NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Daclatasvir for treating chronic hepatitis C

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of daclatasvir in combination with other anti-hepatitis medications 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 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.

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, on an individual basis, between the patient and clinician. NICE guidance on hepatitis C (technology appraisals 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 patients who are unable to tolerate ribavirin or for whom ribavirin is contraindicated. NICE technology appraisal 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 recommends 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

Daclatasvir (brand name unknown, Bristol-Myers Squibb) is an inhibitor of a non-structural viral protein (NS5A). NS5A is a multifunctional phosphoprotein, which plays a role in hepatitis C virus replication. It is administered orally.

Daclatasvir does not currently have a UK marketing authorisation for treating people with chronic hepatitis C. It has been studied in clinical trials in combination with peginterferon alfa-2a and ribavirin compared with placebo plus peginterferon alfa-2a and ribavirin in previously untreated adults with genotype 4 HCV; and compared with telaprevir in combination with peginterferon alfa-2a and ribavirin in previously untreated adults with genotype 1 HCV. Daclatasvir in combination with peginterferon alfa- 2a and ribavirin has also been studied in single arm trials in previously untreated adults with genotype 1 HCV with or without HIV co-infection.

Daclatasvir in combination with sofosbuvir is also being studied in adults with genotype 3 HCV who have or have not been previously treated. This combination regimen is also being studied in adults with genotype 1, 2, 3, 4, 5, or 6 HCV who are also infected with HIV-1 and who have or have not received previous treatment for chronic hepatitis C. Daclatasvir in combination with sofosbuvir and ribavirin is being studied in adults with genotype 1, 2, 3, 4, 5, or 6 HCV who have cirrhosis or in those who have received a liver transplant who have or have not received previous treatment.

Intervention(s)	Daclatasvir in combination with other anti-hepatitis medications
Population(s)	Adults with chronic hepatitis C infection: • who have not been previously treated • in whom previous treatment has not resulted in a sustained virological response

Comparators	• Peginterferon alfa and ribavirin • Telaprevir in combination with peginterferon alfa and ribavirin (genotype 1 only) • Boceprevir in combination with peginterferon alfa and ribavirin (genotype 1 only) • Simeprevir in combination with peginterferon alfa and ribavirin (genotype 1 or 4) (subject to ongoing NICE appraisal) • Sofosbuvir in combination with ribavirin, with or without peginterferon alfa (subject to ongoing NICE appraisal)
Outcomes	The outcome measures to be considered include: • sustained virological response (SVR) • 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: • Co-infection with HIV • Cirrhosis status • Patients who have received a liver transplant • Response to previous treatment (non-response, partial response, relapsed) 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: 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 on static list. Technology appraisal No. 106, Aug 2006, 'Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C' (partially updated in TA200). Guidance on static list. 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 on static list. Technology appraisal in preparation, 'Sofosbuvir for treating chronic hepatitis C'. Earliest anticipated date of publication October 2014. Technology appraisal in preparation, 'Simeprevir for treating genotype 1 or 4 chronic hepatitis C'. Earliest anticipated date of publication January 2015. Technology appraisal in preparation,, 'Faldaprevir for treating genotype 1 chronic hepatitis C'. Earliest anticipated date of publication June 2015. Proposed technology appraisal, 'Sofosbuvir-lidepasvir for treating genotype 1 chronic hepatitis C'. Publication TBC. Proposed technology appraisal, 'ABT-450/ritonavir/ ombitasvir with or without dasabuvir for treating chronic hepatitis C'. Publication TBC. Related Guidelines: Proposed Clinical Guideline, 'Hepatitis C: Diagnosis and management of hepatitis C'. 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 testing', Pathway created: Dec 2012 http://pathways.nice.org.uk/
Related National Policy	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

Questions for consultation

Which anti-hepatitis C medications are likely to be used in combination with daclatasvir in clinical practice for chronic hepatitis C?

Is daclatasvir in combination with other anti-hepatitis therapies likely to be used to treat specific genotype(s) of the hepatitis C virus?

- If so, which combination regimens will be used for each specific genotype?
- Are treatment regimens expected to differ depending on previous treatment history, that is, are regimens for treatment-naive and treatment-experienced people with chronic hepatitis C likely to differ in terms of the combination of treatments received and the duration of treatment?

Have all relevant comparators for daclatasvir in combination with other anti-hepatitis medications been included in the scope? Which treatments are considered to be established clinical practice in the NHS for chronic hepatitis C infection?

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

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 daclatasvir in combination with other anti-hepatitis medications 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 daclatasvir in combination with other anti-hepatitis medications 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 daclatasvir in combination with other anti-hepatitis medications 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/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)