NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ombitasvir–paritaprevir–ritonavir with or without dasabuvir in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ombitasvir–paritaprevir–ritonavir with or without dasabuvir in the NHS in England.

For further details, see the guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 19 August 2015

Second Appraisal Committee meeting: 03 September 2015

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

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

1 Appraisal Committee's preliminary recommendations

1.1 Ombitasvir–paritaprevir–ritonavir with or without dasabuvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1.

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

HCV genotype, liver disease stage	Treatment	Duration (weeks)	Recommendation according to treatment history	
			Untreated	Treated
1b, without cirrhosis	Ombitasvir–paritaprevir–ritonavir + dasabuvir	12	Recommended	Recommended
1b, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir + dasabuvir + ribavirin	12	Recommended	Recommended
1a, without cirrhosis	Ombitasvir–paritaprevir–ritonavir + dasabuvir + ribavirin	12	Recommended	Recommended
1a, with compensated cirrhosis	Ombitasvir–paritaprevir–ritonavir + dasabuvir + ribavirin*	24	Not recommended	Not recommended
4, without cirrhosis	Ombitasvir–paritaprevir–ritonavir + ribavirin	12	Not recommended	Recommended
4, with	Ombitasvir–	24	Not	Not

compensated cirrhosis	paritaprevir–ritonavir + ribavirin		recommended	recommended
HCV; hepatitis C virus				

1.2 It is recommended that access to the drugs used to treat hepatitis C is managed through the specialised commissioning programme put in place by NHS England with prescribing decisions made by multidisciplinary teams/centres to ensure that treatment is prioritised for patients with the highest unmet clinical need.

1.3 People whose treatment with ombitasvir–paritaprevir–ritonavir with or without dasabuvir is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

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, taken orally.

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 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 hepatitis C virus (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 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 £3100 and £6200 respectively (both excluding VAT: MIMS, February 2015). Costs may vary in different settings because of negotiated procurement discounts.

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

of adverse reactions and contraindications, see the summaries of product characteristics.

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
HCV; hepatitis C virus 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		

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Abbvie and a review of this submission by the Evidence Review Group (ERG; section 9).

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.

Genotype 1a or 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.

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

- **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.

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

Completed trials

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

Ongoing trials

- **MALACHITE I**: 3D plus ribavirin compared with telaprevir plus peginterferon and ribavirin, for previously untreated genotype 1 HCV.
- **MALACHITE II**: 3D plus ribavirin, compared with telaprevir plus peginterferon 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 and without ribavirin for genotype 1 HCV in adults who had a liver transplant.

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 characteristics		**Trial evidence** [a]			
Population	*Treatment (duration)*	*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=91)
		PEARL III	1b	3D + RBV versus 3D	3D treatment arm (n=209)
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 (n=322/473)
		SAPPHIRE II	1a and 1b	3D + RBV versus placebo	GT1a, (n=173/297)
		PEARL IV	1a	3D + RBV versus 3D	3D plus ribavirin 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: versus 2D (TN) 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 [b]			
[a] Treatment duration in trials was 12 weeks unless stated otherwise					

[b] The European Medicines Agency noted that data from PEARL I demonstrated the efficacy of 2D in genotype 1b HCV with cirrhosis and concluded that the efficacy of 2D plus ribavirin is likely to be the same.

HCV: hepatitis C virus, GT: genotype, RBV: ribavirin, TN: treatment naive, TE: treatment experienced, 2D: ombitasvir–paritaprevir–ritonavir without dasabuvir, 3D: ombitasvir–paritaprevir–ritonavir with dasabuvir

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 the marketing authorisation, and the results of trials included in the company's economic model, are presented in table 4.

