NICE National Institute for Health and Care Excellence

NICE guidance

Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C

Technology appraisal guidance
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1 Recommendations

1.1 Ombitasvir–paritaprevir–ritonavir with or without dasabuvir is recommended, within its marketing authorisation, as an option for treating genotype 1 or 4 chronic hepatitis C in adults, as specified in table 1, only if the company provides ombitasvir–paritaprevir–ritonavir and dasabuvir at the same price or lower than that agreed with the Commercial Medicines Unit.

Table 1 Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating adults with chronic hepatitis C

HCV genotype, liver disease stage	Treatment	Duration (weeks)	Recommendation according to treatment history
1a, without cirrhosis	Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin	12	Recommended
1a, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin	24	Recommended
1b, without cirrhosis	Ombitasvir–paritaprevir–ritonavir with dasabuvir	12	Recommended
1b, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin	12	Recommended
4, without cirrhosis	Ombitasvir–paritaprevir–ritonavir with ribavirin	12	Recommended
4, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir with ribavirin	24	Recommended

Abbreviation: HCV, hepatitis C virus.

Note: Treated – the person's hepatitis C has not adequately responded to interferon-based treatment.

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1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.

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2 The technology

2.1 Ombitasvir–paritaprevir–ritonavir (Viekirax, AbbVie) is a fixed-dose combination of 2 direct-acting anti-hepatitis C virus drugs (ombitasvir and paritaprevir) and ritonavir. Each tablet contains 12.5 mg ombitasvir, 75 mg paritaprevir, and 50 mg ritonavir. Ombitasvir inhibits non-structural viral protein NS5A; paritaprevir inhibits NS3/4A serine protease; and ritonavir increases the bioavailability of paritaprevir. The recommended dose is 2 tablets once daily. It is taken orally for 12 or 24 weeks with or without dasabuvir, with or without ribavirin.

2.2 Dasabuvir (Exviera, AbbVie) is a direct-acting anti-hepatitis C virus drug which inhibits a viral enzyme (NS5B) that has a role in viral genome replication. The recommended dose is 1 tablet (250 mg) twice daily. It is taken orally for 12 or 24 weeks with ombitasvir–paritaprevir–ritonavir and with or without ribavirin. The recommended treatment duration and whether ribavirin is co-administered depends on the subtype of genotype 1 hepatitis C virus (HCV) and the presence of cirrhosis.

2.3 Ombitasvir–paritaprevir–ritonavir has a marketing authorisation in the UK for the treatment of chronic hepatitis C in adults in combination with other medicinal products. The marketing authorisation recommends specific treatment combinations and durations for genotypes 1 and 4 HCV depending on genotype, subtype and whether or not the person has cirrhosis (see table 2). Dasabuvir has a marketing authorisation in the UK for the treatment of chronic hepatitis C in adults in combination with other medicinal products. However, the marketing authorisation recommends specific treatment durations for subtypes of genotype 1 HCV only. For full details of the recommended treatment durations with ombitasvir–paritaprevir–ritonavir with and without dasabuvir, see the summary of product characteristics. For a summary, see table 2.

2.4 The summary of product characteristics lists the following adverse reactions as common with ombitasvir–paritaprevir–ritonavir with or without dasabuvir and ribavirin: insomnia, nausea, pruritus (itching), asthenia (weakness), fatigue and anaemia. For full details of adverse reactions and contraindications, see the summaries of product characteristics.

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2.5 Ombitasvir–paritaprevir–ritonavir costs £10,733.33 excluding VAT for 28 days' supply. The total costs of a 12-week and a 24-week course of ombitasvir–paritaprevir–ritonavir are £32,200 and £64,400 respectively (both excluding VAT: MIMS, February 2015). Dasabuvir costs £933.33 excluding VAT for 28 days' supply. The total costs of a 12-week and a 24-week course of dasabuvir are £2,800 and £5,600 respectively (both excluding VAT: MIMS, February 2015). The company has agreed a nationally available price reduction for ombitasvir–paritaprevir–ritonavir with or without dasabuvir with the Commercial Medicines Unit. The contract prices agreed through the framework are commercial in confidence.

Table 2 Marketing authorisation treatment schedule for ombitasvir–paritaprevir–ritonavir by HCV genotype

HCV genotype, liver disease stage	Treatment	Duration (weeks)
1b, without cirrhosis	Ombitasvir–paritaprevir–ritonavir **with** dasabuvir	12
1b, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir **with** dasabuvir **and** ribavirin	12
1a, without cirrhosis	Ombitasvir–paritaprevir–ritonavir **with** dasabuvir **and** ribavirin	12
1a, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir **with** dasabuvir **and** ribavirin	24
4, without cirrhosis	Ombitasvir–paritaprevir–ritonavir **without** dasabuvir **and with** ribavirin	12
4, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir **without** dasabuvir **and with** ribavirin	24

Abbreviation: HCV, hepatitis C virus.

Notes: Follow the genotype 1a dosing recommendation in people with an unknown genotype 1 subtype or with mixed genotype 1 infection. Follow the same dosing recommendations in people with HIV-1 co-infection.

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3 The company's submission

The Appraisal Committee considered evidence submitted by AbbVie and a review of this submission by the Evidence Review Group (ERG).

Clinical effectiveness

3.1 The company presented 6 completed clinical trials of ombitasvir–paritaprevir–ritonavir with dasabuvir (referred to as 3D), and 1 completed trial of ombitasvir–paritaprevir–ritonavir without dasabuvir (referred to as 2D). The populations in the trials differed with respect to hepatitis C virus (HCV) genotype and subtype, whether they had cirrhosis and whether they previously had peginterferon alfa.

Genotype 1a and 1b HCV

- **SAPPHIRE I** (randomised controlled trial): 12-week treatment with 3D plus ribavirin (n=473), compared with placebo (n=158), for previously untreated HCV without cirrhosis.
- **SAPPHIRE II** (randomised controlled trial): 12-week treatment with 3D plus ribavirin (n=297), compared with placebo (n=97), for previously treated HCV without cirrhosis.
- **TURQUOISE II** (randomised controlled trial): 12-week treatment with 3D plus ribavirin (n=208), compared with 24-week treatment with 3D plus ribavirin (n=172), for previously untreated or treated HCV with compensated cirrhosis.

Genotype 1b HCV

- **PEARL II** (randomised controlled trial): 12-week treatment with 3D plus ribavirin (n=91), compared with 3D alone (n=95), for previously treated HCV without cirrhosis.
- **PEARL III** (randomised controlled trial): 12-week treatment with 3D plus ribavirin (n=210), compared with 3D plus placebo (n=209), for previously untreated HCV without cirrhosis.

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Genotype 1a HCV

- **PEARL IV** (randomised controlled trial): 12-week treatment with 3D plus ribavirin (n=100), compared with 3D plus placebo (n=205), for previously untreated HCV without cirrhosis.

Genotype 4 HCV

3.2 The company submitted 2 completed and 4 ongoing clinical trials as supporting evidence:

- **PEARL I** (randomised controlled trial): 12-week treatment with 2D for previously untreated HCV (n=44), and 12-week treatment with 2D plus ribavirin for previously untreated (n=42) or treated (n=49) HCV.

Completed trials

- **AVIATOR** and **M14-103**: 3D plus ribavirin for previously untreated or treated genotype 1 HCV without cirrhosis.

Ongoing trials

The treatment groups that provided evidence for the treatments specified in the summary of product characteristics are presented in table 3.

Table 3 Trial treatment arms or subgroups that informed the treatments specified in the summary of product characteristics

Summary of product characteristic	Summary of product characteristics	Trial	HCV genotype	Comparison	Trial arm or subgroup
Genotype 1b HCV without cirrhosis	3D (12 weeks)	PEARL II	1b	3D+RBV versus 3D	3D treatment arm (n=95)
Genotype 1b HCV without cirrhosis	3D (12 weeks)	PEARL III	1b	3D+RBV versus 3D	3D treatment arm (n=209)

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Summary of product characteristic	Summary of product characteristics	Trial	HCV genotype	Comparison	Trial arm or subgroup
Genotype 1b HCV with compensated cirrhosis	3D+RBV (12 weeks)	TURQUOISE II	1a and 1b	3D+RBV: 12 weeks versus 24 weeks	GT1b, 12 week treatment arm (n=68/208)
Genotype 1a HCV without cirrhosis	3D+RBV (12 weeks)	SAPPHIRE I	1a and 1b	3D+RBV versus placebo	GT1a, 3D+RBV arm (n=322/473)
Genotype 1a HCV without cirrhosis	3D+RBV (12 weeks)	SAPPHIRE II	1a and 1b	3D+RBV versus placebo	GT1a, 3D+RBV arm (n=173/297)
Genotype 1a HCV without cirrhosis	3D+RBV (12 weeks)	PEARL IV	1a	3D+RBV versus 3D	3D plus RBV treatment arm (n=100)
Genotype 1a HCV with compensated cirrhosis	3D+RBV (24 weeks)	TURQUOISE II	1a and 1b	3D+RBV: 12 weeks versus 24 weeks	GT1a, 24-week treatment arm (n=121/172)
Genotype 4 HCV without cirrhosis	2D+RBV (12 weeks)	PEARL I	4	2D+RBV (TN) versus 2D (TN) and 2D+RBV (TE)	Treatment arms with 2D plus ribavirin, TN (n=42) TE (n=49)
Genotype 4 HCV with compensated cirrhosis	2D+RBV (24 weeks)	No data	No data	No data	No data

Abbreviations: HCV, hepatitis C virus; GT, genotype; RBV, ribavirin; TN, treatment naive (no previous treatment); TE, treatment experienced (previously treated); 2D, ombitasvir–paritaprevir–ritonavir without dasabuvir; 3D, ombitasvir–paritaprevir–ritonavir with dasabuvir.

