotype 3 treatment-naive HCV subgroup. 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 manufacturer'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 manufacturer'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-naive 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 manufacturer'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 manufacturer's base-case ICERs for people with treatment-naive HCV and reduced the ICERs for people with treatment-experienced HCV across all genotypes. In people with genotype 3 treatment-naive 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 manufacturer's base case to £30,175 per QALY gained. The ICERs for people with genotype 1 treatment-naive 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 manufacturer's model. The resulting ICERs increased across all subgroups and were higher than those estimated in the manufacturer's base case (ranging from £9458 per QALY gained [in, people with genotype 1 treatment-naive HCV for whom interferon therapy was suitable for sofosbuvir compared with boceprevir plus peginterferon alfa and ribavirin] to £61,077 per QALY gained [in people with genotype 1 treatment-naive HCV, for whom interferon treatment is unsuitable, for sofosbuvir compared with no treatment]).

3.58 The ERG explored the effect on the manufacturer'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 specialist stated that it would be unlikely that more than 1–2% of people would be considered better off with longer therapy and that this group would be identified in the summary of product characteristics as needing consideration for longer treatment periods. Another clinical specialist 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 manufacturer's economic model allows for a 12 week regimen of sofosbuvir plus peginterferon alfa and ribavirin for people with genotype 1 treatment-naive HCV for whom interferon therapy was suitable and a 12 week regimen of sofosbuvir and ribavirin for people with genotype 2 treatment-naive 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-naive 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 manufacturer's base-case results (which assumed that these patient groups only have 12 weeks of sofosbuvir and ribavirin).

3.60 The ERG conducted 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 £6717 per QALY gained (using 35 years) to £9170 per QALY gained (using 55 years) in people with genotype 1 treatment-naive HCV for whom interferon therapy was suitable for sofosbuvir compared with boceprevir plus peginterferon alfa and ribavirin. The highest ICERs ranged from £47,254 per QALY gained (using 35 years) to £60,976 per QALY gained (using 55 years) in people with genotype 2 treatment-naive HCV for whom interferon therapy was suitable for sofosbuvir compared with 24 weeks of peginterferon alfa-2a and ribavirin treatment.

3.61 The ERG also conducted sensitivity analyses to explore the effect on the manufacturer's ICERs of using different utility increments (0 and 0.04

[taken from Vera-Llonch et al. 2013], compared with the manufacturer's estimate of 0.05) after sustained virological response. The resulting ICERs in the ERG's sensitivity analysis were consistently higher than the manufacturer's base-case results. When using a utility increment of 0.04, the ICERs ranged from £7899 per QALY gained in people with genotype 1 treatment-naive HCV for whom interferon therapy was suitable for sofosbuvir compared with boceprevir plus peginterferon alfa and ribavirin to £53,793 per QALY gained in people with genotype 1 treatment-naive HCV, for whom interferon treatment is unsuitable, for sofosbuvir compared with no treatment. When using a utility increment of 0, the ICERs ranged from £12,732 per QALY gained in people with genotype 1 treatment-naive HCV for whom interferon therapy was suitable for sofosbuvir compared with boceprevir plus peginterferon alfa and ribavirin to £92,795 per QALY gained in people with genotype 1 treatment-naive HCV, for whom interferon treatment is unsuitable, for sofosbuvir compared with no treatment.

3.62 The ERG also explored the effect on the manufacturer's base-case ICERs for people with genotype 1 treatment-naive HCV for whom interferon therapy was suitable when alternative estimates of sustained virological response for peginterferon alfa plus ribavirin to those used by the manufacturer (from McHutchison et al. 2009) were applied. 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 manufacturer'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 conducted a scenario analysis that considered the combined impact on the manufacturer'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 HCV genotype treatment-naive, interferon-eligible population (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 manufacturer's base case (ranging from £9415 per QALY gained [in people with genotype 1 treatment-naive HCV for whom interferon therapy was suitable for sofosbuvir plus peginterferon alfa and ribavirin compared with boceprevir plus peginterferon alfa and ribavirin] to £109,526 per QALY gained [in people for whom interferon is unsuitable with genotype 1 treatment-naive HCV for sofosbuvir plus ribavirin compared with no treatment]).

### *Additional analyses*

3.64 During consultation the Committee asked that the manufacturer provide additional evidence, which the Committee believed would permit it to come to a better informed conclusion. Specifically, the Committee requested that the manufacturer 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. (2010)
- alternative sustained virological response estimates for peginterferon alfa and ribavirin (for example from Hadziyannis et al. [2004])

- 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. [2013]) and
- alternative costs for ribavirin (for example, the cost of generic ribavirin as calculated by eMIT) 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 week
- assuming that an increased proportion of people for whom interferon therapy was 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. (2006).

3.65 The manufacturer provided the additional analyses requested, although the revised base-case assumptions were slightly different to those requested by the Committee. The manufacturer justified each change to the revised base-case assumptions, which included a transition from the sustained virological response-cirrhotic and 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. (2013), 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. (2006). The manufacturer chose to use the sustained virological response rates for peginterferon alfa and ribavirin from McHutchison et al. (2009) for its revised base case, and provided a sensitivity analysis incorporating the sustained virological response rates from Hadziyannis et al. (2004) (see section 3.74).

3.66 The manufacturer presented ICERs to the Committee for subgroups stratified by genotype, treatment history, interferon eligibility and cirrhosis status. The manufacturer 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 manufacturer 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-naive genotype 1HCV for whom interferon therapy was suitable, the manufacturer'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-naive HCV for whom interferon therapy was not suitable, the manufacturer'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 manufacturer'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 the treatment-naïve peginterferon eligible population was £25,237 per QALY gained for people without cirrhosis, and £5352 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 £2819 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 £4253 per QALY gained for people with cirrhosis For people with genotype 1 treatment-naive HCV for whom interferon therapy was not suitable, the manufacturer's base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment stratified by the 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 manufacturer provided the Committee with an estimated cost-effectiveness calculation for this subgroup. The manufacturer explained that historically, approximately 50% of people with genotype 1 treatment-naive HCV had disease that responded to treatment with peginterferon alfa and ribavirin, but in the interim analysis provided to the US regulator 89% of people with genotype 1 treatment-naive HCV in NEUTRINO had disease that responded to sofosbuvir plus peginterferon alfa and ribavirin. The regulator accepted that the higher rate of overall sustained virological response observed in NEUTRINO was likely driven by those patients who were virus-free 12 weeks after the end of treatment, but who would have not 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 regulator assumed that the increase in sustained virological response from 50% to 89% represented the efficacy of sofosbuvir plus peginterferon alfa and ribavirin in that 50% of people that would have been non-responders based on the response rate of historical controls in the treatment naïve population. The regulator calculated that given the high sustained virological response rates in NEUTRINO an approximate sustained virological response rate of 78% for people with