Table 4 SVR12 outcome from trial arms or subgroups in which treatment matched the marketing authorisation

Population	Treatment (duration)	Trial	SVR12		
			n/N	% (95% CI)	Historical control (telaprevir, 95% CI)[1]
Genotype 1b HCV, without cirrhosis	3D (12 weeks)	PEARL III (previously untreated)	209/209	100.0 (98.2–100.0)	80 (75–84)
		PEARL II (previously treated)	91/91	100.0 (95.9–100.0)	69 (62–75)
Genotype 1b HCV, with compensated cirrhosis	3D plus ribavirin (12 weeks)	TURQUOISE II	67/68	98.5 (95.7–100.0)	Not available
Genotype 1a HCV, without cirrhosis	3D plus ribavirin (12 weeks)	SAPPHIRE I (previously untreated)	308/322	95.7 (93.4–97.9)	72 (68–75)
		PEARL IV (previously untreated)	97/100	97.0 (93.7–100.0)	72 (68–75)
		SAPPHIRE II (previously treated)	166/173	96.0 (93.0–98.9)	59 (53–65)
Genotype 1a HCV, with compensated cirrhosis	3D plus ribavirin (24 weeks)	TURQUOISE II	115/121	95.0 (91.2–98.9)	Not available
Genotype 4 HCV, without cirrhosis	2D plus ribavirin (12 weeks)	PEARL I (previously untreated)	42/42	100.00 (91.6–100)	Not available
		PEARL I (previously treated)	49/49	100.00 (92.7–100)	

[1] The data for telaprevir were from the clinical trials ILLUMINATE, ADVANCE and REALIZE

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

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. The following analyses were carried out using a random-effect model:

- all active treatment groups in completed phase III clinical trials (SAPPHIRE I, SAPPHIRE II, PEARL II, PEARL III, PEARL IV and TURQUOISE II) plus 1 phase II study, M14–103
- all treatment groups in the completed phase III trials in line with the marketing authorisation for 3D
- 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 various instruments comprising 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 the 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 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 of treatment

3.11 The company presented data on adverse reactions from the 6 completed trials evaluating 3D and the trial evaluating 2D. The most frequently reported adverse events in the trials 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 reaction ranged from 67% (for 3D in genotype 1b HCV in PEARL III) to 92% (for 3D plus ribavirin in genotype 1a in PEARL IV. Generally higher rates of adverse events were seen in the groups who had a longer treatment duration and those including 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 respectively. The structure of the model was adapted from the model used in the NICE 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 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–F1)
- moderate chronic HCV (METAVIR fibrosis stage F2–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 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. People were further divided by subtypes 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 presented and 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 and the average age of previously untreated and previously treated people at baseline was 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 and ribavirin (PR), sofosbuvir plus PR and simeprevir plus PR. In addition 3D was compared with telaprevir plus PR and boceprevir plus PR. 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.

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 definition 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 EQ-5D 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
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
HCV; hepatitis C virus		

3.22 The utility differences associated with the 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 and ribavirin in people who had previous treatment) to a utility gain of 0.110 (for boceprevir plus peginterferon 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 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 utility values for each health state used in scenario 2, as academic in confidence and therefore they cannot be presented here. The incremental cost-effectiveness ratios (ICERs) for the scenario analyses are presented below (see 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.

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 management of progressive liver disease (in people whose HCV does not respond to treatment) and post-treatment surveillance after treatment is stopped 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 recovered 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 stages, namely decompensated cirrhosis, hepatocellular carcinoma and liver transplant, were

based on the models used in the NICE 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, costs associated with on-treatment monitoring for response and adverse events to treatment.

Results

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

Table 6 ICERs according to treatments in the summary of product characteristics

Treatment	Incremental costs*	Incremental QALYs*	ICER (£/QALY gained)
Genotype 1a HCV without cirrhosis; previously untreated			
PR	NA	NA	NA
Boceprevir + PR	£9226	0.51	Extended dominance
Telaprevir + PR	£13,320	0.81	Extended dominance
Simeprevir + PR	£14,507	0.85	Extended dominance
3D + R (for 12 weeks)	£19,067	1.47	**£12,949**
Sofosbuvir + PR	£21,256	1.38	Dominated
Genotype 1a HCV without cirrhosis; previously treated			
PR	NA	NA	NA
Telaprevir + PR	£14,231	0.86	Extended dominance
3D + R (for 12 weeks)	£17,617	1.84	**£9589**
Simeprevir + PR	£18,005	0.86	Dominated
Sofosbuvir + PR	£22,429	1.31	Dominated
Genotype 1a HCV with cirrhosis; previously untreated			
PR	NA	NA	NA
Telaprevir + PR	£10,850	0.92	Extended dominance
Simeprevir + PR	£12,775	0.85	Extended

