NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ledipasvir-sofosbuvir for treating chronic hepatitis C

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: ***Dr Helen Harris BSc PhD FFPH***

Name of your organisation: ***Public Health England***

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)
- ***I am a Clinical Scientist (Epidemiology) at the Centre for Infectious Disease Surveillance and Control (CIDSC) at Public Health England (PHE). My expert area is hepatitis C. I lead a programme of work on hepatitis C natural history/disease burden, and edit the Hepatitis C in the UK report, which summaries current knowledge about hepatitis C infection and reports on the progress of UK action plans in tackling the infection.***

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

While it is acknowledged that both hospital episode statistics and death certification underestimate true numbers of admissions and deaths from HCV-related end stage liver disease (ESLD) and hepatocellular carcinoma (HCC), national data shows that levels of both are continuing to rise in the UK. Hospital admissions have risen from 608 in 1998 to 2,390 in 2012, while deaths have risen from 98 in 1996 to 428 in 2012. An overall increase in UK registrations for liver transplants where post-hepatitis C cirrhosis is given as either the primary, secondary or tertiary indication for transplant is also observed, from 45 in 1996 to 188 in 2013.[1]

NICE approved treatments for hepatitis C exist in England and comprise interferon plus ribavirin for those with non-1 genotypes, and for those with genotype 1 infection the addition of either Boceprevir or Telaprevir can be recommended (see guidance summary below):

• National Institute for Health and Clinical Excellence (NICE). TA75 Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. 2004. Available at: http://www.nice.org.uk/nicemedia/pdf/TA075guidance.pdf. [Accessed 18/07/2014].
• National Institute for Health and Clinical Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. London; 2006. Available at: http://www.nice.org.uk/nicemedia/live/11590/33534/33534.pdf. [Accessed 18/07/2014].
• National Institute for Health and Clinical Excellence (NICE). TA200 Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. Part review of NICE technology appraisal guidance 75 and 106. September 2010. Available at: http://www.nice.org.uk/nicemedia/live/13180/50856/50856.pdf. [Accessed 18/07/2014].

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• National Institute for Health and Clinical Excellence (NICE). Telaprevir for the treatment of genotype 1 chronic hepatitis C]. Available at: http://guidance.nice.org.uk/TA252. [Accessed 18/07/2014].
• National Institute for Health and Clinical Excellence (NICE). Boceprevir for the treatment of genotype 1 chronic hepatitis C. (2012) Available at: http://guidance.nice.org.uk/TA253. [Accessed 18/07/2014].}

NHS England has also made Sofosbuvir + Daclatasvir/Ledipasvir +/- Ribivirin available for a defined group of patients with Hepatitis C via an early access programme [2]

Despite the availability of these therapies, numbers accessing treatment are low, at around 3% per year of the total estimated chronically infected population. These low treatment levels indicate that many individuals are failing to access appropriate management country-wide [3]

Recent work by Public Health England has shown that the burden of HCV-related liver disease is set to continue rising for the next 15 years and not decrease substantially for many more, unless improvements can be made in numbers being treated and the efficacy of available treatments. [3]

There is evidence that the number of people being treated each year is levelling off or starting to decline when an increase in the numbers treated is urgently needed. [3] Part of the problem may be that many of those that are willing and "easy" to treat have already been treated, partly this may be due to people waiting for improved treatments rather than undergoing more difficult-to-tolerate regimens with lower rates of sustained viral response (SVR). In any case, the knowledge that short courses of effective treatment, with minimal side effects, are available is highly likely to result in increased uptake. This will be helped further if treatment can be rolled out in community settings and be made more accessible to those who need it (see later section). Although many of those in mild and moderate states are unlikely to be at risk of developing severe disease for many years, it is still unclear whether long-term prognosis of those with severe liver damage is as good as those who are treated sooner.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

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If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Current NICE approved therapies have poorer rates of response (SVR) in those with more advanced disease, and SVR rates also decrease as age increases. In England we are currently facing the prospect of an ageing population of HCV-infected individuals in increasingly advanced disease states, and current treatments are insufficient to prevent this mounting health problem. In addition, whilst existing NICE approved DAAs offer an improvement in SVR rates for those with genotype 1 infection, they have been associated with higher rates of adverse events in individuals with advanced disease [4] New drugs with improved safety profiles and higher SVR rates in those with more advanced disease, are urgently required. [3]

Key groups affected by hepatitis C include people who inject drugs (around half of people who inject psychoactive drugs in England are thought to be infected) as well as people born or brought up in a country with a high prevalence of HCV [1] Although around 0.4% of adults are thought to be chronically infected in England (approximately 160,000 people), this varies around the country being concentrated in areas with high levels of current/past injecting drug use and high numbers of black and minority ethnic (BME) populations who have close links to countries with a high prevalence of HCV infection. As such, hepatitis C is concentrated in populations who are marginalised and underserved and therefore have poorer healthcare access and health outcomes. If we are to access and treat these populations, then treatment regiments that are easy to administer (all-oral, interferon-free), are of short duration, with improved side effect profiles and high efficacy are urgently required. These therapies, have the potential to be more accessible as they can be more easily rolled out in community settings, including drug services, prisons, and primary care. Improved reach to these groups will also help reduce health inequalities and the excess premature mortality from liver disease in these groups. Reaching people who inject drugs is important because modelling work has shown that treating this group can result in reductions in prevalence, and that reducing transmission via oral substitution therapy and needle exchange alone is not sufficient [5]

As with other similar antiviral technologies, there is the potential to develop resistance in the future.

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Equality and Diversity

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 this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/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 lead to recommendations that 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

Treatment is for adults and does not appear to exclude anybody protected by equality legislation. Treatment is for all adults whether they are treatment experienced of treatment naïve.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Because this new technology is likely to be expensive, there are issues of cost. Although it is likely to be within NICE thresholds for those with advanced disease, it may not be for those with mild disease. Several new drugs of similar efficacy are at various stages of the approval process, and the more options that are available, the better. Competition will inevitably help to drive prices down over time, meaning that drugs may fall within cost-effectiveness thresholds for mild disease in the future.

References

[1] PHE, Hepatitis C in the UK 2014 report. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/337115/HCV_in_the_UK_2014_24_July.pdf [Accessed 28/10/2014].

[2] NHS England. Interim Clinical Commissioning Policy Statement: Sofosbuvir + Daclatasvir/Ledipasvir +/- Ribivirin for defined patients with Hepatitis C. (2014). Available at: http://www.england.nhs.uk/wp-content/uploads/2014/04/sofosbuvir-pol-stat.pdf [Accessed 25/06/2014].)

[3] Harris R et al. J Hepatol 2014; Available at: http://www.ncbi.nlm.nih.gov/pubmed/24824282 [Accessed 09/07/2014].

[4] Hezode C et al. Safety of Telaprevir or Boceprevir in combination with Peginterferon alfa/Ribavirin, incirrhotic non responders. First results of the French early access program (ANRS CO20-CUPIC). In: 47th Meeting of the European Association for the Study of the Liver (EASL), Barcelona; 2012.

[5] Martin et al. Hepatology 2013; 58(5): 1598–1609. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3933734/ [Accessed 03 Nov 2014]