NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ledipasvir-sofosbuvir for treating chronic hepatitis C

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ledipasvir-sofosbuvir within its licensed indication 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. However, the remainder develop chronic hepatitis C 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). About 30% of people with chronic hepatitis C will develop cirrhosis; the time for progression to cirrhosis varies, but takes 40 years on average. Cirrhosis can progress to become 'decompensated', where 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. 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 are chronically infected with HCV in England, and that approximately 90% of these people are infected with genotype 1 or genotype 3. However, more than half of people with chronic hepatitis C are unaware of their infection.

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 treatment decisions and response. 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) recommends 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 guidance also recommend telaprevir in combination with peginterferon alfa and ribavirin (NICE technology appraisal guidance 252) or boceprevir in combination with peginterferon alfa and ribavirin (NICE technology appraisal guidance 253).

The technology

Ledipasvir-sofosbuvir (brand name unknown, Gilead Sciences) is a fixed-dose combination product. Sofosbuvir is a uridine nucleotide analogue that inhibits HCV polymerase, and ledipasvir is a macrocyclic antiviral agent and an inhibitor of the HCV NS5a protein. They both act to inhibit viral replication. Sofosbuvir-ledipasvir is administered orally.

Ledipasvir-sofosbuvir does not currently have a marketing authorisation in the UK for treating chronic hepatitis C. It has been studied with and without ribavirin as an 8, 12 or 24 week regimen in adults with chronic hepatitis C genotype 1 (without HIV) who have or have not received previous treatment. It has also been studied in adults with genotypes 2, 3, 4, 5 and 6 chronic hepatitis C.

Intervention(s)	Ledipasvir-sofosbuvir with or without ribavirin
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 with ribavirin (genotypes 1-6) • Telaprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only) • Boceprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only) • Sofosbuvir in combination with ribavirin, with or without peginterferon alfa (genotypes 1-6; subject to ongoing NICE appraisal ID654) • Simeprevir in combination with peginterferon alfa and ribavirin (genotype 1 or 4) (subject to ongoing NICE appraisal [ID668]) • Simeprevir in combination with sofosbuvir, with or without ribavirin (for people who have genotype 1 or 4 disease and are ineligible for or intolerant to interferon treatment) (subject to ongoing NICE appraisal [ID668]) • Best supportive care (watchful waiting) (genotypes 1-6)
Outcomes	The outcome measures to be considered include: • sustained virological response • development of resistance to ledipasvir-sofosbuvir • 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 evidence allows the following subgroups will be considered: • Genotype • Co-infection with HIV • People with and without cirrhosis • People who have received treatment pre- and post-liver transplantation • Response to previous treatment (non-response, partial response, relapsed) • People who are intolerant to or ineligible for interferon treatment If 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 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: Technology appraisal No. 253, Apr 2012, 'Boceprevir for the treatment of genotype 1 chronic hepatitis C'. Review Proposal Date April 2015. Technology appraisal No. 252, Apr 2012, 'Telaprevir for the treatment of genotype 1 chronic hepatitis C'. Review Proposal Date April 2015. Technology appraisal No. 200, Sep 2010, 'Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C'. Guidance added to static list Dec 2013. Technology appraisal No. 106, Aug 2006, 'Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C (partially updated in TA200)'. Guidance added to static list Dec 2013 Technology appraisal No. 75, Jan 2004, 'Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C (partially updated in TA200)'. Guidance added to static list Dec 2013 Technology appraisal in preparation, ID654 'Sofosbuvir for treating chronic hepatitis C'. Earliest anticipated date of publication TBC. Technology appraisal in preparation, ID668 'Simeprevir for treating genotype 1 or 4 chronic hepatitis C'.

	Earliest anticipated date of publication January 2015. Technology appraisal in preparation, ID731 'Paritaprevir/ritonavir/ombitasvir with or without dasabuvir for treating chronic hepatitis C'. Earliest anticipated date of publication publication TBC. Proposed technology appraisal, 'Daclatasvir for treating chronic hepatitis C'. Publication TBC Related Guidelines: Clinical Guideline in Preparation, 'Hepatitis C: Diagnosis and management of hepatitis C'. Earliest anticipated date of publication TBC. Related Public Health Guidance: Public Health Guidance No. 43, Dec 2012, 'Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection'. Public Health Guidance No. 18, Feb 2009, 'Needle and syringe programmes' Related Quality Standards: Quality Standard No. 23, Nov 2012, 'Quality standard for drug use disorders' Review Proposal Date Nov 2017. Related NICE Pathways: NICE Pathway 'Hepatitis B and C'. Pathway created: Dec 2012. Available at: http://pathways.nice.org.uk/pathways/hepatitis-b-and-c-testing
Related national Policy	NHS England (2014) Interim Clinical Commissioning Policy Statement: Sofosbuvir + Daclatasvir/Ledipasvir +/- Ribavirin for defined patients with Hepatitis C http://www.england.nhs.uk/wp-content/uploads/2014/04/sofosbuvir-pol-stat.pdf Department of Health Hepatitis C Action Plan for England (Jul 2004). http://www.nhs.uk/hepatitisc/SiteCollectionDocuments/pdf/hepatitis-c-action-plan-for-england.pdf