treatment experienced genotype 1 HCV. Additionally, the manufacturer 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 response rates in this group were 74% after treatment with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. Using the estimated sustained virological response rate of 78% presented to the FDA, the manufacturer'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 manufacturer'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 £8203 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-naive HCV for whom interferon therapy was suitable, the manufacturer'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-naive HCV for whom interferon therapy was unsuitable, the manufacturer'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 was suitable, the manufacturer'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 was unsuitable, the manufacturer'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 for whom interferon therapy was suitable, with genotype 3 treatment-naive HCV, the manufacturer'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 £6556 per QALY gained for people with cirrhosis. In people with genotype 3 treatment-naive HCV for whom interferon therapy was unsuitable, the manufacturer'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 was suitable , the manufacturer'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 £6260 per QALY gained in people with cirrhosis.. In people with genotype 3 treatment-experienced HCV for whom interferon therapy was unsuitable, the manufacturer'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 manufacturer provided a separate economic analysis for people co-infected with HIV and HCV. The manufacturer 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 manufacturer 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-naive HCV having sofosbuvir and ribavirin for 24 weeks compared with no treatment.

### Additional sensitivity analyses

3.74 The Committee asked that the revised base include the sustained virological responses from Hadziyannis et al. (2004) rather than from McHutchison et al. (2009) for peginterferon alfa and ribavirin in people with genotype 1 treatment-naive HCV. The manufacturer 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 manufacturer also commented that people in the McHutchison et al. study were more representative of people in the NEUTRINO study. Therefore, the manufacturer 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-naive 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 manufacturer presented a scenario analysis assuming that 100% of people with genotype 3 HCV for whom interferon therapy was suitable would have 24 weeks of sofosbuvir and ribavirin. The ICER for people with genotype 3 treatment-naive HCV for whom interferon therapy was

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 was £46,956 per QALY gained. The ICER for people with genotype 3 treatment-experienced HCV for whom interferon therapy was 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 was £48,306 per QALY gained. The manufacturer also presented the results of a scenario analysis using the upper (20%) and lower (2%) proportion of people for whom interferon therapy was suitable with genotype 3 HCV expected to have sofosbuvir and ribavirin for 24 weeks as provided by the ERG's clinical advisers. The ICER for people with genotype 3 treatment-naive HCV for whom interferon therapy was 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 was £22,385 per QALY gained, and £27,062 per QALY gained when 20% was used. The ICER for people with genotype 3 treatment-experienced HCV for whom interferon therapy was 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 was £14,467 per QALY gained and £19,890 per QALY gained when 20% was used.

3.76 The ERG reviewed the manufacturer's additional evidence. The ERG noted that the manufacturer had used most of the Committee's preferred base case assumptions (see section 3.64). It further noted that the manufacturer did not provide a sensitivity analysis exploring the impact of using utility data collected in the clinical trials on the ICER. The ERG conducted an exploratory analysis in which it used all of the Committee's preferred assumptions to calculate the ICERs for people with genotype 1 and 3 HCV and also conducted 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 for people with treatment-naive genotype 1HCV for whom interferon therapy was suitable that was £30,993 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 £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-naive HCV for whom interferon therapy was 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 £2274 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 £24,509 per QALY gained for people without cirrhosis and £4680 per QALY gained for people with cirrhosis. compared with telaprevir plus peginterferon alfa and ribavirin. For people with genotype 1 treatment-naive HCV for whom interferon therapy was unsuitable, the s base-case ICER for sofosbuvir plus ribavirin for 24 weeks compared with no treatment £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 was suitable, with genotype 3 treatment-naive 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-naive HCV for whom interferon therapy was 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 was 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 was unsuitable, the manufacturer'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 absence or presence of cirrhosis in people with genotype 3 treatment-naive HCV for whom interferon therapy was 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 £8318 per QALY gained for people with cirrhosis. In people with genotype 3 treatment-naive HCV for whom interferon therapy was 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 was 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 £8093 per QALY gained in people with cirrhosis. In people with genotype 3 treatment-experienced HCV for whom interferon therapy was 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.

3.80 Full details of all the evidence are in the evaluation report.

# 4 Consideration of the evidence

4.1 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 specialists. It also took into account the effective use of NHS resources.

4.2 The Committee heard from the clinical specialists 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 manufacturer'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.

4.3 The Committee discussed the clinical management of chronic hepatitis C in adults. It heard from the clinical specialists 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 (Boceprevir for the treatment of genotype 1 chronic hepatitis C [NICE technology appraisal guidance 253]) or telaprevir plus peginterferon alfa and ribavirin (Telaprevir for the treatment of genotype 1 chronic hepatitis C [NICE technology appraisal guidance 252]) 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 specialists 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 specialists 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 limited

circumstances, would make it a valuable treatment option for people with chronic hepatitis C.

4.4 The Committee acknowledged that the UK marketing authorisation for sofosbuvir allows for use in adults with chronic hepatitis C irrespective of genotype. It heard from the clinical specialists 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 heard from the clinical specialists 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 concluded that most people with chronic hepatitis C are likely to have at least some benefit from adding sofosbuvir to their treatment regimen.

## *Clinical effectiveness*

4.5 The Committee considered the clinical effectiveness of sofosbuvir plus ribavirin, with or without peginterferon alfa, for people with genotype 1–6 chronic hepatitis C. It noted the concerns of the Evidence Review Group (ERG) that because of the lack of head-to-head studies against current standard of care comparators, most of the evidence provided by the manufacturer did not directly address the decision problem. The Committee acknowledged that the manufacturer was able to provide evidence from only 1 head-to-head trial (FISSION, in people with genotype 2 or 3 treatment-naive HCV for whom interferon therapy was suitable; see sections 3.8–3.9) 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 for people with genotype 3 HCV recommends 24 weeks of sofosbuvir and ribavirin treatment, 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 which it is licensed once stratified 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 specialists 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 specialists 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. Furthermore, the clinical specialists highlighted to the Committee that, in their opinion, the inclusion criteria for the sofosbuvir trials were broader than for previous trials in hepatitis C; therefore there was good reason to expect that the people in the trials reflected those who are currently being treated in UK clinical practice. 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 exclusion criteria meant that people who use injectable drugs were not included in any studies. The Committee acknowledged the limitations of conducting trials for hepatitis C, and concluded that there was considerable uncertainty surrounding the evidence base presented by the manufacturer, and therefore the true magnitude of the effect of sofosbuvir in each subgroup could not be robustly estimated.