			dominance
Boceprevir +PR	£12,967	–0.11	Dominated
Sofosbuvir + PR	£16,290	1.70	£9,555
3D + R (for 24 weeks)	£46,450	2.11	**£75,360**
Genotype 1a HCV with cirrhosis; previously treated			
PR	NA	NA	NA
Telaprevir + PR	£13,823	0.68	Extended dominance
Simeprevir + PR	£17,109	0.72	Extended dominance
Sofosbuvir + PR	£18,692	1.42	£13,157
3D + R (for 24 weeks)	£44,105	2.38	£26,516
Genotype 1b HCV without cirrhosis; previously untreated			
PR	NA	NA	NA
Boceprevir + PR	£9265	0.50	Extended dominance
Telaprevir + PR	£13,271	0.82	Extended dominance
Simeprevir + PR	£14,128	0.92	Extended dominance
3D (for 12 weeks)	£18,833	1.39	**£13,515**
Sofosbuvir + PR	£23,659	0.95	Dominated
Genotype 1b HCV without cirrhosis; previously treated			
PR	NA	NA	NA
Telaprevir + PR	£11,633	1.29	Extended dominance
Simeprevir + PR	£14,376	1.46	Extended dominance
3D (for 12 weeks)	£15,489	2.09	**£7401**
Sofosbuvir + PR	£21,427	1.47	Dominated
Genotype 1b HCV with cirrhosis; previously untreated			
PR	NA	NA	NA
PR + telaprevir	£10,766	0.93	Extended dominance
3D + R (for 12 weeks)	£12,090	2.04	£5924
Simeprevir + PR	£12,136	0.94	Dominated
PR + boceprevir	£13,033	–0.12	Dominated
Sofosbuvir + PR	£20,338	1.16	Dominated
Genotype 1b HCV with cirrhosis; previously treated			
PR	NA	NA	NA
3D + R (for 12 weeks)	£7874	2.55	£3087
Telaprevir+ PR	£9159	1.25	Dominated
Simeprevir + PR	£10,640	1.51	Dominated
Sofosbuvir + PR	£16,822	1.65	Dominated
Genotype 4 HCV without cirrhosis; previously untreated			
PR	NA	NA	NA
Simeprevir + PR	£14,415	0.41	Extended dominance
2D + R for 12 weeks	£17,204	0.85	**£20,351**
Sofosbuvir + PR	£21,951	0.81	Dominated

Genotype 4 HCV without cirrhosis; previously treated			
No treatment	NA	NA	NA
2D + R for 12 weeks	£20,350	2.27	**£8977**
Simeprevir + PR	£21,236	1.72	Dominated
Sofosbuvir + PR	£28,150	1.64	Dominated
Genotype 4 HCV with cirrhosis; previously untreated			
PR	NA	NA	NA
Simeprevir + PR	£9555	0.96	£9902
Sofosbuvir + PR	£15,955	1.41	£14,238
2D + R for 24 weeks	£39,781	2.01	**£40,025**
Genotype 4 HCV with cirrhosis; previously treated			
No treatment	NA	NA	NA
Simeprevir + PR	£20,879	1.27	Extended dominance
Sofosbuvir + PR	£22,827	1.84	£12,432
2D + R for 24 weeks	£44,112	2.79	**£22,331**

* Incremental cost and QALY represent increments from reference (base-line) treatment

ICER: incremental cost-effectiveness ratio, 3D: ombitasvir–paritaprevir–ritonavir with dasabuvir, 2D: ombitasvir–paritaprevir–ritonavir without dasabuvir, NA: not applicable, PR: peginterferon and ribavirin, QALY: quality-adjusted life year, R: ribavirin.

