NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Sofosbuvir and velpatasvir for treating chronic hepatitis C

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of the combination of sofosbuvir and velpatasvir within its marketing authorisation for treating chronic hepatitis C.

Background

The hepatitis C virus (HCV) causes inflammation of the liver and affects the liver's ability to function. HCV is a blood-borne virus, meaning that it is spread by exposure to infected blood. Contaminated needles used to inject drugs are currently the most common route of transmission. Symptoms of chronic hepatitis C are typically mild and non-specific, including fatigue, flu-like symptoms, anorexia, depression, sleep disturbance, pain, itching and nausea. Often, people with hepatitis C do not have any symptoms, and 15 to 20% of infected people naturally clear their infections within 6 months.[1] However, most people develop chronic hepatitis which can be life-long.

Chronic hepatitis C is categorised according to the extent of liver damage, as mild, moderate, or severe (where severe refers to cirrhosis). Cirrhosis is severe scarring that has spread throughout the liver. About 30% of people with chronic hepatitis C develop cirrhosis;[2] the time for progression to cirrhosis varies, but it takes 40 years on average.[1] Cirrhosis can progress to become 'decompensated', which means the remaining liver can no longer compensate for the loss of function. A small percentage of people with chronic hepatitis and cirrhosis also develop hepatocellular carcinoma. Liver transplantation may be needed for people with decompensated cirrhosis or hepatocellular carcinoma.

The true prevalence of HCV infection is difficult to establish and likely to be underestimated because many people do not have symptoms and more than half of people with chronic hepatitis C are unaware of their infection.[3] There are 6 major genotypes and several subtypes of HCV; the prevalence of each varies geographically. Recent estimates (2012) suggest that around 160,000 people have been diagnosed with chronic hepatitis C in England, and that approximately 90% of these people are infected with genotype 1 or 3.[4]

The aim of treatment is to cure the HCV infection, and prevent liver disease progression, hepatocellular carcinoma development, and HCV transmission. The HCV genotype influences response to treatment and therefore the treatment decisions. For those with mild hepatitis C, a 'watchful waiting'

approach may be agreed between the patient and clinician on an individual basis. NICE guidance on hepatitis C (technology appraisal guidance 75 and 106) recommend combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b for people with chronic hepatitis C regardless of disease severity or genotype. Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended for people who are unable to tolerate ribavirin or for whom ribavirin is contraindicated. NICE technology appraisal guidance 200 recommends that people who have been previously treated with peginterferon alfa and ribavirin or with peginterferon alfa monotherapy have an option to receive further courses of peginterferon alfa and ribavirin. Shortened courses of combination therapy are also recommended as an option for certain patients depending on their genotype and their initial response to treatment.

For people with genotype 1 chronic hepatitis C, who have or have not been previously treated, NICE recommends telaprevir or boceprevir, each in combination with peginterferon alfa and ribavirin (NICE technology appraisal guidance 252 and 253 respectively).

For people with genotype 1 or 4 chronic hepatitis C, whose disease has or has not been previously treated, NICE recommends simeprevir plus peginterferon alfa and ribavirin (NICE technology appraisal guidance 331).

For people with genotypes 1 to 6 chronic hepatitis C, whose disease has or has not been previously treated, NICE recommends sofosbuvir plus ribavirin, with or without peginterferon alfa, for some people (NICE technology appraisal guidance 330).

The technology

Co-formulated sofosbuvir and velpatasvir (brand name unknown, Gilead Sciences) is an oral, fixed-dose combination of 2 anti-hepatitis C virus drugs. Sofosbuvir is a pan-genotypic nucleotide analogue that inhibits the non-structural protein 5B (ns5b), and velpatasvir is a pan-genotypic NS5A inhibitor.

The fixed-dose combination of sofosbuvir and velpatasvir does not currently have a marketing authorisation in the UK for treating chronic hepatitis C. It has been studied in clinical trials, with or without ribavirin, for treating genotypes 1–6 HCV in adults with or without cirrhosis. The clinical trials included people with untreated HCV and those with previously treated HCV.