4.6 The Committee acknowledged that in the NEUTRINO trial, people with genotype 1 (89% of people in the trial), 4, 5 or 6 treatment-naive 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 manufacturer. 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-naive genotype 1, 4, 5 and 6 HCV.

4.7 The Committee considered the clinical effectiveness of sofosbuvir plus peginterferon alfa and ribavirin in people with treatment experienced genotype 1, 4, 5 and 6 HCV. No trial data were available on the clinical effectiveness of sofosbuvir in people with these genotypes who had previously received treatment for HCV. The Committee heard from the clinical specialists that there was no reason to expect a different response in treatment-experienced HCV than in treatment-naive HCV. The Committee also heard from clinical experts that it was unlikely for further studies of sofosbuvir plus peginterferon alfa and ribavirin in people with treatment experienced HCV to be started because emerging interferon-free regimens are rapidly replacing older interferon-based regimens. The Committee was aware of the evidence from the manufacturer that the US Food and Drug Administration had accepted that the increase in sustained virological response in people with genotype 1 treatment-naive 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. (2014) on the efficacy of sofosbuvir plus peginterferon alfa and ribavirin in people with genotype 1 treatment-experienced HCV, which the manufacturer 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 genotypes 4, 5 and 6 in the NEUTRINO study, the sustained virological response rates 12 weeks after sofosbuvir treatment were approximately 97%, which was similar to that in people with genotype 1 HCV. The Committee concluded that although there was uncertainty about the robustness of the evidence base in people with HCV genotypes 1, 4, 5 and 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 and 6 treatment-experienced HCV.

4.8 The Committee also discussed the design of the clinical trials for sofosbuvir plus ribavirin in people with genotype 2 and 3 HCV. It noted that the main trial evidence came from 4 trials (FISSION, [treatment-naive, interferon-eligible], FUSION, [treatment-experienced], POSITRON [treatment-naive and treatment-experienced, interferon ineligible, intolerant or unwilling] and VALENCE [treatment-naive 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 arms. 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 receiving peginterferon alfa and ribavirin alone (78%). The Committee noted that people with genotype 3 HCV receiving 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.

4.9 The Committee considered the results for the VALANCE study, which showed that longer treatment with sofosbuvir was needed for people with genotype 3 treatment-naive 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 shown; 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 3.16). 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 acknowledged that 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 better sustained virological response in people with genotype 3 HCV compared with current standard of care (24 weeks of peginterferon alfa and ribavirin treatment), but only when sofosbuvir plus ribavirin treatment was extended to 24 weeks. In addition, the Committee considered it was plausible that sustained virological response in people with genotype 2 HCV after treatment for 12 weeks with sofosbuvir plus ribavirin was likely to be better than the current standard of care. However, taking into account the limitations of the trial designs and the use of historical controls, the Committee concluded that 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.

4.10 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 efficacy to that seen in people genotype 1 HCV would be expected in people genotype 3 HCV when peginterferon alfa was added to sofosbuvir and ribavirin. This was supported by the relevant results from PROTON and ELECTRON which showed a sustained virological response 12 weeks after the end of treatment was 90% and 100%, respectively in people with genotype 3 HCV. The Committee was aware that these were 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 treatment naïve genotype 3 HCV.

4.11 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 manufacturer'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 previous treatment for hepatitis C, and people with genotype 2 or 3 HCV and HIV who had been previously treated. The Committee subsequently considered the evidence provided by the manufacturer 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 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'.

4.12 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 specialists 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.

4.13 The Committee discussed the manufacturer's mixed treatment comparison. It heard from the manufacturer that a network could not be formed for all the relevant populations and a comparison could be performed only for treatment-naive people with genotypes 1, 2 and 3 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 manufacturer 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 manufacturer's mixed treatment comparison was not robust and therefore concluded it was reasonable for the manufacturer not to use it to inform its cost-effectiveness analyses.

### *Cost effectiveness*

4.14 The Committee considered the manufacturer's original economic model provided in the manufacturer's submission, the assumptions underlying the values of the parameters, and the critique and exploratory analyses conducted by the ERG. The Committee also considered the revised base-case model submitted by the manufacturer in response to the additional analyses requested by the Committee. The Committee noted that the manufacturer'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 specialists that this approach was reasonable and consistent with how people are currently diagnosed in clinical practice. It heard from the clinical specialists 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 manufacturer'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 manufacturer was appropriate

4.15 The Committee acknowledged that, in response to consultation, the manufacturer presented a revised base-case model that incorporated most of the its preferred assumptions. The manufacturer explained and justified deviations from Committee's preferred assumptions which were included in the revised model using transition probabilities from Cardoso et al. for the sustained virological response with cirrhosis health state to the hepatocellular carcinoma health state and the cirrhosis without a sustained virological response health state to the hepatocellular carcinoma health state (section 3.65), sustained virological response estimates for peginterferon alfa and ribavirin from McHutchison (section 3.74) and assuming a distribution of 61% men and 39% women for all-cause mortality as reported in Wright et al. (section 3.65). As requested by the Committee (see sections 3.64), the manufacturer also presented sensitivity analysis that:

- explored the impact of assuming that up to 2%, 20% or 100% of people with genotype 3 HCV receive treatment with sofosbuvir and ribavirin for 24 weeks
- explored the effect of varying the starting age of people entering the model on the ICER.

The Committee also considered the ERG critique of the assumptions in the manufacturer's revised base-case model and the exploratory analyses that incorporated different underlying assumptions, which it considered best reflected the Committee's preferences. The Committee considered the probabilistic ICERs presented by the manufacturer and noted that they were very similar to the deterministic ICERs presented across each

genotype and subgroup. The Committee concluded that the manufacturer had adequately addressed the Committee's request for additional analysis in the first appraisal consultation document.