Note: Treatment duration in trials was 12 weeks unless stated otherwise.

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3.3 Although recommended in the marketing authorisation, 2D plus ribavirin for 24 weeks was not studied for genotype 4 HCV with cirrhosis. The European public assessment report states that data from PEARL I demonstrated that this treatment was efficacious for genotype 1b HCV with cirrhosis. Because the in vitro effects and pharmacodynamics for both components of 2D (paritaprevir and ombitasvir) are similar for genotype 1b and genotype 4 HCV, the report concluded that 24-week treatment with 2D plus ribavirin for genotype 4 HCV with cirrhosis was likely to be as efficacious as for genotype 1b HCV with cirrhosis.

3.4 The primary outcome in all the included trials was sustained virological response at week 12 (SVR12), defined as an HCV RNA level of less than 25 IU per millilitre at 12 weeks after treatment ends. All the completed trials except PEARL I (genotype 4 HCV) planned a comparison with the historical control, telaprevir. Analyses were based on the intention-to-treat population (all people who were randomised) or the modified intention-to-treat population (all people who were randomised and had at least 1 dose of study treatment).

3.5 The results of trials of 3D and 2D, with or without ribavirin, in which treatment matched that specified in the marketing authorisation, and the results of trials included in the company's economic model, are presented in table 4.

Table 4 Sustained virological response rates at 12 weeks; outcome from trial arms or subgroups in which treatment matched the marketing authorisation

Population	Treatment (duration)	Trial	SVR12	SVR12	SVR12
Genotype 1b HCV, without cirrhosis	3D (12 weeks)	PEARL III (previously untreated)	209/209	100.0 (98.2 to 100.0)	80 (75 to 84)
Genotype 1b HCV, without cirrhosis	3D (12 weeks)	PEARL II (previously treated)	91/91	100.0 (95.9 to 100.0)	69 (62 to 75)
Genotype 1b HCV, with compensated cirrhosis	3D plus ribavirin (12 weeks)	TURQUOISE II	67/68	98.5 (95.7 to 100.0)	47 (41 to 54)

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Population	Treatment (duration)	Trial	SVR12	SVR12	SVR12
Genotype 1a HCV, without cirrhosis	3D plus ribavirin (12 weeks)	SAPPHIRE I (previously untreated)	308/322	95.7 (93.4 to 97.9)	72 (68 to 75)
Genotype 1a HCV, without cirrhosis	3D plus ribavirin (12 weeks)	PEARL IV (previously untreated)	97/100	97.0 (93.7 to 100.0)	72 (68 to 75)
Genotype 1a HCV, without cirrhosis	3D plus ribavirin (12 weeks)	SAPPHIRE II (previously treated)	166/173	96.0 (93.0 to 98.9)	59 (53 to 65)
Genotype 1a HCV, with compensated cirrhosis	3D plus ribavirin (24 weeks)	TURQUOISE II	115/121	95.0 (91.2 to 98.9)	47 (41 to 54)
Genotype 4 HCV, without cirrhosis	2D plus ribavirin (12 weeks)	PEARL I (previously untreated)	42/42	100.00 (91.6 to 100)	Not applicable
Genotype 4 HCV, without cirrhosis	2D plus ribavirin (12 weeks)	PEARL I (previously treated)	49/49	100.00 (92.7 to 100)	Not applicable

Abbreviations: SVR12, sustained virological response at week 12; CI, confidence interval; HCV, hepatitis C virus; 2D, ombitasvir–paritaprevir–ritonavir without dasabuvir; 3D, ombitasvir–paritaprevir–ritonavir with dasabuvir.

Note: The data for telaprevir were from the clinical trials ILLUMINATE, ADVANCE and REALIZE.

- **MALACHITE I**: 3D plus ribavirin compared with telaprevir plus peginterferon alfa and ribavirin, for previously untreated genotype 1 HCV.
- **MALACHITE II**: 3D plus ribavirin, compared with telaprevir plus peginterferon alfa and ribavirin, for previously treated genotype 1 HCV.
- **TURQUOISE I**: 3D plus ribavirin for genotype 1 HCV in adults co-infected with HIV-1.
- **CORAL I**: 3D with ribavirin for genotype 1 HCV in adults who had a liver transplant.

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Meta-analysis

3.6 The company presented 3 meta-analyses in which it pooled SVR12 rates from single-arm trials evaluating 3D for genotype 1 HCV. Analyses were done on the following groups using a random-effect model:

- all active treatment groups in completed phase 3 clinical trials (SAPPHIRE I, SAPPHIRE II, PEARL II, PEARL III, PEARL IV and TURQUOISE II) plus 1 phase 2 study, M14–103
- all treatment groups in the completed phase 3 trials in line with the marketing authorisation for 3D and
- all active treatment groups in the clinical trial programme for genotype 1 HCV, including from the dose-finding AVIATOR study, and interim results from 2 ongoing trials, TURQUOISE I and CORAL I.

  The pooled SVR12 rate from the meta-analysis for the 3D treatments recommended in the marketing authorisation was 96.5%.

3.7 The company stated that a network meta-analysis to generate relative estimates of efficacy for 3D and 2D compared with the comparators outlined in the final scope issued by NICE was not feasible.

Health-related quality of life

3.8 The completed trials also reported data on health-related quality of life. This was measured using the SF-36 physical component score and mental component score; the EQ-5D-5L health index score and visual analogue score; and the HCV-PRO (a patient-reported outcome tool specific to chronic hepatitis C, which consists of 16 items focusing on physical health, emotional health, productivity, social interactions, intimacy and perception).

3.9 Results for health-related quality of life were reported as the mean change from baseline to the last treatment visit and to 12 weeks after treatment ends. In general, no statistically significant differences in the mean change over either of these periods were seen between treatment groups in most of the trials for most

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of the patient-reported outcomes.

3.10 The EQ-5D-5L health index scores from the trials were used to inform the on-treatment utility values in the economic model. The EQ-5D-5L health index scores were obtained using country-specific algorithms to map the 5L values to the 3L tariff scores. The US mapping algorithm to convert the 5L values to 3L was used when an individual country-specific algorithm was not available. The EQ-5D-5L scores are academic in confidence and cannot be reported here.

Adverse events

3.11 The company presented data on adverse events from the 6 completed trials evaluating 3D and the trial evaluating 2D. The most frequently reported adverse events were fatigue, headache, nausea, pruritus, insomnia, irritability, diarrhoea, anaemia, asthenia, shortness of breath, cough, muscle ache, itching and rash. The proportion of people who had at least 1 adverse event ranged from 67% (for 3D in genotype 1b HCV in PEARL III) to 92% (for 3D plus ribavirin in genotype 1a HCV in PEARL IV). Generally higher rates of adverse events were seen in the groups who had longer treatment and those who had ribavirin. The proportion of people stopping treatment because of adverse events was consistently low across the trials and the highest dropout rate was seen in TURQUOISE II, in people with compensated cirrhosis (2.3% in the 24-week arm and 1.9% in the 12-week arm).

Cost effectiveness

Model structure

3.12 The company submitted a Markov state transition model estimating the cost effectiveness of 3D and 2D for people with genotype 1 or 4 HCV. The structure of the model was adapted from the model used in NICE's technology appraisal guidance on peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C and peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. The model simulated the lifetime disease progression of people with

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chronic HCV infection. The model adopted a lifetime time horizon (70 years) and a cycle length of 1 year. The model applied half-year cycle corrections. Costs and health effects were discounted at an annual rate of 3.5%. The perspective of the analysis on costs was that of the NHS and personal social services.

3.13 The model had 6 health states simulating progressive liver disease, 3 health states simulating recovery from HCV (for people who had an SVR), and 1 death state.

Health states simulating progressive liver disease:

- mild chronic HCV (METAVIR fibrosis stage F0 to F1)
- moderate chronic HCV (METAVIR fibrosis stage F2 to F3)
- compensated cirrhosis (METAVIR fibrosis stage F4)
- decompensated cirrhosis
- hepatocellular carcinoma and
- liver transplant.

Health states simulating recovery from HCV (SVR):

- recovered, history of mild disease
- recovered, history of moderate disease and
- recovered, history of compensated cirrhosis.

3.14 People entered the model in one of the following health states: mild chronic HCV, moderate chronic HCV, or compensated cirrhosis. They had treatment in the first year of the model. If they had an SVR, people moved to one of the recovery states, which depended on the previous state in which they had treatment. Once in a recovery state, the disease could not progress further. However, reinfection with chronic hepatitis C was possible, with a constant risk across the time horizon. People who did not have an SVR could stay in the same state, or move through the states simulating progressive liver disease (from mild to moderate to compensated cirrhosis, depending on their previous state and the rate of fibrosis

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progression). From compensated cirrhosis, the disease could progress to decompensated cirrhosis or hepatocellular carcinoma. From decompensated cirrhosis, the person could develop hepatocellular carcinoma, or have a liver transplant. From hepatocellular carcinoma, the person could have a liver transplant. People in the model risked dying at any time, but those with decompensated cirrhosis, hepatocellular carcinoma, and those who had a liver transplant had an additional risk of death from liver disease.