Intervention(s)	Fixed-dose combination of sofosbuvir and velpatasvir

Population(s)	Adults with chronic hepatitis C: • who have not had treatment for chronic hepatitis C before (treatment-naive) • who have had treatment for chronic hepatitis C before (treatment-experienced)

Comparators	• Peginterferon alfa and ribavirin, alone (genotypes 1-6) or in combination with:
	  ○ Sofosbuvir (genotypes 1-6)
	  ○ Simeprevir (genotype 1 or 4)
	  ○ Daclatasvir (genotype 4 only; subject to ongoing NICE appraisal ID766)
	• Regimens without peginterferon alfa:
	  ○ Sofosbuvir plus ribavirin (genotypes 2 or 3)
	  ○ Ledipasvir–sofosbuvir with or without ribavirin (genotype 1, 3 or 4; subject to ongoing NICE appraisal ID742)
	  ○ Daclatasvir plus sofosbuvir with or without ribavirin (genotype 1, 3 or 4; subject to ongoing NICE appraisal ID766)
	  ○ Ombitasvir–paritaprevir–ritonavir with or without dasabuvir, co-administered with or without ribavirin (genotype 1 or 4; subject to ongoing NICE appraisal ID731)
	  ○ Watchful waiting (genotypes 1-6)

Outcomes	The outcome measures to be considered include: • sustained virological response • development of resistance to treatment • mortality • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered: • genotype • co-infection with HIV • people with and without cirrhosis • people who have received treatment before liver transplantation, and those who have received it after liver transplantation • response to previous treatment (non-response, partial response, relapsed) • people who are intolerant to or ineligible for interferon treatment. If the evidence allows, the impact of treatment on reduced onward HCV transmission will also be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals**: Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C (2015) NICE Technology appraisal 331. Review date February 2016. Sofosbuvir for treating chronic hepatitis C (2015) NICE Technology appraisal 330. Review date February 2016.

	Boceprevir for the treatment of genotype 1 chronic hepatitis C (2012) NICE Technology appraisal 253. Review date to be confirmed. Telaprevir for the treatment of genotype 1 chronic hepatitis C (2012) NICE Technology appraisal 252. Review date to be confirmed. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (2010) NICE Technology appraisal 200. Added to static list December 2013. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C' (partially updated in TA200) (2006) NICE Technology appraisal 106. Added to static list December 2013. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C' (partially updated in TA200) (2004) NICE Technology appraisal 75. Added to static list December 2013. *Appraisals in development* Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C Technology appraisals guidance. [ID731] Publication expected November 2015 Daclatasvir for treating chronic hepatitis C Technology appraisals guidance. [ID766] Publication expected November 2015 Ledipasvir-sofosbuvir for treating chronic hepatitis C Technology appraisals guidance. [ID742] Publication expected November 2015 Simeprevir in combination with sofosbuvir for treating chronic hepatitis C Technology appraisals guidance. [ID887] Publication expected June 2016 **Related guidelines**: *Guideline in development* Hepatitis C: Diagnosis and management of hepatitis C Publication date to be confirmed **Related Public Health Guidance**: Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012) NICE Public Health Guidance 43 Needle and syringe programmes (2009) NICE Public Health Guidance 18

	Related Quality Standards: Quality standard for drug use disorders (2012) NICE quality standard 23 http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp **Related NICE Pathways**: Hepatitis B and C testing (2012) NICE pathway http://pathways.nice.org.uk/pathways/hepatitis-b-and-c-testing Liver conditions NICE pathway http://pathways.nice.org.uk/pathways/liver-conditions
Related National Policy	NHS England, Manual for prescribed specialised services for 2013/14, Chapter 65, Jan 2014. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf NHS England, Clinical Commissioning Policy Statement: Treatment of chronic Hepatitis C in patients with cirrhosis. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/06/hep-c-cirrhosis-polcy-statmnt-0615.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Questions for consultation

Have all relevant comparators for sofosbuvir in combination with velpatasvir been included in the scope?

- Which treatments are considered to be established clinical practice in the NHS for chronic hepatitis C?
- Are telaprevir or boceprevir, each in combination with peginterferon alfa and ribavirin, used for treating people with genotype 1 chronic hepatitis C?

Are the regimens containing interferon relevant comparators for sofosbuvir in combination with velpatasvir?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom sofosbuvir in combination with velpatasvir is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider sofosbuvir in combination with velpatasvir will fit into the existing NICE pathway, Liver Conditions?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which sofosbuvir in combination with velpatasvir will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider sofosbuvir in combination with velpatasvir to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of sofosbuvir in combination with velpatasvir can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)

References

1. Hepatitis C Trust (2014). About hepatitis C. Accessed April 2015. Available at: http://www.hepctrust.org.uk/about-hepatitis-c
2. World Health Organisation (2015). Hepatitis C. Accessed April 2015. Available at: http://www.who.int/csr/disease/hepatitis/Hepc.pdf?ua=1

3. Department of Health (2004). Hepatitis C: Essential information for professionals and guidance on testing. Accessed April 2015. Available at: http://www.nhs.uk/hepatitisc/SiteCollectionDocuments/pdf/essential-information-for-professionals-and-guidance-on-testing.pdf
4. Public Health England (2014). Hepatitis C in the UK: 2014 report. Accessed April 2015. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/337115/HCV_in_the_UK_2014_24_July.pdf