4.16 The Committee acknowledged that the ICERs from the manufacturer's original economic model were a combined cohort of people with and without cirrhosis (hereafter referred to as 'combined cohort'). The Committee heard from clinical experts that it was standard clinical practice to treat people with and without cirrhosis as separate subgroups, as it affected a person's likelihood of a sustained virological response. The Committee considered individual ICERs presented by the manufacturer for each genotype by treatment history, interferon eligibility and cirrhosis status 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 response rates were in some cases as high as in people without cirrhosis. The Committee heard from clinical experts that sustained virological response rates 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 factor 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 response rates which 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 were not robust. The Committee noted that the ICER from the combined cohort appeared artificially low, considering that the majority of the subgroup would not have cirrhosis. The Committee concluded that the consideration of the cost effectiveness of sofosbuvir for each genotype should take in to

consideration both the combined cohort ICER and also the potential ICERs for people with and without cirrhosis.

4.17 The Committee discussed the manufacturer's assumptions used in the original economic model. It noted that people entered the model at 45 years, had an average weight of 79 kg and that the number of men and women were assumed to be equal. The Committee heard from the ERG that these assumptions were consistent with previous appraisals for hepatitis C treatments with the exception that the original model did not allow for transition from the sustained virological response cirrhotic health state to the hepatocellular carcinoma health state. The Committee asked that the manufacturer to submit a revised base-case model that incorporated assumptions that were more generalisable to the UK population with chronic hepatitis C and more accurately reflected the age and sex statistics for England ( 61% men and 39% women [Wright et al 2006]). The Committee considered the assumptions in the manufacturer's revised base-case model submitted during consultation. 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) in its model using data from Cardoso et al. (2010) as requested by the Committee. In addition, the manufacturer 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 specialists 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 specialists 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 relevant population 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 state and the health state of cirrhosis without a sustained virological response, that Cardoso et al. was an acceptable source for transition probabilities for the manufacturer'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 reside somewhere between the Cardoso et al. and Fattovich et al. estimates.

4.18 The Committee considered the impact of using alternative sustained virological responses for peginterferon alfa and ribavirin on the results from revised economic model. The Committee noted that the manufacturer preferred the sustained virological responses for peginterferon alfa and ribavirin treatment in people with genotype 1 HCV from McHutchison et al. (2009) 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 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. The Committee heard from the clinical specialists that there is a wide variety in the 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

specialists noted the heterogeneity of sustained virological response in clinical practice and 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 manufacturer showed that the ICERs for people with genotype 1 treatment-naive HCV for sofosbuvir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone 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 inclusion in its base-case model but noted that the sustained virological response rates could lie between those provided by the McHutchison and Hadziyannis datasets.

4.19 The Committee considered the cost of ribavirin used in the manufacturer's model. The Committee noted that the manufacturer used the cost of ribavirin from the BNF 2014 in the original model (Copegus; £246.65) and asked that the manufacturer 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 manufacturer 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 peginterferon 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 and that sensitivity analyses around the generic costs of comparator treatment was appropriate.

4.20 The Committee noted that the marketing authorisation for sofosbuvir allows 24 weeks dual therapy with sofosbuvir plus ribavirin as an alternative to sofosbuvir plus peginterferon alfa and ribavirin for people with genotype 3 HCV. It heard from the clinical specialists that it is plausible that at least 10% of people, such as those with cirrhosis or who have interferon intolerance, may need extended treatment. The Committee noted that the possibility of extending treatment to 24 weeks was not accounted for in the manufacturer's model and asked that the manufacturer explore the impact of extended treatment duration in a sensitivity analysis on the revised base-case model in which the proportion of people having dual therapy was varied between 2% and 100%. The Committee noted exploratory analyses carried out by the manufacturer that modelled the effect on the revised base-case ICERs of increasing sofosbuvir plus ribavirin treatment from 12 to 24 weeks in people with genotype 3 HCV (see section 3.76). The Committee noted that varying the proportion of people with genotype 3 HCV who have 24 weeks of sofosbuvir and ribavirin treatment had a substantial impact on the ICER. The ICERs 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% received sofosbuvir and ribavirin in the treatment-naive population The Committee noted that when stratified by cirrhosis status, the revised base case ICERs increased in the subgroup without cirrhosis to £41,700 and £51,300 per QALY gained when it was assumed that 2% and 20% received sofosbuvir and ribavirin in the treatment-naive population. In the subgroup with cirrhosis, the ICERs increased to £6800 and £8400 per QALY gained using the same assumptions. The ICERs also increased for the population for whom interferon therapy is suitable and were treatment-experienced 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% received 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, although it heard from clinical

specialists and commissioners that sofosbuvir and ribavirin treatment for 24 weeks would only be appropriate for people for whom interferon therapy is unsuitable .

4.21 The Committee discussed the utility values used in the manufacturer'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 manufacturer 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 manufacturer 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. 2006) after sustained virological response in the manufacturer's base-case analysis. However it asked that the manufacturer 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 manufacturer 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. 2013) after a sustained virological response. The Committee noted that using this utility increment increased the manufacturer'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.

4.22 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 manufacturer in response to consultation, which are weighted by genotype, treatment history and the presence or absence or cirrhosis) or separately for each

genotype. The Committee was unconvinced by the global ICER approach put forward by the manufacturer because the evidence from the clinical specialists suggested that in clinical practice treatment is stratified by genotypes, treatment history and other characteristics, including cirrhosis status. This is because the capacity to benefit from treatment for chronic hepatitis C differs for depends 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 manufacturer's base-case analyses.

## *Genotype 1*

### Treatment naive, interferon eligible

4.23 The Committee considered the cost effectiveness of sofosbuvir plus peginterferon alfa and ribavirin for people with treatment-naive genotype 1 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 £5400 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 £2800 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 £4200 and

£22,300 per QALY gained, respectively. The Committee also considered the ERG's exploratory analyses (see section 3.77). 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 cost effective, 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-naive genotype 1 HCV.

**Treatment experienced, interferon eligible**

4.24 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 manufacturer was accepted by the European Medicines Agency and clinical specialists. 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 (£8200 per QALY gained) or 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-naive 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 in 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 than the ICER for sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks and the ICER for peginterferon alfa and ribavirin alone for 48 weeks for people with cirrhosis and without cirrhosis, 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**

4.25 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-naive 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 manufacturer stated that although it is necessary to have options for this subgroup of patients for whom interferon treatment is unsuitable, that this group has a with high unmet need, it is anticipated that the number of people in this group receiving 24 weeks of sofosbuvir plus ribavirin would be extremely low. The Committee also heard from the manufacturer 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-naive 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.

**Treatment experienced, intolerant to or ineligible for interferon treatment**

4.26 The Committee considered the lack of evidence 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 regulator for the genotype 1 treatment-experienced HCV interferon eligible population, 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-naive HCV for whom interferon is unsuitable). Assuming that the relative difference between the ICERs in the treatment naive 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-naive 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-naive 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 significantly 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, given the high ICERs, the Committee was disappointed that sofosbuvir plus ribavirin for this subgroup could not be considered a cost effective use of NHS resources. However, the Committee concluded that based on

the very uncertain evidence presented, 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.