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.

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

Population	Scenario	Previously untreated		Previously treated	
		No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis
Genotype 1a HCV	Revised base case	£12,949	£75,360	£9589	£26,516
	Scenario 1	£17,833	£92,828	£13,613	£33,332
	Scenario 2	£17,028	£65,696	£17,047	£23,296
Genotype 1b HCV	Revised base case	£13,515	£5924	£7401	£3087
	Scenario 1	£18,538	£7316	£10,480	£3861
	Scenario 2	£17,431	£4837	£13,831	£2477
Genotype 4 HCV	Revised base case	£20,351	£40,025	£8977	£22,331

	Scenario 1	£27,422	£48,791	£13,027	£27,877
	Scenario 2	£18,673	£38,911	£8370	£17,355
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 and ribavirin treatment at all (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. 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/L or more and albumin 35 g/L 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 and ribavirin treatment at all 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 plus ribavirin were £5985 per QALY gained for the previously untreated HCV group and £8812 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 genotype 4 HCV with cirrhosis. In these 2 populations sofosbuvir plus peginterferon 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 but noted that one included phase II study (AVIATOR) did not meet the inclusion criteria. This was because in that study,

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 essentially 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 or the other comparators relevant to the decision problem. During the clarification stage, the company stated that it was not possible to examine the baseline characteristics for the specific matched historical controls, because individual patient data for the baseline characteristics for 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 historical comparator telaprevir trials, 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 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 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 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.

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 without any 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 doing 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 diseased 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 effects. However, the ERG acknowledged that this is less likely to be a significant problem here, because only a few people stopped treatment in the trials because of adverse effects.

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 recovered 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.

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 sexual dysfunction and 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 because of the association of chronic hepatitis C 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 disease. It concluded that treatments that give very high levels of sustained virological response (SVR; which is considered equivalent to a cure), and that consequently help reduce the rate of hepatitis C virus (HCV) transmission and the stigma associated with having chronic hepatitis C, are of significant importance.

4.2 The Committee considered the clinical management of chronic hepatitis C in adults. It was aware 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 genotypes 1a, 1b, and 4 HCV. For people with genotype 1 HCV, the Committee noted that boceprevir plus peginterferon alfa and ribavirin or telaprevir plus peginterferon alfa and ribavirin (see the NICE technology appraisal guidance on boceprevir for the treatment of genotype 1 chronic hepatitis C and telaprevir for the treatment of genotype 1 chronic hepatitis C) are commonly used, and that for people with genotypes 1 and 4 HCV,

peginterferon alfa plus ribavirin is also used in clinical practice (see the NICE 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 heard from the patient expert that the long-term effects of interferon are not well documented, but that interferon-based treatment may cause chronic side effects (such as insulin-dependent diabetes). It may therefore pose another barrier to people starting and completing treatment. Without treatment people risk further disease progression, for example, to decompensated cirrhosis or liver cancer. 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 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 technology appraisal guidance on simeprevir recommends simeprevir plus peginterferon alfa and ribavirin as an option for treating genotype 1 and 4 chronic hepatitis C. The Committee was also aware that the NICE 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 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 with effective direct-acting antivirals, it would be possible to treat people easily, 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 subtypes of genotype 1, 1a and 1b HCV. 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 the separate clinical-effectiveness data for 3D regimens were available for subtypes of genotype 1 (1a and 1b). The Committee concluded that it would examine the clinical and cost-effectiveness of subtypes of genotype 1 separately.

