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THE HEPATITIS C TRUST

Response from The Hepatitis C Trust to the NICE ACD for Sofosbuvir+Ledipasvir

1. **Has all of the relevant evidence been taken into account?**
2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
3. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

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-efective. The decision not 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

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cirrhosis for some time before they receive treatment and are therefore at risk of liver 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).

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