Populations, intervention and comparators

3.15 In its original analyses, the company modelled previously untreated and previously treated HCV separately. These groups were further divided by subtype of HCV (genotypes 1a or 1b). In total, the company's original base-case analyses included 4 different populations.

3.16 After the first Appraisal Committee meeting, the company presented revised base-case analyses separately for previously treated and previously untreated HCV for each treatment regimen as specified in the summary of product characteristics. The results of the revised analyses supersede the original analyses. Therefore only the revised analyses are discussed here.

3.17 The baseline characteristics of people in the model, such as age, weight, sex and disease severity, were based on a clinical audit of people with HCV who had treatment at a liver clinic at a London teaching hospital. Overall, 70% of the modelled population were male. The average ages at baseline of people whose HCV was previously untreated and previously treated were 40 and 45 years respectively. The company modelled 3D with or without ribavirin for genotype 1 HCV and 2D with ribavirin for genotype 4 HCV, as per the marketing authorisation. It compared 3D and 2D with peginterferon alfa and ribavirin, sofosbuvir plus peginterferon alfa and ribavirin and simeprevir plus peginterferon alfa and ribavirin. In addition 3D was compared with telaprevir plus peginterferon alfa and ribavirin and boceprevir plus peginterferon alfa and ribavirin. The comparators were modelled in line with their respective marketing authorisations. The company estimated the durations of each modelled treatment from the rates at which people stopped that treatment in the respective clinical trials.

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SVR rates and model transitions

3.18 Clinical effectiveness was modelled as the probability of moving to a recovery state, which was based on the SVR12 rates reported in the clinical trials for 3D, 2D and the comparators. The company included estimates of effectiveness from separate trials without any statistical adjustments. When SVRs were available from more than 1 trial, the company pooled the results from the different trials. Because 2D was not studied in people with genotype 4 HCV with cirrhosis the SVR for this group was assumed to be 97%, as reported for the 2D 24-week treatment in people with genotype 1b HCV in PEARL I.

3.19 The company highlighted 2 limitations with the available clinical effectiveness data for simeprevir used in the revised base-case analyses:

- The marketing authorisation for simeprevir does not allow treatment in people with Q80K positive polymorphism (a genetic mutation) and SVRs for the Q80K negative subgroups were not available.
- The definitions of mild and moderate fibrosis in the simeprevir trials were different from the definitions used in the company's model. The company used pooled SVR from the intention-to-treat population in QUEST I and QUEST II and the definitions of fibrosis used in the simeprevir trials in the revised base-case analyses.

3.20 The company assumed in the model that the natural history of genotype 1 and 4 HCV was similar, and so applied the same transition probabilities for both HCV genotypes. Data were sourced from the published literature.

Utility values and costs

3.21 For the health states in the model, the company used utility values obtained from the EQ-5D scores collected in the UK mild hepatitis C trial and valued using the UK general population tariff (see table 5).

Table 5 Health state utility values

Health state	Utility	Source
Mild HCV	0.77	Wright et al. 2006

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Health state	Utility	Source
Moderate HCV	0.66	Wright et al. 2006
Compensated cirrhosis	0.55	Wright et al. 2006
Recovered (no HCV, history of mild fibrosis)	0.82	Calculated – add 0.05 to utility for mild HCV
Recovered (no HCV, history of moderate fibrosis)	0.71	Calculated – add 0.05 to utility for moderate HCV
Recovered (no HCV, history of compensated cirrhosis)s	0.60	Calculated – add 0.05 to utility for compensated cirrhosis
Decompensated cirrhosis	0.45	Wright et al. 2006
Hepatocellular carcinoma	0.45	Wright et al. 2006
Liver transplant	0.45	Wright et al. 2006
Post-liver transplant	0.67	Wright et al. 2006

Abbreviation: HCV, hepatitis C virus.

3.22 The utility differences associated with treatment were also accounted for in the model. On-treatment utility decrements or gains were applied during the first year (first cycle) of the model. To estimate the on-treatment utility difference for 3D and 2D, the company calculated the difference between the EQ-5D-3L score at the end of treatment and baseline. EQ-5D-3L scores were calculated using a UK mapping algorithm from the EQ-5D-5L scores collected in the trials for 3D and 2D. The utility differences associated with the comparator treatments were from other NICE technology appraisal guidance and ranged from a decrement of 0.154 (for telaprevir plus peginterferon alfa and ribavirin in people who had previous treatment) to a utility gain of 0.110 (for boceprevir plus peginterferon alfa and ribavirin in people who had previous treatment).

3.23 The company also did 2 scenario analyses around utility values. In scenario 1, the company estimated the utility gain for having an SVR from the difference between the pooled EQ-5D values collected at baseline and at 12 weeks after

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treatment in people who had an SVR in the trials (instead of 0.05 used in the base case). In scenario 2, the company explored using alternative values for each health state, estimated from its trials. The company marked the alternative estimate of utility gain used in scenario 1, as well as the utility values for each health state used in scenario 2, as academic in confidence and therefore they cannot be presented here.

3.24 The company included 2 categories of resource use in the model that is; health state costs and treatment costs. The health state costs were associated with managing progressive liver disease (in people whose HCV does not respond to treatment) and surveillance after stopping treatment in people who have an SVR. The company's estimate of resource use for health states was based on 2 sources:

- A retrospective chart review of people with chronic hepatitis C that reported resource use according to disease response to treatment (SVR or non-SVR) done in the East Midlands region of the UK (Backx et al. 2014). The company used these data to estimate costs for all 3 recovery health states and 2 disease states, moderate fibrosis and compensated cirrhosis.
- The cost for the remaining health states, that is mild fibrosis and 3 more advanced disease states, namely decompensated cirrhosis, hepatocellular carcinoma and liver transplant, were based on the models used in NICE's technology appraisal guidance on peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C and peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. The costs were updated to current values using the Personal and Social Services Research Unit pay and prices inflation index.

3.25 Treatment-related costs included drug acquisition costs and costs associated with on-treatment monitoring for response and adverse events.

Results

3.26 The results of the fully incremental analyses for the treatments recommended in the summary of product characteristics for different groups stratified by treatment history, as requested by the Committee, are in table 6 (using the list

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price for ombitasvir–paritaprevir–ritonavir with or without dasabuvir). The incremental cost-effectiveness ratios (ICERs) for the scenario analyses are presented in table 7. Using alternative utility values estimated from the trials increased the ICERs for the 3D (genotype 1 HCV) and 2D (genotype 4 HCV) treatments modestly for most of the populations. The company commented that in the trials, EQ-5D data at 12 weeks after treatment were collected before people knew their SVR results and therefore, did not capture the psychological and emotional benefit of being cured.

Table 6 ICERs according to treatments in the summary of product characteristics (using the list price for ombitasvir–paritaprevir–ritonavir with or without dasabuvir)

Treatment	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Genotype 1a HCV without cirrhosis; previously untreated PR	NA	NA	NA
Genotype 1a HCV without cirrhosis; previously untreated Boceprevir+PR	£9,226	0.51	Extended dominance
Genotype 1a HCV without cirrhosis; previously untreated Telaprevir+PR	£13,320	0.81	Extended dominance
Genotype 1a HCV without cirrhosis; previously untreated Simeprevir+PR	£14,507	0.85	Extended dominance
Genotype 1a HCV without cirrhosis; previously untreated **3D+RBV (for 12 weeks)**	£19,067	1.47	**£12,949**
Genotype 1a HCV without cirrhosis; previously untreated Sofosbuvir+PR	£21,256	1.38	Dominated
Genotype 1a HCV without cirrhosis; previously treated PR	NA	NA	NA

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Treatment	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Genotype 1a HCV without cirrhosis; previously treated Telaprevir+PR	£14,231	0.86	Extended dominance
Genotype 1a HCV without cirrhosis; previously treated **3D+RBV (for 12 weeks)**	£17,617	1.84	**£9,589**
Genotype 1a HCV without cirrhosis; previously treated Simeprevir+PR	£18,005	0.86	Dominated
Genotype 1a HCV without cirrhosis; previously treated Sofosbuvir+PR	£22,429	1.31	Dominated
Genotype 1a HCV with cirrhosis; previously untreated PR	NA	NA	NA
Genotype 1a HCV with cirrhosis; previously untreated Telaprevir+PR	£10,850	0.92	Extended dominance
Genotype 1a HCV with cirrhosis; previously untreated Simeprevir+PR	£12,775	0.85	Extended dominance
Genotype 1a HCV with cirrhosis; previously untreated Boceprevir+PR	£12,967	-0.11	Dominated
Genotype 1a HCV with cirrhosis; previously untreated Sofosbuvir+PR	£16,290	1.70	£9,555
Genotype 1a HCV with cirrhosis; previously untreated **3D+RBV (for 24 weeks)**	£46,450	2.11	**£75,360**
Genotype 1a HCV with cirrhosis; previously treated PR	NA	NA	NA