4.6 The Committee was aware that for people with genotype 1a and 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 at all 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 were more than 90%, except in people who have had treatment before and who did not respond at all 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 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/L or more and albumin 35 g/L 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 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 comparisons with historical results for telaprevir were sufficient to demonstrate efficacy. The Committee noted that the ongoing MALACHITE I and MALACHITE II trials directly compared 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 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 II 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 for 2D on the basis that it 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.

4.9 The Committee considered the clinical effectiveness evidence for 3D and 2D in people who cannot have interferon. The Committee understood that this population consists of people who cannot have interferon because of a medical or psychiatric comorbidity or who 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 trial. 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 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 people with 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 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 did not use the health-related quality of life data from the clinical trials to estimate the utility benefit of having an SVR in the base case or revised base-case analyses. Instead it assumed an absolute increment of 0.05 from the literature. The Committee was aware that the utility benefits from Wright et al. (0.05) and Vera-Llonch et al. (0.041) had been used in the NICE technology appraisal guidance for both sofosbuvir and simeprevir for treating chronic hepatitis C. The Committee discussed the difference between the pooled EQ-5D values at baseline and at 12 weeks after treatment in people who had an SVR in the trials. This was calculated by the company at the Committee's request and was much lower than 0.05. The Committee was aware that previously it had cautiously accepted higher values in the absence of a more robust estimate. The Committee heard that final EQ-5D values were collected before the person was aware of their SVR status and therefore, the psychological and emotional benefits of being cured were less likely to be captured. The Committee accepted that the

psychological and emotional aspects of having an SVR may not have been reflected in this estimate. However in the absence of a more robust estimate, the Committee concluded that the utility benefit for SVR estimated from the trials was the most accurate estimate it has seen so far and should be used in the cost-effectiveness analyses. The Committee was concerned that the higher utility benefit associated with SVR used in the revised base case would underestimate the incremental cost-effectiveness ratios (ICERs). The Committee concluded that the scenario that incorporated utility gain as estimated from the trials (scenario 1) was the most plausible scenario and should inform its decisions.

4.14 The Committee discussed the health state utility values estimated from the trials and used in the scenario analysis 2. The Committee noted that the health state utility values used in this scenario were higher than the health state values used in the base case or revised base case. The Committee noted that, contrary to the Committee's request for using aggregated values as used in scenario 20 of the company's original submission, the company had used 4 different sets of health state values based on HCV genotype (1 and 4), and treatment history (previously untreated or treated).The Committee was aware of the counterintuitive utility values in this scenario, which showed a lower utility for the recovery state than for the disease state, particularly for compensated cirrhosis. The Committee understood that it may be because these values are based on a small number of people in each health state. Therefore the Committee concluded that the health state values used in scenario 2 are uncertain and not reliable.

Preliminary recommendations

4.15 Having concluded that scenario 1 (which incorporated utility gain as estimated from the trials) was the most plausible scenario (see

section 4.13), the Committee discussed the corresponding ICERs for the different treatments in the summary of product of characteristics (see table 7).

Genotype 1b

4.16 The Committee noted that the ICERs 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 QALY gained for its preferred scenario. 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 for the 24-week treatment in people with genotype 1a HCV with compensated cirrhosis (£33,000 to £93,000 per QALY gained; compared with sofosbuvir plus peginterferon and ribavirin) were much higher than those for the 12-week treatment in people without cirrhosis (£14,000 to £18,000 per QALY gained; compared with peginterferon and ribavirin) for its preferred scenario. The Committee understood that this was because the treatment duration for people with cirrhosis was twice as long as for those without cirrhosis, resulting in higher treatment costs. The Committee was aware that people with compensated cirrhosis have a higher risk of developing decompensated cirrhosis or liver cancer, but noted the clinical evidence base in people with compensated cirrhosis is relatively small and the results are subject to more uncertainty. 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), but not in those with cirrhosis (24 week treatment duration).