## *Genotype 2*

4.27 The Committee considered the cost effectiveness of sofosbuvir plus ribavirin compared with the standard of care (peginterferon alfa and ribavirin) in people with genotype 2 HCV. The Committee noted that the ICER from the manufacturer'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-based therapy and who have treatment-naive HCV, and £12,500 per QALY gained in people who have treatment-experienced HCV and are eligible for treatment with interferon-based therapy. The ICER for sofosbuvir and ribavirin compared with no treatment for people who are intolerant to or ineligible for interferon was £8200 per QALY gained for people with treatment-naive HCV, and £8600 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-naive HCV who are eligible for treatment with interferon-based therapy. However, the Committee concluded that sofosbuvir plus ribavirin was a cost-effective use of NHS resources for adults with genotype 2 treatment-naive HCV for people who have treatment-experienced HCV, regardless of their interferon eligibility.

## *Genotype 3*

### Treatment naive, interferon eligible

4.28 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-naive

HCV who are eligible for treatment with interferon. The Committee noted from the manufacturer'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 state, the ICER for people with treatment-naive 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 effect of combining the ICERs for the larger subgroup without cirrhosis with a high ICER and the smaller subgroup with cirrhosis with a very low ICER, resulted in a combined cohort ICER that was artificially low (£21,900 per QALY gained). The Committee noted that the ICERs for this subgroup of patients with or without cirrhosiswere highly uncertain due to the small patient numbers included in the studies.. . The Committee considered that despite the uncertainty in the ICER for the combined cohort and people without cirrhosis, there was more confidence around the ICER for the subgroup with cirrhosis because 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-naive HCV who are eligible for interferon treatment and who have cirrhosis but was not a cost effective use of NHS resources in people who do not have cirrhosis..

### 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 manufacturer's revised base-case ICER for the combined cohort was £13,900 per QALY gained. When stratified by cirrhosis state, the ICER for people without cirrhosis was £18,600 per QALY gained, whereas the ICER for people with cirrhosis was £6300 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 response rates usually seen in people with cirrhosis. The Committee was willing to accept this uncertainty because the ICERs were low in the group without cirrhosis and very low in the group with cirrhosis. The ICERs remained low 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.

**Treatment naive, interferon ineligible**

4.30 The Committee considered the cost effectiveness of sofosbuvir and ribavirin for 24 weeks compared with no treatment in people with genotype 3 treatment-naive HCV who are ineligible for treatment with interferon. The Committee noted the manufacturer's revised base-case ICER for this population was £21,000 per QALY gained which was calculated based on sustained virological responses seen in VALANCE. The Committee noted that the VALANCE study was unblinded when treatment was extended for all people with genotype 3 HCV and that the goals of the study were redefined to be descriptive rather than hypothesis testing. Therefore it was of poor quality and open to potential bias. The Committee noted that when the population was. stratified by cirrhosis state, 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-naive 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-naive HCV and cirrhosis.

**Treatment experienced, interferon ineligible**

4.31 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 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 manufacturer's revised base-case ICER of approximately £27,500 per QALY gained in 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 VALANCE, a study which the Committee considered to be of low quality and open to potential bias (see section 3.16 and 4.30). When the ICERs were stratified by cirrhosis, the manufacturer's revised base case ICER for the non-cirrhotic subgroup 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 manufacturer's revised base case ICER for sofosbuvir plus

ribavirin for 24 weeks compared to 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 which there is currently no other licensed treatment options. While 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, on the balance of probabilities 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 it could be considered a cost effective use of NHS resources, as the true ICER was likely to be between the manufacturer's revised base case and the ERG's exploratory estimates.

## *Genotypes 4, 5 and 6*

### Treatment naïve, interferon eligible

4.32 The Committee considered the manufacturer'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 treatment naïve genotype 4, 5, and 6 HCV for whom interferon was suitable. Evidence on the cost effectiveness was not available by cirrhosis status. The Committee noted that this ICER was much higher than the ICER from the subgroup of people with genotype 1 treatment-naive HCV subgroup for whom interferon was suitable. The Committee considered that, potentially the ICERs for both the cirrhotic and non-cirrhotic subgroups were likely to be high. The Committee also noted that if the ERG's exploratory assumptions were applied, it was likely the ICERs would increase further. The Committee also considered that there was even more uncertainty in the ICER for people with genotypes 4, 5 and 6 HCV as the number of participants with genotypes 4, 5 and 6 HCV in the studies was much smaller than those with genotype 1 HCV. The Committee was aware that

for this population the UK marketing authorisation permits treatment with sofosbuvir and ribavirin dual therapy, and that even a small proportion of dual therapy use in this population would also increase the ICERs significantly, although the summary of product characteristics specifies that sofosbuvir plus ribavirin for 24 weeks should only be used in people for whom interferon therapy is unsuitable. Although the manufacturer stated that sofosbuvir plus ribavirin for 24 weeks was unlikely to be used to treat chronic hepatitis C in people or whom interferon therapy is suitable, the Committee agreed that there was some uncertainty as to whether this would be the case in clinical practice. For all these reasons, the Committee concluded that sofosbuvir plus peginterferon alfa and ribavirin could not be recommended as a cost effective treatment option in adults with genotype 4, 5 and 6 treatment-naive HCV for whom interferon therapy is suitable.

**Treatment experienced, interferon eligible**

4.33 The Committee considered cost effectiveness evidence presented for people with treatment experienced genotypes 4, 5 and 6 HCV for whom interferon is suitable. The Committee noted that the manufacturer did not provide an ICER for this group. However, the Committee considered that, if the ICER for sofosbuvir plus peginterferon alfa and ribavirin treatment compared with peginterferon alfa and ribavirin for 48 weeks was £26,800 per QALY gained (based on the ICER in the treatment naïve genotype 4, 5 and 6 HCV group, see section 4.32), the ICER for the treatment experienced group would be slightly less. The Committee noted that the ICER would increase when using the ERG's exploratory analyses assumptions, and that if there was any use of sofosbuvir plus ribavirin for 24 weeks in this group, that the ICERs would further increase. The Committee noted that where the evidence presented is uncertain, as for this population where no evidence was presented, the Committee must be mindful of the health benefits that would be forgone by displacing other treatments elsewhere in the NHS by recommending a technology with a high and uncertain ICER. Due to the lack certainty around the high ICERs,

the Committee concluded that sofosbuvir in combination with peginterferon alfa and ribavirin was not a cost effective use of NHS resources and could not be recommended for adults with treatment experienced genotype 4, 5 and 6 HCV for whom interferon is suitable.