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Treatment	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Genotype 1a HCV with cirrhosis; previously treated Telaprevir+PR	£13,823	0.68	Extended dominance
Genotype 1a HCV with cirrhosis; previously treated Simeprevir+PR	£17,109	0.72	Extended dominance
Genotype 1a HCV with cirrhosis; previously treated Sofosbuvir+PR	£18,692	1.42	£13,157
Genotype 1a HCV with cirrhosis; previously treated **3D+RBV (for 24 weeks)**	£44,105	2.38	£26,516
Genotype 1b HCV without cirrhosis; previously untreated PR	NA	NA	NA
Genotype 1b HCV without cirrhosis; previously untreated Boceprevir+PR	£9,265	0.50	Extended dominance
Genotype 1b HCV without cirrhosis; previously untreated Telaprevir+PR	£13,271	0.82	Extended dominance
Genotype 1b HCV without cirrhosis; previously untreated Simeprevir+PR	£14,128	0.92	Extended dominance
Genotype 1b HCV without cirrhosis; previously untreated **3D (for 12 weeks)**	£18,833	1.39	**£13,515**
Genotype 1b HCV without cirrhosis; previously untreated Sofosbuvir+PR	£23,659	0.95	Dominated
Genotype 1b HCV without cirrhosis; previously treated **PR**	**NA**	**NA**	**NA**

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Treatment	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Genotype 1b HCV without cirrhosis; previously treated Telaprevir+PR	£11,633	1.29	Extended dominance
Genotype 1b HCV without cirrhosis; previously treated Simeprevir+PR	£14,376	1.46	Extended dominance
Genotype 1b HCV without cirrhosis; previously treated **3D (for 12 weeks)**	£15,489	2.09	**£7,401**
Genotype 1b HCV without cirrhosis; previously treated Sofosbuvir+PR	£21,427	1.47	Dominated
Genotype 1b HCV with cirrhosis; previously untreated PR	NA	NA	NA
Genotype 1b HCV with cirrhosis; previously untreated PR+telaprevir	£10,766	0.93	Extended dominance
Genotype 1b HCV with cirrhosis; previously untreated **3D+RBV (for 12 weeks)**	£12,090	2.04	£5,924
Genotype 1b HCV with cirrhosis; previously untreated Simeprevir+PR	£12,136	0.94	Dominated
Genotype 1b HCV with cirrhosis; previously untreated PR+boceprevir	£13,033	-0.12	Dominated
Genotype 1b HCV with cirrhosis; previously untreated Sofosbuvir+PR	£20,338	1.16	Dominated
Genotype 1b HCV with cirrhosis; previously treated PR	NA	NA	NA

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Treatment	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Genotype 1b HCV with cirrhosis; previously treated **3D+RBV (for 12 weeks)**	£7,874	2.55	£3,087
Genotype 1b HCV with cirrhosis; previously treated Telaprevir+PR	£9,159	1.25	Dominated
Genotype 1b HCV with cirrhosis; previously treated Simeprevir+PR	£10,640	1.51	Dominated
Genotype 1b HCV with cirrhosis; previously treated Sofosbuvir+PR	£16,822	1.65	Dominated
Genotype 4 HCV without cirrhosis; previously untreated PR	NA	NA	NA
Genotype 4 HCV without cirrhosis; previously untreated Simeprevir+PR	£14,415	0.41	Extended dominance
Genotype 4 HCV without cirrhosis; previously untreated **2D+RBV for 12 weeks**	£17,204	0.85	**£20,351**
Genotype 4 HCV without cirrhosis; previously untreated Sofosbuvir+PR	£21,951	0.81	Dominated
Genotype 4 HCV without cirrhosis; previously treated No treatment	NA	NA	NA
2D+RBV for 12 weeks	£20,350	2.27	**£8,977**
Genotype 4 HCV without cirrhosis; previously treated Simeprevir+PR	£21,236	1.72	Dominated
Genotype 4 HCV without cirrhosis; previously treated Sofosbuvir+PR	£28,150	1.64	Dominated

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Treatment	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Genotype 4 HCV with cirrhosis; previously untreated PR	NA	NA	NA
Genotype 4 HCV with cirrhosis; previously untreated Simeprevir+PR	£9,555	0.96	£9,902
Genotype 4 HCV with cirrhosis; previously untreated Sofosbuvir+PR	£15,955	1.41	£14,238
Genotype 4 HCV with cirrhosis; previously untreated **2D+RBV for 24 weeks**	£39,781	2.01	**£40,025**
Genotype 4 HCV with cirrhosis; previously treated No treatment	NA	NA	NA
Genotype 4 HCV with cirrhosis; previously treated Simeprevir+PR	£20,879	1.27	Extended dominance
Genotype 4 HCV with cirrhosis; previously treated Sofosbuvir+PR	£22,827	1.84	£12,432
Genotype 4 HCV with cirrhosis; previously treated **2D+RBV for 24 weeks**	£44,112	2.79	**£22,331**

Abbreviations: HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; 3D, ombitasvir–paritaprevir–ritonavir with dasabuvir; 2D, ombitasvir–paritaprevir–ritonavir without dasabuvir; NA, not applicable; PR, peginterferon alfa and ribavirin; QALY, quality-adjusted life year; RBV, ribavirin.

Notes: Dominated – treatment gives fewer QALYs at greater cost than cost than comparator. Extended dominance – a combination of 2 of its comparators provides equal health at a reduced cost. Incremental costs and QALYs represent increments from reference (baseline) treatment.

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Table 7 ICERs (£/QALY gained) for 3D or 2D in the revised base case and scenario analyses

Population	Scenario	Previously untreated No cirrhosis	Previously untreated Cirrhosis	Previously treated	Previously treated Cirrhosis
Genotype 1a HCV	Revised base case	£12,949	£75,360	£9,589	£26,516
Genotype 1a HCV	Scenario 1	£17,833	£92,828	£13,613	£33,332
Genotype 1a HCV	Scenario 2	£17,028	£65,696	£17,047	£23,296
Genotype 1b HCV	Revised base case	£13,515	£5,924	£7,401	£3,087
Genotype 1b HCV	Scenario 1	£18,538	£7,316	£10,480	£3,861
Genotype 1b HCV	Scenario 2	£17,431	£4,837	£13,831	£2,477
Genotype 4 HCV	Revised base case	£20,351	£40,025	£8,977	£22,331
Genotype 4 HCV	Scenario 1	£27,422	£48,791	£13,027	£27,877
Genotype 4 HCV	Scenario 2	£18,673	£38,911	£8,370	£17,355

Abbreviations: HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; 3D, ombitasvir–paritaprevir–ritonavir with dasabuvir; 2D, ombitasvir–paritaprevir–ritonavir without dasabuvir; QALY, quality-adjusted life year.

3.27 The company stated that in its opinion the marketing authorisation allows for a 12-week treatment in some people with genotype 1a HCV with cirrhosis. The company presented separate SVRs for genotype 1a and genotype 1b HCV from TURQUOISE II. The results were further stratified for each genotype by treatment history and response to previous treatment. For genotype 1a HCV treated with a 12-week regimen, the SVR was more than 90% for all subgroups except for people whose HCV did not respond to previous peginterferon alfa and ribavirin

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treatment (SVR 80%). The company stated that in its regulatory submission it proposed a 24-week treatment only for this subgroup of people with genotype 1a HCV with cirrhosis. Results presented in the summary of product characteristics showed higher relapse rates in genotype 1a HCV treated with a 12-week regimen than with a 24-week regimen. In TURQUOISE II there were 13 incidences of relapse and 11 of these were in people with genotype 1a HCV treated with a 12-week regimen.

3.28 The company did a post-hoc analysis to identify the predictors of relapse in genotype 1a HCV treated with a 12-week regimen and found that for people with 3 favourable baseline laboratory values (alpha fetoprotein [AFP] less than 20 ng/ml, platelets 90×10^9/litre or more and albumin 35 g/litre or more), relapse rates were similar with the 12 and 24-week treatments. The company noted that the summary of product characteristics acknowledged this post-hoc analysis. On that basis, the company considered a 12-week regimen for people with genotype 1a HCV with cirrhosis and these favourable baseline laboratory values to be within the marketing authorisation. However, the company did not provide SVR data or any economic analyses exclusively for this group.

3.29 The company also explored scenarios assuming that some people with genotype 1a HCV with cirrhosis would have treatment for 12 weeks. It assumed that everyone except those whose HCV did not respond to previous peginterferon alfa and ribavirin treatment would have a 12-week treatment. All people with genotype 1a HCV with cirrhosis had a 24-week treatment in the base case. To inform these analyses the company used corresponding SVRs for each population from the subgroup analyses of TURQUOISE II. The resulting ICERs for 3D plus ribavirin compared with peginterferon alfa plus ribavirin were £5,985 per quality-adjusted life year (QALY) gained for the previously untreated HCV group and £8,812 per QALY gained for the previously treated HCV group.

3.30 The company presented probabilistic sensitivity analyses for 32 different populations. These also included the 12 populations for whom the Committee requested revised base-case analyses. The company presented the results graphically in the form of cost-effectiveness acceptability curves. The results showed that for a maximum acceptable ICER of £30,000 per QALY gained, 3D or 2D were the optimal treatment strategies for most of the revised base-case population except for people with genotype 1a HCV with cirrhosis and

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genotype 4 HCV with cirrhosis. In these 2 populations sofosbuvir plus peginterferon alfa and ribavirin was the optimal treatment strategy.