Genotype 4

4.18 The Committee noted that as for genotype 1a HCV, the ICERs for the 24-week treatment in people with genotype 4 HCV with compensated cirrhosis were much higher (£28,000 to £49,000 per QALY gained; compared with sofosbuvir plus peginterferon and ribavirin) than those for people without cirrhosis (12-week treatment). The Committee was also aware that the company did not present any clinical trial evidence for people with genotype 4 HCV with compensated cirrhosis. In the absence of any trial evidence, the cost effectiveness based on extrapolated evidence from a different population is subject to a high degree of uncertainty. The Committee concluded that a 24-week treatment of 2D plus ribavirin could not be considered a cost-effective use of NHS resources. For the 12-week treatment in people without cirrhosis, the company noted that the ICER for previously untreated HCV (£27,000 per QALY gained; compared with peginterferon and ribavirin) is substantially higher than for previously treated HCV (£13,000 per QALY gained; compared with peginterferon and ribavirin). The Committee considered the associated uncertainty with these ICERs because the clinical effectiveness evidence was based on a small number of patients in the PEARL I trial (see section 3.1). The Committee concluded that it would recommend 2D plus ribavirin for 12 weeks only for people with genotype 4 HCV who have had treatment before.

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 3D and 2D offer oral, shortened, and 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 compared with peginterferon alfa and ribavirin. 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.

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)
- 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 were 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. With this in mind, people with chronic hepatitis C may accept prioritising treatment for those with more severe disease (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 NHS England's estimates were significantly overestimated. 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 robust, and that they omitted potential savings from reducing onwards transmission. The Committee further understood that NHS England is exploring other ways of managing the financial impact of use of these new drugs, such as tendering, and that some argue that the rebate provided by companies as part of the 2014 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 of objectives of 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 the Guide to 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 for whom it was recommended in NICE's preliminary recommendations. The Committee emphasised that, if the uncertainties were accounted for in the modelling of the cost effectiveness (for example, incremental QALYs gained from achieving SVR12, the costs and benefits associated with treatment of reinfection, and savings from prevention of onward transmission), the ICERs for the recommended regimens were likely to remain below the lower threshold of £20,000 per QALY gained.

4.23 The Committee understood that, given the rapid sequential assessment of direct antiviral drug combinations now licensed for the treatment of 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 patients, clinicians and the NHS. The Committee agreed that further work by NICE to support this should be initiated sooner rather than later.

Pharmaceutical Price Regulation Scheme

4.24 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 for

the consideration of the cost effectiveness of ombitasvir–paritaprevir–ritonavir with or without dasabuvir.

Equality Issues

4.25 The Committee noted the potential equality issue raised by the company that minority ethnic groups are more highly represented in the genotype 4 HCV population than in the genotype 1 HCV population. However, having decided that 3D and 2D treatments have been recommended in subgroups of people with genotype 1 and genotype 4 HCV for whom they could be considered a cost-effective use of NHS resources, based on the treatment regimens specified in the marketing authorisation, the Committee concluded that no further consideration of this potential equality issue was necessary to meet NICE's obligation to promote equality of access to treatment. The Committee also noted the comment from the company which stated that efficacy of 3D is not expected to differ in patients with HIV co-infection and therefore recommendations on the use of 3D or 2D should not differ for patients with or without HIV co-infection. The Committee noted that the summary of product characteristics recommended the same treatment regimens for people with HIV co-infection. The Committee was satisfied that its recommendations did not restrict access of 3D and 2D treatments for people with HIV co-infection.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title: Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C**	**Section**
Key conclusion		
The Committee noted that the company's approach to estimating the relative effectiveness of 3D (ombitasvir–paritaprevir–ritonavir with		4.11