### Treatment naïve, interferon unsuitable

4.34 The Committee considered the group of people with treatment naïve genotype 4, 5 and 6 HCV for whom interferon therapy is unsuitable. The Committee noted that the manufacturer did not provide an ICER for this population. As before, the starting point was the only cost-effectiveness evidence seen for people with genotype 4, 5, or 6 HCV, namely the ICER of £26,800 per QALY gained for people with genotype 4, 5 or 6 treatment-naive HCV for whom interferon therapy was suitable. The Committee anticipated that the ICERs in people with genotype 4, 5 or 6 HCV for whom interferon therapy is unsuitable would increase significantly and was likely to increase further using the ERG's exploratory assumptions. The Committee considered that, based on the limited evidence provided for these genotypes that 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 high unmet need and the Committee was disappointed at the quality of the evidence and level of uncertainty, as well as the high cost associated with sofosbuvir plus ribavirin 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 and 6 treatment-naive HCV, for whom interferon therapy is not suitable

### Treatment experienced, interferon unsuitable

4.35 The Committee considered the group of people with treatment experienced genotype 4, 5 and 6 HCV for whom interferon is unsuitable. The Committee noted that the manufacturer did not provide an ICER for this subgroup. Once again, the Committee took a pragmatic view on how

to estimate an ICER for this subgroup. As before, the Committee noted the ICER of £26,800 per QALY gained for people with treatment-naive genotype 4, 5 or 6. HCV for whom interferon treatment is suitable. The Committee anticipated that the ICERs for people with treatment-experienced genotype 4, 5 or 6 HCV for whom interferon is unsuitable would increase significantly. The Committee noted that the ICER was still likely to increase further using the ERG's exploratory assumptions. The Committee considered that, based on the limited evidence provided in this genotype as with the other subgroups with genotype 4, 5 and 6 HCV without an ICER, that it was necessary to make a value judgment. As with the treatment naïve, interferon eligible subgroup, the Committee was disappointed at the quality of the evidence and level of uncertainty, as well as the high cost associated with sofosbuvir plus ribavirin for 24 weeks. The Committee concluded that sofosbuvir plus ribavirin for 24 weeks could not be recommended as a cost effective use of NHS resources for treating people with treatment-experienced genotype 4, 5 and 6 HCV for whom interferon therapy is not suitable

4.36 The Committee noted the manufacturer 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 patients with genotypes 1, 2 and 3 treated for 12 or 24 weeks with sofosbuvir and ribavirin and the 1910 study provided results for genotype 1 and 3 treated patients with sofosbuvir 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 manufacturer's model. On balance, the Committee concluded that based on the evidence presented and considered for this population, it was reasonable to include group of people co-infected with HCV and HIV

within 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.

4.37 The Committee discussed the discount rate used in the manufacturer'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 the Guide to the methods of technology appraisal. The Committee noted that the manufacturer'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 manufacturer suggested that the ICERs were particularly sensitive to the discount used. The Committee heard from the clinical specialists that a person who does not have cirrhosis and experiences 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 restored. Therefore, the Committee concluded that sofosbuvir did not meet the criteria for differential discounting of health benefits, and agreed that the manufacturer's approach to using the standard discount rate of 3.5% was appropriate.

4.38 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 specialists 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.

4.39 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 the treatment of chronic hepatitis C, but was aware that there is substantial uncertainty around the magnitude of benefit that it offers each subgroup. The Committee agreed with the clinical specialists 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.

## *Summary of Appraisal Committee's key conclusions*

| TAXXX | Appraisal title: Sofosbuvir for treating chronic hepatitis C | Section |
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| **Key conclusions** | | |
| **Genotype 1**<br>The Committee considered sofosbuvir plus ribavirin with or without peginterferon alpha to be clinically effective in people with treatment naïve | | 1.1-1.7, 4.6- 4.7<br>4.6-4.7 |

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| and experienced genotype 1 HCV. The Committee considered treatment with sofosbuvir plus peginterferon and ribavirin compared with peginterferon and ribavirin in people who were eligible for interferon treatment to be cost effective regardless of previous treatment (with ICERs of approximately £17,500 per QALY gained in treatment naive patients).The Committee also considered sofosbuvir plus peginterferon alpha and ribavirin to be cost effective compared with boceprevir plus peginterferon and ribavirin, and telaprevir in combination with peginterferon alpha and ribavirin (ICERs of approximately £10,300 and £15,400 per QALY gained respectively). The Committee considered sofosbuvir plus peginterferon alfa and ribavirin to be cost effective in treatment-experienced patients compared with peginterferon and ribavirin, boceprevir and ribavirin and telaprevir and ribavirin with ICERs of approximately £12,600, £700 and £8200 per QALY gained respectively. | 4.23<br>4.24 |
| Sofosbuvir plus ribavirin was not recommended in people for whom interferon was unsuitable (regardless of previous treatment) because of the high ICER compared with standard care (no treatment) which was in excess of £47,500 per QALY gained in the combined cirrhotic and non-cirrhotic cohort. | 4.25<br>4.26 |
| **Genotype 2**<br>The Committee considered sofosbuvir plus ribavirin to be clinically effective compared with peginterferon and ribavirin in people with genotype 2 HCV who were eligible for treatment with peginterferon alfa. The treatment was not recommended in the treatment naive group because of the high ICER of £46,300 per QALY gained but was recommended in people who were treatment-experienced because of the ICER of £12,500 per QALY gained. | 4.8<br>4.27 |
| The Committee considered sofosbuvir plus ribavirin to be clinically effective and cost effective compared with no treatment in people for whom treatment with interferon was unsuitable regardless of treatment experience (with ICERs of approximately £12,500 and £8500 per QALY gained respectively). | |
| **Genotype 3**<br>The Committee considered the extended treatment duration (24 weeks) of sofosbuvir plus with ribavirin to be clinically effective compared with peginterferon alfa and ribavirin. The Committee considered sofosbuvir plus peginterferon alfa and ribavirin to be cost effective in people who were treatment naive with cirrhosis (with an ICER of approximately £6600 per QALY gained) but not in people who were treatment naive without cirrhosis (with a high ICER of approximately £40,600 per QALY gained). Treatment was recommended in treatment-experienced patients regardless or cirrhotic status with ICERs of below approximately £19,000 per QALY gained | 4.9, 4.10<br>4.28<br>4.29 |
| The Committee considered the cost effectiveness of sofosbuvir plus ribavirin to be acceptable in people who were not eligible for peginterferon alfa regardless of previous treatment in people who had cirrhosis with ICERs of approximately £10,500 per QALY gained in treatment naive and £19,200 per QALY gained treatment experienced patients. The Committee did not consider sofosbuvir in combination with ribavirin to be cost effective in non-cirrhotic patients with ICERs of approximately £28,000 and £31,400 | 4.30, 4.31 |