ERG comments on the clinical effectiveness

3.31 The ERG was satisfied overall with the literature searches done by the company. However, it noted that one included phase 2 study (AVIATOR) did not meet the inclusion criteria because dasabuvir (a component of 3D), was administered at a dose (400 mg twice daily) higher than the licensed dose (250 mg twice daily).

3.32 The ERG was concerned about the lack of randomised controlled trials for 3D and 2D, and commented that all the completed trials included in the company's submission provided non-randomised, observational data for the primary outcome of SVR12 (from individual trial arms or subgroups).

3.33 The ERG commented that the company did not provide sufficient detail about the similarity of people in the 3D trials to those in the telaprevir trials (ADVANCE, ILLUMINATE and REALIZE) used for the historical comparison of the other comparators relevant to the decision problem. During clarification, the company stated that it was not possible to examine the baseline characteristics for the specific matched historical controls, because these individual patient data for the telaprevir studies were not available.

3.34 The ERG commented that there were higher proportions of people with mild fibrosis (that is, fibrosis scores of F0 and F1) in the 3D trials than in the telaprevir trials used for historical comparison, which may have biased the SVR estimates in favour of 3D.

3.35 The ERG commented that in some trials (for example SAPPHIRE I and SAPPHIRE II) a subgroup provided the efficacy data on the licensed treatment. The subgroups were unlikely to be powered to demonstrate non-inferiority and superiority over the historical control (telaprevir) because power calculations were based on the sample sizes of the whole trial population.

3.36 The ERG commented that the meta-analysis that pooled data from the study treatment arms that are in line with the marketing authorisation for 3D is the most

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appropriate for this appraisal. The ERG noted that the company only presented results from the random-effect model. The ERG re-ran the meta-analysis using an alternative software package, for random-effect and fixed-effect models, and obtained similar results for SVR (random-effect model 96.5%, 95% confidence interval [CI] 94.6 to 97.7, fixed-effect model 96.2%, 95% CI 94.7 to 97.3).

3.37 The ERG commented that the meta-analysis only provided illustrative information about the average efficacy of 3D across a range of the licensed treatments in people with genotype 1 HCV. It noted that the company did not use the meta-analysis findings for the economic analyses.

3.38 The ERG agreed that it was not possible to do a robust network meta-analysis with the trials included in the company's submission. However, it commented that a network meta-analysis of the comparator treatments would have been preferable for estimating their effectiveness for the economic analyses. The ERG also noted that it would be possible to do a network meta-analysis for the population included in the ongoing MALACHITE trials (which directly compare 3D with telaprevir treatments).

ERG comments on the cost effectiveness

3.39 The ERG commented that in general, the modelling approach by the company was reasonable and consistent with the sources of evidence used in developing the model.

3.40 The ERG commented that the company did not compare the baseline characteristics of the population in the clinical audit (used to inform the baseline characteristics of the modelled population) with the baseline characteristics of the population in the clinical trials from which the clinical data were obtained.

3.41 The ERG was concerned that the method used by the company to estimate average duration of the treatments may not fully capture early stopping rules for patients unlikely to have an SVR with peginterferon-based treatments, or who had response-guided treatment with telaprevir or boceprevir. It also noted that the company used the same SVRs for both interferon-eligible and interferon-ineligible populations without justification.

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3.42 The ERG noted that using SVR for simeprevir from the intention-to-treat population of the trials would underestimate its effectiveness. This is because the intention-to-treat population included people with Q80K polymorphism, which causes resistance to simeprevir and the 'true' SVR would be higher in people for whom simeprevir is licensed.

3.43 The ERG commented that the model outcomes should be interpreted with caution because the SVRs were from different trials and there was no statistical adjustment to account for the heterogeneity between trials. The ERG suggested that an alternative to the company's approach could be to derive a consistent evidence network for the comparators in the model, then do a threshold analysis when introducing 3D and 2D into the model.

3.44 The ERG noted that to populate the model, the company generalised some SVRs across populations with different characteristics such as HCV genotype and fibrosis stage. Sometimes this relied on data from small subgroups and on analyses for which the original trials were not powered. The ERG stated that the modelling did not reflect the additional uncertainty introduced by these assumptions.

3.45 The ERG questioned the rationale for using different on-treatment utility decrements or gains for 3D and 2D stratified by fibrosis stage and treatment history for each genotype subtype. The ERG commented that the company did not discuss the clinical interpretation or statistical interaction of the different on-treatment utility gains or decrements identified in the trials. The ERG was concerned that the modelling of on-treatment utility difference, which was supposed to capture the disutility associated with adverse events, showed a utility gain for a number of groups (meaning that people are better on treatment than off it). The ERG commented that this could double count the utility benefit associated with SVR, which was already captured by the change in the health state from disease to recovery.

3.46 The ERG also questioned the method used for the on-treatment utility difference calculation. The calculation was based on people's responses at the end of treatment, which was likely to miss people who had stopped treatment because of adverse events. However, the ERG acknowledged that this is less likely to be a significant problem, because only a few people stopped treatment in the trials

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because of adverse events.

3.47 For scenario 1 of the utility analysis, the ERG could not independently verify the utility gain associated with SVR estimated from trials because no details were provided by the company. For scenario 2, the ERG commented that no methodological detail was provided by the company on how it estimated utility values for each health state. The ERG noted that the company used 4 different values for each health state based on HCV genotype (1 and 4) and treatment history (previously untreated or previously treated). The ERG highlighted that in some cases utility values for the recovery states were lower than the corresponding disease states, for example, the utility values for the recovery states from the compensated cirrhosis states were lower than for the compensated cirrhosis states for genotype 1 HCV (both previously untreated and previously treated) and previously untreated genotype 4 HCV.

3.48 The ERG noted that the model did not allow for the methodological uncertainty from unadjusted indirect comparisons of alternative treatments. The ERG also noted that the company did not provide any sources or rationales for variation around parameter values, except for SVRs. The ERG also noted that the company presented only charts showing multiple cost-effectiveness acceptability curves without providing any summary results or comparison with the deterministic results and many presented analyses were not relevant to the revised base case. The ERG highlighted that the probabilistic analyses did not capture additional uncertainty introduced by data imputation as well as uncertainties arising from using SVR from different populations. Therefore the analyses were likely to underestimate the uncertainty in the cost-effectiveness results.

Additional evidence

3.49 The company submitted revised cost-effectiveness analyses using reduced prices for 3D and 2D based on contract pricing arrangements between the company and the Commercial Medicines Unit. The contract prices are the relevant prices paid by the NHS for 3D and 2D and are commercial in confidence. The ICERs are also commercial in confidence because they allow the contract prices to be calculated. Using the contract prices, the base-case ICERs for 3D and 2D with or without ribavirin compared with the relevant comparators from the

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fully incremental analyses were below £20,000 per QALY gained for all genotypes considered, regardless of the presence of cirrhosis or treatment history.

3.50 The company also presented separate analyses using the utility assumptions in scenario 1 and scenario 2 of the original analysis (see section 3.23). For scenario 1, which was the Committee's preferred scenario, the ICERs for 3D and 2D with or without ribavirin were also below £20,000 per QALY gained, except for the untreated genotype 4 HCV subgroup without cirrhosis. In this group, the ICER for 2D and ribavirin compared with peginterferon alfa and ribavirin was above £20,000 per QALY gained but below £30,000 per QALY gained. The company emphasised that the utility in scenario 1 underestimates the quality-of-life benefits of an SVR because the final EQ-5D values were collected before people were aware of their SVR status. Therefore, the psychological and emotional benefits of being cured were less likely to be captured. The company also expressed concerns that the approach taken by the Committee was inconsistent with other related hepatitis C appraisals, in which higher utility values from published studies were accepted. For scenario 2, the ICERs for 3D and 2D with or without ribavirin were all under £20,000 per QALY gained.

3.51 The ERG commented that it was able to replicate the company's results. It confirmed that the model inputs and assumptions were consistent with those in the company's original analysis, with the exception of the contract prices.

3.52 Full details of all the evidence are in the committee papers.

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4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ombitasvir–paritaprevir–ritonavir with or without dasabuvir, having considered evidence on the nature of chronic hepatitis C and the value placed on the benefits of ombitasvir–paritaprevir–ritonavir with or without dasabuvir by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee heard from the clinical and patient experts about the nature of chronic hepatitis C. The patient expert stated that some people with chronic hepatitis C do not have any symptoms, but others may have chronic fatigue, mood swings and symptoms of sexual dysfunction. The severity of symptoms does not depend on the stage of fibrosis. The clinical and patient experts also commented that the psychological effect of having chronic hepatitis C can impair people's social life and ability to work, and that people can have anxiety about transmitting the virus. There is also stigma about having chronic hepatitis C because it is associated with drug use. The Committee heard from the patient expert that people who have chronic hepatitis C are a disadvantaged population. The patient expert anticipated that the availability of clinically effective treatment options of short treatment duration, such as ombitasvir–paritaprevir–ritonavir with dasabuvir (3D) and ombitasvir–paritaprevir–ritonavir without dasabuvir (2D), will encourage more people to seek diagnosis and treatment. It would also allow access to treatment for people who have found it difficult to access treatment before, such as people in prison, people who use injectable drugs and migrant populations. The Committee recognised the effect of chronic hepatitis C on the lives of people with the virus. It concluded that treatments that give very high levels of sustained virological response (which is considered equivalent to a cure), and so help reduce the rate of hepatitis C virus (HCV) transmission and the stigma associated with having chronic hepatitis C, are of major importance.

