Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of sofosbuvir–velpatasvir–voxilaprevir 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 20% of people with chronic hepatitis C develop cirrhosis;[2] the time for progression to cirrhosis varies, but it takes up to 40 years (20 years on average).[1] Cirrhosis can progress to become 'decompensated', which means the remaining liver can no longer compensate for the loss of function. Approximately 1-7% of people with chronic hepatitis and cirrhosis also develop hepatocellular carcinoma[3]. 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.[4] 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 chronic hepatitis C in England, and that approximately 90% of these people are infected with genotype 1 or 3.[5]

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.

NICE guidance on hepatitis C (NICE technology appraisal guidance 75, 106, 200, 252, 253, 330, 331, 363, 364, 365, 413 and 430) recommends:

- combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b for people with chronic hepatitis C regardless of disease severity, genotype or treatment experience.

- 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.

- telaprevir in combination with peginterferon alfa and ribavirin for people with genotype 1 chronic hepatitis C.

- boceprevir in combination with peginterferon alfa and ribavirin for people with genotype 1 chronic hepatitis C.

- sofosbuvir in combination with ribavirin, with or without peginterferon alfa, as an option for specific people with genotypes 1–6 chronic hepatitis C.

- simeprevir in combination with peginterferon alfa and ribavirin as an option for people with genotype 1 or 4 chronic hepatitis C

- ledipasvir–sofosbuvir as an option for specific people with genotype 1 or 4 chronic hepatitis C

- daclatasvir in combination with sofosbuvir, with or without ribavirin, as an option for specific people with genotype 1, 3 or 4 chronic hepatitis C

- daclatasvir in combination with peginterferon alfa and ribavirin, as an option for specific people with genotype 4 chronic hepatitis C

- ombitasvir–paritaprevir–ritonavir with or without dasabuvir or ribavirin as an option for genotype 1 or 4 chronic hepatitis C.

- elbasvir–grazoprevir, as an option for genotype 1 or 4 chronic hepatitis C.

- sofosbuvir–velpatasvir, as an option for specific people with genotype 1-6 chronic hepatitis C.

The technology

Sofosbuvir–velpatasvir–voxilaprevir (brand name unknown, Gilead Sciences) is a fixed-dose combination of 3 anti-hepatitis C virus drugs. Sofosbuvir is a pan-genotypic nucleotide analogue that inhibits the non-structural protein 5B (ns5b); velpatasvir is a pan-genotypic NS5A inhibitor; and voxilaprevir is a second generation NS3/4A protease inhibitor. Sofosbuvir–velpatasvir–voxilaprevir is taken orally.

Sofosbuvir–velpatasvir–voxilaprevir 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)	Sofosbuvir–velpatasvir–voxilaprevir
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	• Best supportive care (no active pharmacological treatment) (genotypes 1-6) • Daclatasvir in combination with sofosbuvir, with or without ribavirin (for specific people with genotype 1, 3 or 4; as recommended by NICE) • Elbasvir–grazoprevir (for genotype 1 or 4) • Ledipasvir–sofosbuvir (for specific people with genotype 1 or 4; as recommended by NICE) • Ombitasvir–paritaprevir–ritonavir with or without dasabuvir or ribavirin (for genotype 1 or 4) • Peginterferon alfa with ribavirin (for genotypes 1-6) • Sofosbuvir in combination with ribavirin, with or without peginterferon alfa (for specific people with genotypes 1-6; as recommended by NICE) • Sofosbuvir-velpatasvir (for specific people with genotype 1-6; as recommended by NICE))
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.
Other considerations	If the evidence allows the following subgroups will be considered: • genotype • co-infection with HIV • people with and without cirrhosis • previous treatment received (with or without direct-acting antiviral-containing regimens) • 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**: Sofosbuvir-velpatasvir for treating chronic hepatitis C (2017) NICE technology appraisal 430. Review date January 2020. Elbasvir-grazoprevir for treating chronic hepatitis C (2016) NICE technology appraisal 413. Review date October 2019. Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C (2015) NICE

	Technology appraisal 365. Review date to be confirmed. Daclatasvir for treating chronic hepatitis C (2015) NICE Technology appraisal 364. Review date to be confirmed. Ledipasvir-sofosbuvir for treating chronic hepatitis C (2015) NICE Technology appraisal 363. Review date to be confirmed. Simeprevir in combination with sofosbuvir for treating chronic hepatitis C (2015) Terminated NICE Technology appraisal 361. Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C (2015) NICE Technology appraisal 331. Review date to be confirmed. Sofosbuvir for treating chronic hepatitis C (2015) NICE Technology appraisal 330. Review date to be confirmed. 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 (including suspended appraisals)* 'Faldaprevir for treating genotype 1 chronic hepatitis C' Suspended NICE technology appraisal guidance [ID670]. 'Glecaprevir-pibrentasvir for treating chronic hepatitis C' Proposed NICE technology appraisal [ID1085]. Publication date to be confirmed **Related Guidelines**: *Guidelines in development*

	Hepatitis C: Diagnosis and management of hepatitis C Publication date to be confirmed. **Related Public Health Guidance/Guidelines**: 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. **Related NICE Pathways**: Hepatitis B and C testing (last updated August 2014) NICE pathway Liver conditions (last updated November 2015) NICE pathway
Related National Policy	NHS England, Manual for prescribed specialised services for 2013/14, Chapter 65, Jan 2014. NHS England, Clinical Commissioning Policy Statement: Treatment of chronic Hepatitis C in patients with cirrhosis. Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013.

References

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3. Goossens N, Hoshida Y. Hepatitis C virus-induced hepatocellular carcinoma. Clinical and Molecular Hepatology. 2015;21(2):105-114. doi:10.3350/cmh.2015.21.2.105.

4. 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

5. 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