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| per QALY gained in treatment-naive and experienced patients respectively.<br><br>**Genotypes 4, 5 and 6**<br>The Committee considered sofosbuvir in combination with ribavirin with or without peginterferon alpha to be clinically effective compared with peginterferon and ribavirin in people with treatment naïve and experienced HCV genotypes 4, 5 and 6.<br>The Committee did not consider sofosbuvir in combination with peginterferon alpha and ribavirin in people who were eligible for interferon to be cost effective in the treatment naive or experienced populations given the high degree of uncertainty in ICERs in excess of approximately £26,800 per QALY gained. In addition the Committee did not consider sofosbuvir plus ribavirin in people who were not eligible for interferon to be cost effective given the high degree of uncertainty in ICERs of approximately £26,800 per QALY gained. | | 4.6-4.7<br>4.32-4.35 |
| Current practice | | |
| Clinical need of patients, including the availability of alternative treatments | The Committee recognised the effect of chronic hepatitis C on the lives of people with the virus, and concluded that treatments that give a sustained virological response, and that consequently help reduce the rate of HCV transmission and the stigma associated with having chronic hepatitis C, are of significant importance.<br>The Committee was aware of the adverse effects of interferon-based treatments The Committee noted that the marketing authorisation for sofosbuvir offers people the option to receive shortened courses of peginterferon alfa and ribavirin, or in some circumstances to receive treatment without peginterferon alfa, thereby reducing potential side effects with interferon based therapy. | 4.2, 4.3, 4.5 |
| The technology | | |

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| Proposed benefits of the technology<br>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | The Committee acknowledged that the marketing authorisation for sofosbuvir offers people the option to receive shortened courses of peginterferon alfa and ribavirin, or in some circumstances to receive treatment without peginterferon alfa, thereby reducing potential side effects with interferon based therapy.<br>Clinical specialists considered sofosbuvir to be an important new treatment which 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 heard from the patient experts that the availability of sofosbuvir will encourage more people with hepatitis C to seek diagnosis and treatment.<br>The Committee accepted that sofosbuvir was a valuable new therapy but was aware that there is substantial uncertainty around the magnitude of benefit that it offers each subgroup. It agreed that there were other benefits (such as relief of loss of cognitive ability in people with HCV) and public health benefits (such as reduced onward transmission of HCV) that were not captured in the QALY calculation and that, if taken into account, would decrease the ICERs. | 4.3<br>4.4<br>4.36 |
| What is the position of the treatment in the pathway of care for the condition? | 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. | 4.4 |
| Adverse reactions | 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 |
| Evidence for clinical effectiveness | | |
| Availability, nature and quality of evidence | The Committee acknowledged the limitations of conducting trials for hepatitis C, and concluded that there was considerable uncertainty surrounding the evidence base presented by the manufacturer, and therefore the true magnitude of the effect of sofosbuvir in each subgroup could not be robustly estimated.<br>The Committee concluded that although there was uncertainty about the robustness of the evidence base in people with HCV genotypes 1, 4, 5 and 6 who were treatment-experienced there was sufficient evidence for the Committee to make a recommendation on the use of sofosbuvir in | 4.5-4.11 |

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| | people with genotype 1, 4, 5 and 6 treatment-experienced HCV.<br>The Committee noted that the manufacturer provided evidence from only 1 head-to-head trial (FISSION, in people eligible for interferon with genotype treatment-naive 2 or 3 HCV) that was consistent with the decision problem.<br>The Committee concluded that although there were limited data for the subgroups with HCV and HIV co-infection, the interim analysis of the PHOTON-1 and 1910 studies presented suggests that the efficacy of sofosbuvir plus standard of care is similar to that reported for people with chronic hepatitis C mono-infection. The Committee was aware that 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 acknowledges 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 | |
| Relevance to general clinical practice in the NHS | The Committee was aware that the inclusion criteria for the sofosbuvir trials were broader than for previous trials in hepatitis C; therefore there was good reason to expect that the people in the trials reflected those who are currently being treated in UK clinical practice. | 4.5 |
| Uncertainties generated by the evidence | The Committee acknowledged the limitations of conducting trials for hepatitis C, and concluded that there was considerable uncertainty surrounding the evidence base presented by the manufacturer, and therefore the true magnitude of the effect of sofosbuvir in each subgroup could not be robustly estimated.<br>The Committee was aware that all 4 trials in people with genotype 2 and 3 HCV had small patient numbers and different designs, and concluded that these factors introduced substantial uncertainty around the clinical effectiveness of sofosbuvir and must be taken into account when interpreting the clinical trial results.<br>The Committee concluded that, due to the design of the trials in people with genotype 2 and 3 HCV and the use of historical controls there was uncertainty relating to the true magnitude of benefit of sofosbuvir containing regiments compared with standard of care therapies. | 4.5, 4.7, 4.8 |

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| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | The Committee acknowledged that 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 better sustained virological response in people with genotype 3 HCV compared with current standard of care (24 weeks of peginterferon alfa and ribavirin treatment), but only when sofosbuvir plus ribavirin treatment was extended to 24 weeks. In addition, the Committee considered it was plausible that sustained virological response in people with genotype 2 HCV after treatment for 12 weeks with sofosbuvir plus ribavirin was likely to be better than the current standard of care. However, taking into account the limitations of the trial designs and the use of historical controls, the Committee concluded that there was considerable uncertainty around the true magnitude of benefit of sofosbuvir treatment regimens compared with the standard of care. | 4.8 |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The Committee acknowledged that in the NEUTRINO trial, people with genotype 1 (89% of people in the trial), 4, 5 or 6 treatment-naive 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 manufacturer.<br>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.<br>The Committee agreed with the manufacturer and ERG's view that the mixed treatment comparison conducted by the manufacturer was not robust and therefore it was reasonable for the manufacturer not to use it to inform its cost-effectiveness analyses. | 4.6, 4.8, 4.9, 4.10, 4.11 |
| Evidence for cost effectiveness | | |