4.2 The Committee discussed the clinical management of chronic hepatitis C in adults. It heard from the clinical experts that treatment decisions and response to treatment are influenced by HCV genotype, level of liver damage, comorbidities and treatment history. The Committee was aware that 3D and 2D have a marketing authorisation in the UK for adults with genotype 1a, 1b, or 4 HCV. For

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people with genotype 1 HCV, the Committee noted that boceprevir plus peginterferon alfa and ribavirin or telaprevir plus peginterferon alfa and ribavirin (see NICE's previous technology appraisal guidance on boceprevir for the treatment of genotype 1 chronic hepatitis C and telaprevir for the treatment of genotype 1 chronic hepatitis C) are commonly used, and that for people with genotype 1 or 4 HCV, peginterferon alfa plus ribavirin is also used in clinical practice (see NICE's technology appraisal guidance on peginterferon alfa and ribavirin for the treatment of chronic hepatitis C, peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C and interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C). The clinical experts highlighted that some people with chronic hepatitis C would choose not to have treatment with peginterferon alfa plus ribavirin because it can be associated with severe side effects, such as fatigue, neuropsychological effects and flu-like symptoms. The Committee also heard from the clinical and patient experts that interferon-based treatment may cause chronic side effects (such as insulin-dependent diabetes) that need additional long-term management. It may therefore pose another barrier to people starting and completing treatment. Without treatment people risk further disease progression, for example, to cirrhosis. The Committee recognised the importance of having further treatment options available for people with chronic hepatitis C, and that interferon-free treatments, such as 3D and 2D, would provide a valuable treatment option.

4.3 The Committee discussed whether the technologies in the NICE scope that had recently been granted a marketing authorisation for treating adults with chronic hepatitis C were established clinical practice in England. The Committee was aware that:

- NICE's previous technology appraisal guidance on simeprevir for treating chronic hepatitis C recommends simeprevir plus peginterferon alfa and ribavirin as an option for treating genotype 1 and 4 chronic hepatitis C.
- NICE's technology appraisal guidance on sofosbuvir for treating chronic hepatitis C recommends sofosbuvir plus peginterferon alfa and ribavirin as an option for treating genotype 1 HCV. For genotype 4 HCV this combination is recommended only for people who have cirrhosis.

  The Committee concluded that sofosbuvir plus peginterferon alfa and ribavirin, as well as simeprevir plus peginterferon alfa and ribavirin, as

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recommended in NICE guidance, were relevant comparators for 3D and 2D.

4.4 The Committee considered whether best supportive care was a relevant comparator for 3D and 2D. It was aware that best supportive care, which may include watchful waiting, may be considered an appropriate option for some people. However, it was also aware that this option would likely become a less common choice because direct-acting antivirals can treat hepatitis C effectively, with relatively short durations of treatment and without interferon. The Committee noted that in addition to 3D and 2D, there are other new interferon-free, direct-acting antivirals, for example daclatasvir plus sofosbuvir, ledipasvir–sofosbuvir, simeprevir plus sofosbuvir, and sofosbuvir plus ribavirin. However, it was aware that these are not yet established practice in the NHS. Therefore the Committee concluded that, at present, best supportive care (watchful waiting) was still an appropriate comparator in some populations. The Committee also concluded that for people who cannot have interferon-based treatments, best supportive care was the appropriate comparator.

4.5 The Committee discussed the treatment duration and specific treatment regimens for 3D and 2D for chronic hepatitis C. The Committee noted that the summary of product characteristics recommends different regimens of 3D in terms of concomitant administration of ribavirin and duration of treatment for the subtypes of genotype 1 HCV (1a and 1b). The Committee discussed whether subtypes of genotype 1 HCV were routinely identified in clinical practice and whether the subtypes were managed differently. The Committee heard from the clinical experts that subtypes are identified in clinical practice but that sometimes mixed genotype 1 HCV infection is identified. The Committee noted that the summary of product characteristics recommends using the treatment regimen for subtype 1a HCV if the subtype is not known or for people with mixed genotype 1 HCV infection. The Committee also heard from the clinical experts that genotype 1b HCV is easier to treat with interferon-based regimens than genotypes 1a and 4 HCV and that genotype 1b HCV needs only a short duration of response-guided treatment based on rapid virological response. The Committee was aware that separate clinical effectiveness data for 3D regimens were available for the 1a and 1b subtypes of genotype 1 HCV. The Committee concluded that it would examine the clinical and cost-effectiveness evidence for treating subtypes of genotype 1 HCV separately.

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4.6 The Committee was aware that for people with genotype 1a or 4 HCV and with compensated cirrhosis, the summary of product characteristics recommends a 24-week treatment duration. However, it heard from the company that based on the results from TURQUOISE II (also presented in the summary of the product characteristics), many people with genotype 1a HCV with cirrhosis would have a 12-week treatment, and that the 24-week treatment would be reserved for a subgroup of people who have had treatment before and who did not respond to initial interferon-based therapy. The clinical experts were not in a position to confirm this because there is very limited UK experience with 3D and 2D. The Committee noted that the SVRs in all subgroups of people with genotype 1a HCV with cirrhosis for both treatment durations were more than 90%, except in people who have had treatment before and who did not respond to initial interferon-based therapy. However, the Committee understood that the Committee for Human Medicinal Products (CHMP) decided to recommend a 24-week treatment because of the substantially higher relapse rate seen in people who had the 12-week treatment than in those who had the 24-week treatment in TURQUOISE II (see section 3.27). The Committee noted the company's opinion that the marketing authorisation allows for 12-week treatment in some people with genotype 1a HCV with cirrhosis, specifically for those who have 3 favourable baseline laboratory values, that is alpha fetoprotein (AFP) less than 20 ng/ml, platelets 90×10^9/litre or more and albumin 35 g/litre or more (see section 3.28). The Committee discussed the CHMP's clarification of the marketing authorisation about a 12-week treatment for people with genotype 1a HCV with cirrhosis. This stated that the cut-offs used to define favourable characteristics were 'clinically arbitrary' and 'fraught with uncertainty' and the CHMP 'could not make any recommendation on a 12-week treatment'. The Committee agreed that the regulatory process had not established a benefit-risk balance for a 12-week treatment in people with genotype 1a HCV with cirrhosis. The Committee therefore concluded that in its opinion, any treatment for a shorter duration than 24 weeks in people with genotype 1a HCV with cirrhosis would be considered outside the marketing authorisation.

Clinical effectiveness

4.7 The Committee considered the quality of the clinical trial evidence for the 3D treatments. It was aware that the trials in the company submission did not include

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any of the comparators listed in the final scope issued by NICE, but acknowledged that with treatments for chronic hepatitis C rapidly evolving, this was to be expected. The Committee was aware that the trials for genotype 1 HCV were designed with the European Medicines Agency, which accepted that historical comparisons with telaprevir were sufficient to demonstrate efficacy. The Committee noted that the ongoing MALACHITE I and MALACHITE II trials directly compare 3D with telaprevir in people with genotype 1 HCV. It was reassured that the interim results from these trials were in line with the results of completed trials. The Committee acknowledged the high SVR12 rates reported in all the trials and heard from the clinical and patient experts that the results in people with genotype 1 HCV were impressive. The Committee noted the weaknesses associated with studies that used historical controls rather than a conventional control group, but concluded that the trials showed that the 3D treatments were effective in people with genotype 1 HCV.

4.8 The Committee considered the clinical effectiveness evidence for 2D in people with genotype 4 HCV. The Committee noted that there were limited data available in people with genotype 4 HCV. It agreed that this increased the uncertainty about whether the SVR rates from the genotype 4 HCV population would be seen in clinical practice. The Committee noted that 2D was studied in a phase 2 trial that included only people with genotype 4 HCV without cirrhosis, but that the marketing authorisation also included people with genotype 4 HCV with compensated cirrhosis. The Committee was aware that this population was included in the marketing authorisation on the basis that 2D is effective in genotype 1b HCV with cirrhosis, and by extrapolation, also in genotype 4 HCV with cirrhosis. It questioned whether the SVRs for people with genotype 1b HCV could be generalised to people with genotype 4 HCV. The Committee was aware that generally genotype 1b HCV is considered easier to treat than genotype 4 or 1a HCV and discussed whether it would have been more appropriate to extrapolate SVR from genotype 1a HCV. The Committee noted that no data for the effectiveness of 2D in genotype 1a HCV were available because people with genotype 1a HCV were not included in PEARL I. The Committee remained concerned about the small numbers of people with genotype 4 HCV included in the evidence base. However, it concluded that it would accept that 2D would potentially demonstrate a similar treatment effect in people with genotype 4 HCV with cirrhosis and people with genotype 1b HCV with cirrhosis.