dasabuvir) and 2D (ombitasvir–paritaprevir–ritonavir without dasabuvir) with or without ribavirin compared with the comparators was not robust, and therefore this uncertainty should be taken into account in the decision-making. The Committee noted the higher utility benefit associated with sustained virological response (SVR) used in the revised base case compared with utility gain as estimated from the trials would underestimate the incremental cost-effectiveness ratios (ICERs). The Committee concluded that the scenario that incorporated utility gain as estimated from the trials was the most plausible scenario and should inform its decisions. The Committee concluded that • for genotype 1b HCV, 12-week 3D treatments could be considered a cost-effective use of NHS resources • for genotype 1a HCV, 12-week 3D plus ribavirin treatment could be considered a cost-effective use of NHS resources only in people without cirrhosis • for genotype 4 HCV, 12-week 2D plus ribavirin treatment could be considered a cost-effective use of NHS resources only for people without cirrhosis who have had treatment before.		4.13 4.16 4.17 4.18
Current practice		
Clinical need of patients, including the availability of alternative treatments	Treatment decisions and response to treatment are influenced by HCV genotype, level of liver damage, comorbidities and treatment history. For people with genotype 1 HCV, the Committee heard that boceprevir plus	4.2 4.2

	peginterferon alfa and ribavirin or telaprevir plus peginterferon alfa and ribavirin are commonly used, and that for people with genotypes 1 and 4 HCV, peginterferon alfa plus ribavirin is also used in clinical practice. The Committee concluded that sofosbuvir and simeprevir, as recommended in NICE guidance, were relevant comparators.	4.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health–related benefits?	The Committee noted that treatment with peginterferon alfa plus ribavirin can cause severe side effects and interferon-free treatments, such as 3D and 2D, would provide a valuable treatment option. The Committee agreed that there were other benefits for people with hepatitis C (for example, possible regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV, improved earning capacity).	4.2 4.19
What is the position of the treatment in the pathway of care for the condition?	The Committee recognised the importance of having further treatment options available for people with chronic hepatitis C, and that an interferon-free treatment, such as such as 3D and 2D, would provide a valuable treatment option.	4.2

Adverse reactions	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.	4.10
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee was aware that the trials did not include any of the comparators and noted the weaknesses associated with studies that used historical controls. The Committee noted the limited available evidence in people with genotype 4 HCV.	4.7 4.8
Relevance to general clinical practice in the NHS	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 subtypes of genotype 1, 1a and 1b HCV. The Committee heard from the clinical experts that subtypes are identified in clinical practice but that sometimes mixed genotype 1 HCV infection is identified.	4.5

Uncertainties generated by the evidence	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 trial and compared this with the SVRs of the comparators from different trials without any statistical adjustment. 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 noted that there was limited evidence available in people with genotype 4 HCV and no data were available in people with genotype 4 HCV with compensated cirrhosis.	4.11 4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee was aware that for people with genotype 1a with compensated cirrhosis, the summary of product characteristics recommends a 24-week treatment duration. 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 in TURQUOISE II.	4.6

Estimate of the size of the clinical effectiveness including strength of supporting evidence	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. The Committee noted that 2D was studied in a phase II 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.	4.7 4.8
Evidence for cost effectiveness		
Availability and nature of evidence	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.	4.12
Uncertainties around and plausibility of assumptions and inputs in the economic model	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.	4.12

Incorporation of health–related quality–of–life benefits and utility values Have any potential significant and substantial health–related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee concluded that the utility benefit for SVR estimated from the trials was the most accurate estimate and should be used in the cost-effectiveness analyses. The Committee was concerned that the higher utility benefit associated with SVR used in the revised base case would underestimate the ICERs. The Committee agreed that 3D and 2D offer oral, shortened, and interferon-free treatments, which are particularly important to people, and a major development in the clinical management of 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.	4.13 4.19
Are there specific groups of people for whom the technology is particularly cost effective?	Please refer to the key conclusions above.	