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| Availability and nature of evidence | The Committee noted that the manufacturer'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.<br>The Committee concluded that the manufacturer had adequately addressed the Committee's request for additional analysis in the first appraisal consultation document. | 4.14 |

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| Uncertainties around and plausibility of assumptions and inputs in the economic model | The Committee considered the weighted population in the manufacturer's revised base case (61% men and 39% women [Wright et al 2006] to be more generalisable to the population characteristics for England.<br>The manufacturer's revised base case model included transition probabilities for people with cirrhosis with and without a sustained virological response at 12 weeks from the Cardoso et at. 201- paper (whereas the ERG preferred the Fattovich et at. 1997 estimate for non-sustained virological response as in the manufacturer's original model). The Committee considered there to be significant uncertainty in the absolute reduction in the probability of progression to hepatocellular carcinoma based on sustained virological response but considered the Cardoso et.al. estimates to be acceptable, although it was plausible that the transition probability for people without a sustained virological response may reside lie somewhere between the Cardoso et al. and Fattovich et al. estimates.<br>The Committee considered the use of alternative sustained virological responses for peginterferon alfa and ribavirin based on the results from revised economic model. The clinical specialists noted the heterogeneity of sustained virological response in clinical practice and 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. On balance, the Committee concluded that the sustained virological responses from McHutchison et al. were an acceptable source for inclusion in its base-case model but noted that the sustained virological response rates could like between those provided by the McHutchison and Hadziyannis datasets.<br>The Committee considered the use of different utility value in the economic model from literature and the clinical trials. 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. | 4.17<br>4.18<br>4.21 |

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| Incorporation of health-related quality-of-life benefits and utility values<br>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered? | The Committee understood that the manufacturer obtained SF-36 health-related quality of life data at various time points, including 24 weeks after the end of treatment for some trials. The Committee was aware the manufacturer had instead applied a utility increment of 0.05 after sustained virological response in the manufacturer's base-case analysis from Wright et al. (2006), and presented a revised model exploring the impact of the Vera-Llonch et al. 2013 estimate as requested by the Committee.<br>The Committee appreciated that the manufacturer tried to be pragmatic in its approach to modelling the effects of treatment, but considered that sensitivity analyses that used utility data (which were requested by the Committee but not presented ) from the trial to calculate the utility increment after a sustained virological response would have been preferred<br>The Committee agreed that the possibility of shortened interferon-based treatment regimens, or treatment without interferon therapy in some circumstances that sofosbuvir offers patients is particularly important and a major development in the current clinical management of chronic hepatitis C.<br>The Committee concluded that sofosbuvir did not meet the criteria for differential discounting of health benefits, and agreed that the manufacturer's approach to using the standard discount rate of 3.5% was appropriate.<br>The Committee agreed that there were other benefits (such as relief of loss of cognitive ability in people with HCV) and public health benefits (such as reduced onward transmission of HCV) that were not captured in the QALY calculation and that, if taken into account, would decrease the ICERs. | 4.21, 4.34, 4.36 |
| Are there specific groups of people for whom the technology is particularly cost effective? | The Committee concluded that sofosbuvir in combination with ribavirin with or without peginterferon alpha is cost effective in the following groups:<br>Genotype 1 interferon eligible people who are treatment-naïve and experienced<br>Genotype 2 people for whom interferon alpha is not appropriate and are treatment-experienced, and people who are not eligible for interferon who are both treatment-naïve and experienced.<br>Genotype 3 with cirrhosis (regardless of previous treatment experience) | 4.23, 4.24, 4.25, and 4.26<br><br>1.1 -1.7 |

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| What are the key drivers of cost effectiveness? | The Committee concluded that the duration of treatment with sofosbuvir had a considerable effect on the ICERs particularly in people with genotype 3 HCV. | 4.19 |
| Most likely cost-effectiveness estimate (given as an ICER) | Refer to the key conclusions in first row above. | |
| Additional factors taken into account | | |
| Patient access schemes (PPRS) | Not applicable | |
| End-of-life considerations | Not applicable | |
| Equalities considerations and social value judgements | It was raised during consultation that hepatitis C adversely affects certain populations, who could be considered at risk of being disadvantaged in terms of accessing the healthcare system and therefore at risk of inequity of access to innovative new treatments (such as certain immigrant populations, prison populations and people who inject drugs). The Committee discussed comments from 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 specialists 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 these people 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. | 4.28 |

# 5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning

groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic hepatitis C and the doctor responsible for their care thinks that sofosbuvir is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

# 6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

**Published**

- Boceprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 253 (2012)
- Telaprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 252 (2012)
- Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance 200 (2010)

- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. NICE technology appraisal guidance 106 (2006)
- Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance 75 (2004).
- Needle and syringe programmes. NICE public health guidance 52 (2014)

### Under development

- Simeprevir for treating genotype 1 or 4 chronic hepatitis C. NICE technology appraisal. Publication expected January 2015.
- Hepatitis C: diagnosis and management of hepatitis C. NICE clinical guideline. Publication date to be confirmed.

### NICE pathways

There is a NICE pathway on hepatitis B and C testing.

## 7 Proposed date for review of guidance

7.1 New treatments for chronic hepatitis C are awaiting marketing authorisation. According to clinical experts the approach to treating hepatitis C is likely to change rapidly next year because of the new technologies becoming available. NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 1 year after publication of the guidance.. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, Appraisal Committee
August 2014

# 8 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

**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

**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

**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 & 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 MBC

**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 clinical 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.

**Mr Richard Diaz and Dr Christian Griffiths**

Technical Leads

**Mrs Fiona Pearce and Mrs Eleanor Donegan**

Technical Adviser

**Mrs Kate Moore**

Project Manager

# 9 Sources of evidence considered by the Committee.

- HIV i-Base
- British Association for Sexual Health and HIV

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

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

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Gilead Sciences

II. Professional/specialist and patient/carer groups:

- British Liver Trust
- Liver4Life
- The Hepatitis C Trust
- 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

III. Other consultees:

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

IV. 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

C. The following individuals were selected from clinical specialist 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 written evidence to the Committee. They are invited to comment on the ACD.

- Dr Richard Aspinall, Consultant Hepatologist, nominated by the British Society of Gastroenterology – clinical specialist

- Dr Michael Jacobs, Consultant in Infectious Diseases, nominated by the Royal College of Physicians – clinical specialist
- 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

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

- Gilead Sciences