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4.9 The Committee considered the clinical effectiveness evidence for 3D and 2D in people who cannot have interferon. The Committee understood that these people cannot have interferon because of a medical or psychiatric comorbidity or are unwilling to have interferon because of possible side effects. The Committee heard from the company that although interferon eligibility was not recorded at baseline in the trials, a post-hoc analysis of people with depression (a contraindication to interferon treatment) from SAPPHIRE I, SAPPHIRE II and TURQUOISE II indicated that there was no significant difference in the SVR for this group and the SVR for the whole trial populations. The Committee noted that the company did not provide this post-hoc analysis in its submission, but agreed that there was no reason to assume that the effectiveness of 3D and 2D would differ depending on eligibility for interferon.

4.10 The Committee considered the safety data included in the company's submission and noted that the adverse events reported in the trials were generally consistent with those reported in other studies for hepatitis C treatments. It heard from the clinical experts that 3D and 2D were assumed to have a better safety profile than interferon-containing treatments, and most adverse events reported in the trials were likely to be related to ribavirin rather than 3D and 2D. The Committee concluded that the adverse events associated with 3D and 2D were generally tolerable and 3D and 2D have a better safety profile than interferon-containing treatments.

4.11 The Committee discussed the company's approach to estimating the relative effectiveness of 3D and 2D (with or without ribavirin) compared with the comparators in the final scope issued by NICE. The Committee noted that for the licensed 3D treatments, when data were available from more than 1 trial, the company estimated SVR by simple pooling of the numbers of people whose HCV responded and the total number of people in the trials. The company compared this with the SVRs of the comparators from different trials without any statistical adjustment. The Committee noted that the company did not attempt a mixed treatment comparison because most of the efficacy data for 3D and 2D were from single treatment arms of the trials. It also noted that the results from such a comparison can be difficult to interpret because of the different characteristics of those recruited to the trials. However, it understood from the Evidence Review Group (ERG) that it would have been possible to do a mixed treatment comparison for genotype 1 HCV by including data from the ongoing MALACHITE

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trials. The Committee agreed that the company's approach was not robust and leads to considerable uncertainty in determining the size of the true treatment effect. The Committee also understood from previous NICE technology appraisals for hepatitis C that the SVRs were likely to depend on the characteristics of the populations recruited into the studies, particularly for comparator therapies such as peginterferon alfa plus ribavirin, which may affect the relative treatment effect. The Committee was concerned that the company had selected SVRs from single treatment arms of the trials, particularly because this uncertainty was not captured in the company's estimates of cost effectiveness. The Committee concluded that the company's evidence for estimating the relative effectiveness of 3D and 2D (with or without ribavirin) in genotypes 1 and 4 HCV was not robust, and therefore this uncertainty should be taken into account in the decision-making.

Cost effectiveness

4.12 The Committee considered the company's economic model, the assumptions underlying the values of the parameters, additional analyses by the company and the critique and exploratory analyses from the ERG. The Committee noted that the structure of the model representing the natural history of the disease was similar to models submitted for other NICE technology appraisals for chronic hepatitis C. The Committee was aware of the ERG's concerns that the original model was developed to evaluate interferon-based treatments and might not fully represent the course of the disease in people who are not eligible for interferon. However, the Committee concluded that the structure of the company's model was acceptable for its discussions.

4.13 The Committee noted that the company presented 3 separate analyses; the base-case using a utility benefit of 0.05 from Wright et al., scenario 1 using utility data from the trials and scenario 2 using alternative utility data from the trials (see section 3.23). At the previous meeting, the Committee concluded that the health state values used in scenario 2 were uncertain and not reliable. Therefore it did not consider this scenario any further. At the previous meeting, the Committee also concluded that the utility benefit for SVR estimated from the trials was the most accurate estimate it had seen and that scenario 1 was the most plausible scenario to inform its decisions. However, it noted the comments

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during the previous meeting and the company's comments on the appraisal consultation document that the utility gain in scenario 1 underestimates the quality-of-life benefits of an SVR. The Committee agreed that because the final EQ-5D values were collected before people were aware of their SVR status, the psychological and emotional benefits of being cured were less likely to be captured. The Committee was aware that higher utility benefits from Wright et al. (0.05) and Vera-Llonch et al. (0.041) had been accepted in previous and ongoing NICE technology appraisals for chronic hepatitis C. The Committee emphasised that utility values derived from trials are preferred to those estimated from other sources. However, because the utility benefit from the trials in this appraisal was likely to be underestimated, the Committee concluded that the most appropriate estimate would likely lie between the trial estimate in scenario 1 and the estimate of 0.05 used in the base case.

4.14 The Committee considered the costs used in the company's model. It noted that the list prices of 3D and 2D were used in the original analyses, whereas confidential contract prices were used in the company's revised analyses. The Committee understood that the contract prices were the relevant prices the NHS pays for 3D and 2D. The Committee noted that NICE's guide to the methods of technology appraisal indicates a preference for using nationally available price reductions in the reference-case analysis to reflect the price relevant to the NHS. It understood that analyses based on price reductions for the NHS would only be considered if the reduced prices are transparent and consistently available across the NHS, and if the period for which the specified prices are available is guaranteed. The Committee noted from the evidence submitted by the company that the contract prices were nationally available in England. It was also satisfied that the contract frameworks were transparent because they can easily be accessed by NHS organisations through the Commercial Medicines Unit. The Committee understood that the contract prices were fixed for the duration specified in the framework agreement, after which they will be reviewed annually, and the prices were likely to be the maximum the NHS would pay. The Committee concluded that the contract prices were the most relevant prices to the NHS and therefore the appropriate prices on which to base its decision. It also concluded that its recommendations using the contract prices are conditional on the prices not rising above those considered in this appraisal, otherwise, the guidance will need to be considered for review.

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Recommendations

4.15 Having concluded that the most plausible scenario would likely lie between scenario 1 (which incorporated utility gain as estimated from the trials) and the base-case analysis (which incorporated the utility gain of 0.05 from Wright et al. (see section 4.13), the Committee discussed the corresponding revised incremental cost-effectiveness ratios (ICERs) for 3D and 2D with or without ribavirin compared with the relevant comparators from the fully incremental analysis.

Genotype 1b

4.16 The Committee noted that the ICERs using the contract prices for 3D or 3D plus ribavirin for the 12-week treatment, in all subgroups based on the treatment history and presence of cirrhosis, were below £20,000 per quality-adjusted life year (QALY) gained for both the base case and scenario 1 analyses. The Committee concluded that the 12-week 3D treatments were a cost-effective use of NHS resources for treating genotype 1b HCV.

Genotype 1a

4.17 The Committee noted that the ICERs using the contract prices for 3D plus ribavirin for the 12-week treatment in people without cirrhosis and the 24-week treatment in people with compensated cirrhosis, were below £20,000 per QALY gained regardless of treatment history, for both the base case and scenario 1 analyses. The Committee concluded that 3D plus ribavirin could be considered a cost-effective use of NHS resources in people with genotype 1a HCV without cirrhosis (12-week treatment duration), and with cirrhosis (24-week treatment duration).

Genotype 4

4.18 The Committee noted that the ICERs using the contract prices for 2D plus ribavirin for the 24-week treatment in people with genotype 4 HCV with

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compensated cirrhosis, regardless of treatment history, were below £20,000 per QALY gained for both the base case and scenario 1 analyses. For the 12-week treatment in people without cirrhosis, the Committee noted that the ICER using the contract price for the previously treated subgroup was below £20,000 per QALY gained for both the base case and scenario 1 analyses. However, for the previously untreated subgroup without cirrhosis, the base-case ICER using the contract price was below £20,000 per QALY gained, whereas the ICER for scenario 1 using the contract price was above £20,000 per QALY gained but below £30,000 per QALY gained. Based on its previous conclusion on the most appropriate scenario (see section 4.13), the Committee agreed that the most plausible ICER would likely be below or at most, approximately £20,000 per QALY gained. Therefore, the Committee concluded that 2D plus ribavirin could be considered a cost-effective use of NHS resources in people with genotype 4 HCV without cirrhosis (12-week treatment duration), and with cirrhosis (24-week treatment duration).

Innovation

4.19 The Committee discussed whether 3D and 2D could be considered innovative, and whether the company's economic analysis had captured all changes in health-related quality of life. The Committee agreed that compared with current treatment, 3D and 2D offer oral, shortened, interferon-free treatments, which are particularly important to people, and a major development in the clinical management of chronic hepatitis C. The Committee therefore acknowledged that 3D and 2D are valuable new therapies for treating chronic hepatitis C. The Committee agreed that there were other benefits for people with chronic hepatitis C (for example, possible regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV, improved earning capacity) that were not captured in the QALY calculation and that, if taken into account, were likely to decrease the ICERs. However, the Committee considered that it had taken these potential benefits into account in its conclusions on the cost effectiveness of 3D and 2D for each population.

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NHS England

4.20 The Committee discussed NHS England's submission relating to:

- the implementation of 3 oral treatments for hepatitis C in the NHS (ledipasvir–sofosbuvir, daclatasvir and ombitasvir–paritaprevir–ritonavir with or without dasabuvir)
- NICE's general duties 'to have regard to the broad balance between benefits and costs of the provision of health services or of social care in England and the degree of need of persons for health services or social care in England'.