What are the key drivers of cost effectiveness?	The Committee noted that the ICERs for 3D and 2D in people with genotype 1a HCV with compensated cirrhosis and genotype 4 HCV with compensated cirrhosis were much higher than those for corresponding populations without cirrhosis. The Committee understood that this was because the treatment duration for people with cirrhosis was twice as long as for those without cirrhosis, resulting in higher treatment costs.	4.17 4.18
Most likely cost–effectiveness estimate (given as an ICER)	The Committee concluded that the scenario that incorporated utility gain as estimated from the trials (scenario 1) was the most plausible scenario and should inform its decisions. The most likely ICERs for the Committee's preferred scenario (scenario 1) are presented in table 7 in the evidence section.	4.13
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	
End–of–life considerations	Not applicable	

Equalities considerations and social value judgements	The Committee noted the potential equality issue that minority ethnic groups are more highly represented in the genotype 4 HCV population than in the genotype 1 HCV population. However, having decided that 3D and 2D treatments have been recommended in subgroups of people with genotype 1 and genotype 4 HCV for whom they could be considered a cost-effective use of NHS resources, the Committee concluded that no further consideration of this potential equality issue was necessary to meet NICE's obligation to promote equality of access to treatment. The Committee also noted the comment that efficacy of 3D is not expected to differ in patients with HIV co-infection and therefore recommendations on the use of 3D or 2D should not differ for patients with or without HIV co-infection. The Committee noted that the summary of product characteristics recommended the same treatment regimens for people with HIV co-infection. The Committee was satisfied that its recommendations did not restrict access of 3D and 2D treatments for people with HIV co-infection.	4.25

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social

Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

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

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

6 Related NICE guidance

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

Published

- Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C. NICE technology appraisal guidance 331 (2015).
- Sofosbuvir for treating chronic hepatitis C. NICE technology appraisal guidance 330 (2015).
- Needle and syringe programmes. NICE public health guidance 52 (2014).
- Boceprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 253 (2012).
- Telaprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 252 (2012).
- Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance 200 (2010).
- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. NICE technology appraisal guidance 106 (2006).
- Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance 75 (2004).

Under development

- Daclatasvir for treating chronic hepatitis C. NICE technology appraisal. Publication date to be confirmed.
- Ledipasvir–sofosbuvir for treating chronic hepatitis C. NICE technology appraisal. Publication date to be confirmed.
- Hepatitis C: diagnosis and management of hepatitis C. NICE guideline. Publication date to be confirmed.

NICE pathways

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

7 Proposed date for review of guidance

7.1 It is proposed that all technology appraisal guidance recently developed by NICE for Hepatitis C will be considered for incorporation and contextualisation in the clinical guideline Hepatitis C: diagnosis and management of hepatitis C, the development of which will restarted in the next couple of months.

Dr Lindsay Smith

Chair, Appraisal Committee

July 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

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

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

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

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)
General Practitioner, West Coker Surgery, Somerset

Dr Aomesh Bhatt
Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black
General Practitioner, Mortimer Medical Practice, Herefordshire

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

Dr Alexander Dyker

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

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor John Henderson

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

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

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/Nicola Hay

Technical Adviser(s)

Kate Moore

Project Manager

9 Sources of evidence considered by the Committee

A. 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

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

I. Company:

- AbbVie

II. Professional/expert and patient/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

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

- Department of Health, Social Services and Public Safety 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

C. 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 by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Matthew Cramp, Consultant Hepatologist, nominated by Gilead Sciences – clinical expert
- Professor Geoff Dusheiko, Emeritus Professor of Medicine, nominated by BMS– clinical expert
- Dr Ranjababu Kulasegaram, Consultant Physician, nominated by British HIV Association and British Association for Sexual Health and HIV – clinical expert
- Dr Charles Millson, Consultant Hepatologist, nominated by British Society of Gastroenterology – clinical expert
- Dr Terence Wong, Consultant Gastroenterologist and Hepatologist, nominated by British Society of Gastroenterology – clinical expert
- Richard Hall, nominated by Liver 4 Life – patient expert
- Raquel Peck, nominated Hepatitis C Trust – patient expert

D. The following individuals were nominated as NHS commissioning experts by NHS England. They gave their NHS commissioning personal view on

ombitasvir–paritaprevir–ritonavir with or without dasabuvir by attending the initial Committee discussion and providing a written statement to the Committee. They are 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

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

- AbbVie