NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ledipasvir–sofosbuvir for treating chronic hepatitis C
Expert comments on the Appraisal Consultation Document (ACD)

Comments received from clinical experts and patient experts

Nominating organisation	Comment
Professor Matthew Cramp, Consultant Hepatologist, nominated by Gilead – clinical expert	I think the biggest area of concern remains the treatment experienced cirrhotic patient populations which runs counter to current clinical practice in England and elsewhere. The NHS England EAP has funded 12 weeks of treatment for patients with decompensated cirrhosis from HCV, regardless of genotype and prior treatment experience, and the decision of whether to use ribavirin with the sofosbuvir / ledipasvir or sofosbuvir / dalatasvir combinations was left to the MDT of the treating centres. It is likely that NHS England may extend this programme, using 12 weeks of sofosbuvir / ledipasvir (with or without ribavirin as determined by the treating centre MDT) to all patients with HCV cirrhosis. In the ACD it states: 1.1 The clinical experts agreed it was very challenging to distinguish between high-risk and low-risk cirrhosis without any specific biomarkers, and the data from the ION studies showed benefits for 12-week treatment in most people. The clinical experts agreed with the patient expert that all people with cirrhosis would generally be considered as high risk, but that 12 weeks of ledipasvir–sofosbuvir offers major advantages over currently available treatment options, especially in populations with historically difficult-to-treat HCV. The Committee agreed that it was difficult to define 'low risk of clinical progression'. It concluded that it would make recommendations for each treatment duration separately in people with genotypes 1 and 4 HCV with cirrhosis. The preliminary conclusions of the appraisal committee indicate that "24 weeks' treatment not recommended for people with

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	cirrhosis" for treatment experienced genotype 1 and 4 cases. This is I understand primarily out of concern about the risk of disease progression and the uncertainty over further treatment options (in line with the Harvoni EMA license which indicated that for patients with compensated cirrhosis 24 weeks was recommended whilst 12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options). My concern is that this group of patients stand to gain considerably by being offered treatment for 12 weeks and that the alternative options have lower SVR rates and involve the use of PEG-Interferon with ribavrin and either sofosbuvir or simeprevir. As outlined in the ACD, interferon containing treatment regimens, whilst effective for some, do come with a long list of side effects and tolerability problems. These patients are all treatment experienced so will be aware of the side effects and often not keen on experiencing them again. Whilst 24 weeks of sofosbuvir / ledipasvir has improved SVR compared to 12 weeks, this comes at a very significant incremental cost, and the benefits of 12 weeks treatment are substantial as indicated in the underlined text from the ACD above. I think the recommendation of how to treat treatment experienced geno 1 and 4 cirrhotic populations needs careful review and discussion next week, with particular regard as to whether 12 weeks can be considered. I think the HCV treatment centres are well placed to make sound clinical judgements to identify those cases considered to be at low risk of clinical disease progression through their MDT processes (which will also provide a record of how those decisions were reached). It is this group of cirrhotic treatment experienced patients who will require treatment soon to minimise the risk of them progressing to a more advanced stage of cirrhosis where they would be deemed at high risk of clinical complications developing.
Mr Charles Gore, Chief Executive of the Hepatitis C Trust, nominated by the	We would like to make comments that go to all of the above questions. The Committee has made recommendations for both 12 and 24 weeks' treatment as per the final sentence of ACD paragraph 4.7, with one exception – people with G1 and G4 and cirrhosis who have tried treatment where only 24 weeks is considered. Not surprisingly, this is not cost-effective. The decision not

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Hepatitis C Trust – patient expert	to make a recommendation is obviously the result of the considerations outlined in 4.7 about the marketing authorisation which says that for this population "12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options". During the committee meeting there was discussion of who if anyone could be considered at low risk of progression and it was generally felt that no person with cirrhosis is at low risk. However, this really makes the wording of the marketing authorisation meaningless. It must therefore be interpreted as meaning at lower risk. There was also discussion about how risk could be differentiated and this was felt to be difficult. The EMA felt that it was acceptable to leave the differentiation to clinicians and we support this idea. We would like to argue that it would be perverse not to consider 12 weeks just because of the difficulty of defining lower risk, for the very simple reason that Sofosbuvir-Ledipasvir is highly effective and cost-effective for all people with cirrhosis. In a post-hoc analysis of the major trials presented by Bourliere et al. at AASLD in 2014, 64 out of 71 (90%) treatment experienced patients with cirrhosis who received Sof+Led for 12 weeks achieved SVR. Furthermore, people with cirrhosis who have unsuccessfully tried treatment already are probably the most in need and interferon-based treatment, which is all they would be left with, has a significant risk of causing decompensation. We would also like to argue that although the EMA may not actually be 'recommending' 12 week use (pace ACD 4.21), it is 'authorising' its use in the circumstances spelt out and therefore NICE may consider it. Given the high unmet need in this population, we ask NICE to consider it. Finally, we would like to reiterate four general points: 1. Apart from the fact it is at odds with the NHS's sensible desire to concentrate more on prevention of disease, we feel there is a real ethical issue in saying to a patient: 'You can't have treatment. Come back when you're sicker'. This applies particularly but not exclusively to people with F3 disease. There is no real question that they are going to progress to F4 and, depending on the frequency of their monitoring, they may have cirrhosis for some time before they receive treatment and are therefore at risk of liver

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	cancer during that time. 2. Interferon has acted as a major deterrent to treatment. Even though this fear of interferon may not be well supported by the evidence, nonetheless for these people their choice is between interferon-free regimens and no treatment. We know of people who have developed cirrhosis waiting for interferon-free regimens. 3. People who refuse interferon do so because of its unpleasant side-effects during treatment but also because of the perceived long-term effects that persist beyond treatment cessation. There is an almost total lack of research into this but that in no way implies this is not a real phenomenon. Aside from our methodologically limited study of 500 patients, we have documented evidence. What we do not have is any population-based assessment of quality of life or economic impact. We strongly suggest, however, that, were these available, the ICERs of interferon-free therapies would be significantly lower. 4. There is a possible equity issue. For a variety of reasons, including length of treatment, on-treatment monitoring and side-effect profile, it may be that 12 weeks of treatment with an interferon-free regimen would permit treatment for certain groups such as prisoners, who would not have access to 24-48 weeks of a regimen containing interferon (for example because of movement between prison or between prison and the community).