  The Committee understood that NHS England considered these new oral treatments to be excellent options, but was concerned about the increase in investment and capacity needed for their implementation. The Committee heard from the patient expert that people with chronic hepatitis C appreciated the capacity constraints placed on the NHS in delivering treatment for every eligible person. The Committee recalled that treatment decisions are influenced by clinical characteristics including HCV genotype, level of liver damage, comorbidities and treatment history (see section 4.2). With these factors in mind, people with chronic hepatitis C may accept treatment being prioritised for those with the highest unmet clinical need (including some people without cirrhosis), potentially determined by multidisciplinary teams.

4.21 The Committee heard from NHS England that up to 20,000 people could access treatment each year if NICE recommended these treatments for people with chronic hepatitis C (including people without cirrhosis). However, the Committee understood from the responses to the NHS England submission that this estimate was too high. The Committee heard from the clinical experts that a more realistic estimate for the number of people accessing treatment in England was likely to be between 7000 and 10,000 each year. The Committee was aware that NHS England considered that treating 7000 people with these new oral treatments each year would not be affordable within the current NHS budget. The Committee acknowledged that there would be significant impact on the total budget for specialised services associated with making these drugs available in the NHS. However, the Committee noted the responses from consultees on NHS England's submission that the estimates presented by NHS England were not

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robust, and that they omitted potential savings from reducing transmission of HCV. The Committee further understood that NHS England is exploring other ways of managing the financial impact of using these new drugs, such as tendering, and that it could be argued that the rebate provided by companies as part of the 2014 Pharmaceutical Price Regulation Scheme (PPRS) payment mechanism could be considered as a way of managing the budgetary impact of access to these treatments. The Committee understood, in this context, that one of the key objectives of the PPRS is to 'improve access to innovative medicines commensurate with the outcomes they offer patients by ensuring that medicines approved by NICE are available widely in the NHS'.

4.22 The Committee recognised that NICE's guide to the methods of technology appraisal indicates that there needs to be increasing certainty of the cost effectiveness of a technology as the NHS budget impact of its adoption increases. However, the Committee noted that the ICERs were generally below £20,000 per QALY gained for ombitasvir–paritaprevir–ritonavir with or without dasabuvir for the populations specified in the marketing authorisation. The Committee emphasised that, if the uncertainties were accounted for in the modelling of the cost effectiveness (for example, incremental QALYs gained from an SVR12, the costs and benefits associated with treatment of reinfection, and savings from preventing HCV transmission), the ICERs were likely to remain below £20,000 per QALY gained.

4.23 The Committee understood that, given the rapid sequential assessment of direct-acting antiviral drug combinations now licensed for treating hepatitis C, it will be worthwhile exploring whether there are combinations or sequences of treatments, for example by genotype, treatment experience or cirrhosis status, that could be of particular value to people with chronic hepatitis C, clinicians and the NHS. The Committee agreed that further work by NICE to support this should be started as soon as possible.

4.24 The Committee discussed comments received from NHS England at consultation that proposed an 'only in research' recommendation for people with untreated genotype 1 HCV without cirrhosis. The Committee understood from NHS England that a clinical trial, STOP-HCV-1, will assess SVR rates in people with untreated genotype 1 HCV without cirrhosis who have direct-acting antiviral drugs, including 3D, for shorter durations than stipulated in the marketing authorisation.

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The Committee was aware that the final protocol has not been agreed and STOP-HCV-1 has not started. It considered that the clinical effectiveness evidence available for 3D for people with untreated genotype 1 HCV without cirrhosis was more robust than the evidence available for other populations considered in this technology appraisal and that the ICER was below £20,000 per QALY gained. The Committee further agreed that its recommendation would not stop people from taking part in the proposed STOP-HCV-1 trial because the treatment of chronic hepatitis C will be managed through established operational delivery networks in the NHS. The Committee concluded that an 'only in research' recommendation was not appropriate for 3D in people with untreated genotype 1 HCV without cirrhosis.

Pharmaceutical Price Regulation Scheme

4.25 The Committee considered whether it should take into account the consequences of the PPRS 2014, and in particular the PPRS payment mechanism, when appraising ombitasvir–paritaprevir–ritonavir with or without dasabuvir. The Committee noted NICE's position statement about this, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal of ombitasvir–paritaprevir–ritonavir with or without dasabuvir. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the cost effectiveness of ombitasvir–paritaprevir–ritonavir with or without dasabuvir.

Equality issues

4.26 The Committee noted the potential equality issue raised by consultees that minority ethnic groups and people with HIV co-infection are more highly represented in the genotype 4 HCV population than in the genotype 1 HCV population. The Committee also noted the consultation comment from the Haemophilia Society that any delay in access to treatment would have a

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significant adverse impact on people with haemophilia and other bleeding disorders. However, having decided that 3D and 2D treatments should be recommended for all the groups specified in the marketing authorisation, the Committee concluded that no further consideration of these potential equality issues was necessary to meet NICE's obligation to promote equality of access to treatment. The Committee also noted the comment from the company stating that the efficacy of 3D and 2D is not expected to differ in people with HIV co-infection. Therefore recommendations on the use of 3D or 2D should not differ for people with or without HIV co-infection. The Committee noted that the summary of product characteristics recommends the same treatment regimens for people with HIV co-infection. The Committee was satisfied that its recommendations do not restrict access to 3D and 2D treatments for people with HIV co-infection.

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5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has chronic hepatitis C and the healthcare professional responsible for their care thinks that ombitasvir–paritaprevir–ritonavir with or without dasabuvir is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The contract prices used for decision-making in this appraisal are the relevant prices the NHS pays for ombitasvir–paritaprevir–ritonavir and dasabuvir. These prices are based on contract pricing arrangements between the company and the Commercial Medicines Unit. The contract prices are commercial in confidence. Any enquiries from NHS organisations about the contract prices used in this appraisal should be directed to the Commercial Medicines Unit.

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6 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, Queen's 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, Mortimer Medical Practice, Herefordshire

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Professor David Bowen
Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital, Cardiff

Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon
Professor of Health Economics, University of Sheffield

Mrs Susan Dutton
Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Alexander Dyker
Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

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

Professor Paula Ghaneh
Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin
Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

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

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Dr Tim Kinnaird
Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Dr Warren Linley
Independent Pharmacist and Health Economist

Dr Malcolm Oswald
Lay Member

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

Dr Mohit Sharma
Consultant in Public Health, Public Health England

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

Guideline representatives

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

Professor Matthew Hickman
Professor of Public Health and Epidemiology, University of Bristol

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.

Anwar Jilani
Technical Lead

Nwamaka Umeweni and Nicola Hay

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Technical Advisers

Kate Moore
Project Manager

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7 Sources of evidence considered by the Committee

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

- Jones J, Pickett K, Chorozogolou M, et al. Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C: A Single Technology Appraisal. Southampton Health Technology Assessments Centre, March 2015

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

Company:

- AbbVie

Professional or expert and patient or carer groups:

- Haemophilia Society
- Hepatitis C Trust
- Liver4Life
- British Association for Sexual Health and HIV
- British Association for the Study of the Liver
- British HIV Association
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

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Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Gilead Sciences (sofosbuvir)
- Janssen (simeprevir, telaprevir)
- Meda Pharmaceuticals (ribavirin)
- Merck Sharp & Dohme (boceprevir, peginterferon alfa 2b, ribavirin)
- Mylan UK (ribavirin)
- Roche Products (peginterferon alfa 2a, ribavirin)
- Teva UK (ribavirin)
- Foundation for Liver Research
- Southampton Health Technology Assessments Centre (SHTAC)
- National Institute for Health Research Health Technology Assessment Programme
- Public Health England

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C by attending the initial Committee discussion and providing a written statement to the Committee or attending subsequent Committee discussions. They were also invited to comment on the ACD.

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- Professor Matthew Cramp, Consultant Hepatologist, nominated by Gilead Sciences – clinical expert
- Professor Geoff Dusheiko, Emeritus Professor of Medicine, nominated by Bristol-Myers Squibb – clinical expert
- Dr Helen Harris, Clinical Scientist and Research Associate, nominated by Public Health England – clinical expert
- Dr Ranjababu Kulasegaram, Consultant Physician, nominated by the British HIV Association and British Association for Sexual Health and HIV – clinical expert
- Dr Charles Millson, Consultant Hepatologist, nominated by the British Society of Gastroenterology – clinical expert
- Dr Terence Wong, Consultant Gastroenterologist and Hepatologist, nominated by the British Society of Gastroenterology – clinical expert
- Mr Charles Gore, Chief Executive of the Hepatitis C Trust, nominated by the Hepatitis C Trust – patient expert
- Mr Richard Hall, Co-Founder of Liver4Life, nominated by Liver 4 Life – patient expert
- Mr Robert James, nominated by the British HIV Association and British Association for Sexual Health and HIV – patient expert
- Ms Raquel Peck, nominated by the Hepatitis C Trust – patient expert

The following individuals were nominated as NHS commissioning experts by NHS England. They gave their expert and NHS commissioning personal view on ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C by attending the initial Committee discussion. They were also invited to comment on the ACD.

- James Palmer, Clinical Director, Specialised Commissioning selected by NHS England – NHS commissioning expert
- Malcolm Qualie, Pharmacy Lead, Specialised Services selected by NHS England – NHS commissioning expert

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

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comment on factual accuracy.

- AbbVie

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