Urgent Clinical Commissioning Policy Statement: Retreatment of Chronic Hepatitis C Infection in Adults with Advanced or Decompensated Cirrhosis

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Document Status

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1 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of this policy statement, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

In the interests of delivering an urgent commissioning position, a rapid initial equality impact assessment has been carried out and a full equality health impact assessment will be undertaken when a clinical commissioning policy is published to replace this document.

2 Background

Hepatitis C virus (HCV) infection is a chronic liver condition that leads to cirrhosis, which in turn is complicated by the development of liver failure and liver cancer. Recent developments in the treatment of HCV infection make it possible to cure the infection with a short duration of Direct Acting Antiviral (DAA) therapy. Typically, a course of DAA tablets is given for 8 to 16 weeks (although in some cases longer courses have been used depending on genotype, treatment history and disease severity), and the chance of cure approaches 100% in many studies, including large published real-life experiences. Successful treatment prevents progression to liver failure and liver cancer, and reduces immediately the risk of death. DAA therapy typically involves the administration of a combination of drugs.

HCV treatment is delivered by 22 Operational Delivery Networks (ODNs) across England. Patients are selected for treatment based on highest unmet clinical need and the regimen provided is the lowest acquisition cost option which has been determined as clinically effective by NICE technology appraisals and / or clinical commissioning policy.

However, a small proportion of patients (c10% of patients with cirrhosis) are not cured by the first course of DAAs. Their prognosis remains poor and their need for successful DAA treatment persists. Presented and published clinical trial data show that a large proportion of DAA failure patients can be cured by retreatment, using a longer duration of treatment and/or a different combination of DAAs. Successful retreatment eliminates infection and prevents the development of liver failure and liver cancer.

In England, the majority of DAA treatment failure patients have advanced liver disease with a significant early risk for the development of liver failure and liver cancer. Successful antiviral retreatment of this cohort will be associated with an immediate reduction in the development of liver failure and a later reduction in the development of liver cancer.

Liver failure and liver cancer can be treated by liver transplantation. Prevention of liver failure and liver cancer in patients with decompensated cirrhosis can reduce the need for liver transplantation, thereby enabling donor livers to be used for patients who suffer from non HCV-related liver conditions.

Whilst the success of DAA treatment is defined by a number of published and presented clinical trials, the problem of DAA failure is a very recent development, so there is a limited published literature and the most relevant data are contained in abstracts of presentations made at recent scientific meetings, particularly at the annual meetings of the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD). These data have clearly established the principle that retreatment with a previously failed regimen for a longer duration or a new

regimen (for the licenced or duration or longer) will cure more than 70% of patients. It is expected that cure rates even in those who are to be retreated will continue to rise with new regimens expected to be licenced in 2017.

None of the published NICE Technology Appraisals have addressed the issue of DAA retreatment because studies of retreatment were not part of the data submissions made by pharmaceutical companies. A new pan-genotypic combination treatment of glecaprevir\pibrentasvir has been approved by the Medicines and Healthcare Products Regulatory Authority (MHRA) for use within an Early Access to Medicines Scheme (EAMS) for treatment of selected patients with cirrhosis and prior DAA treatment failure. This is in recognition of the unmet need of cirrhotic DAA failure patients, and the inclusion criteria specifically reflect the retreatment data in the pharmaceutical submission. However, the EAMS does not cover patients with advanced or decompensated cirrhosis as treatment with the glecaprevir component of the EAMS regimen is contraindicated in decompensated cirrhosis.

This urgent clinical commissioning policy statement recommends routine commissioning of the NICE-recommended treatment (sofosbuvir and velpatasvir) which is licenced for use in patients with all genotypes and with advanced or decompensated cirrhosis. This treatment is already commissioned for patients receiving first DAA treatment. This policy statement recommends off-label use of 24 weeks treatment for retreatment of chronic hepatitis C infection in patients with advanced or decompensated cirrhosis whose first course of DAA treatment has failed to achieve cure. This target population has an unmet need for treatment, and has a significant and immediate risk for the development of liver failure and death.

3 Evidence Summary

NHS England has considered the evidence submitted as part of the preliminary policy proposal to establish the urgent clinical commissioning policy statement, including the clinical criteria for initiating and discontinuing the intervention. This

includes up to three of the most clinically impactful publications, identified using a literature search strategy defined by the clinical lead. These publications are summarised below.

Publication 1 (Gane et al 2017))

Phase 2 study in 69 patients who had failed previous direct antiviral therapy re-treated with sofosbuvir/velpatasvir and ribavirin. 63 of 69 patients (91%) achieved an SVR and cleared virus - including 36 of 37 (97%; 95% confidence interval, 86-100%) patients with HCV genotype 1 infection, 13 of 14 (93%; 95% CI, 66-100%) patients with genotype 2 infection, and 14 of 18 (78%; 95% CI, 52-94%) patients with genotype 3 infection.

This was a phase 2 uncontrolled study as it was deemed unethical to include a control arm. The strength of the study is that it included a wide range of patients treated with the combination therapy recommended in this policy statement. The weakness of the study is that patients with decompensated cirrhosis – the group recommended for treatment in this policy - were excluded. However, other studies, including the English Hepatitis C Early Access Programme (EAP), have demonstrated safety and efficacy of similar regimens in this setting.

Publication 2 (Bourliere et al 2017)

This is a combined report of 2 large phase 3 trials that had in common the use of 12 weeks of combination sofosbuvir-velpatasvir-voxilaprevir (sof-vel-vox) or sofosbuvir-velpatasvir (sof-vel) to treat patients who had failed a previous DAA-based regimen. The cure rate for sof-vel-vox was 431/445 (97%) and for sof-vel was 131/151 (90%). The strengths of the paper are that it also illustrates the potential of retreatment to cure HCV infection, that the combined studies included patients with both genotype 1 and 3 infection, and that 50% had established cirrhosis. These features describe a population that includes those to be retreated under this policy statement. Also, the inclusion of a treatment arm that received only sof-vel provides an evaluation of the drug regimen recommended in this policy statement, and this regimen achieved a 90% cure

rate with only 12 weeks of treatment. The weakness, with respect to its relevance to this retreatment policy statement, is that the sof-vel group received only 12 weeks of treatment – as opposed to the 24 weeks treatment recommended in this policy - and that previous non-structural 5A protein (NS5A) failure patients were not included in this cohort.

Publication 3 (Lawitz et al. 2017**)**

This was a single centre phase 2 study that evaluated the use of combination sof-vel-vox to treat 49 genotype 1 patients who had previously failed treatment with a direct acting antiviral DAA-based regimen. 48 of 49 patients were cured by retreatment and this was achieved without significant adverse effects. The strengths of the paper are that it illustrates the potential of retreatment to cure a majority of patients, that a large proportion of those patients had previous exposure to more than 1 class of antiviral drug, and that 50% of the patients had established cirrhosis. These features are likely to apply to patients submitted for retreatment under this policy statement. The weakness, with respect to its relevance to this retreatment policy is that the study was confined to retreatment of genotype 1 infection whereas this policy statement applies to all genotypes.

Voxilaprevir in combination with sofosbuvir and velpatasvir is currently undergoing NICE appraisal which will include an evaluation of its benefits in treating those who have not responded to therapy. However, voxilaprevir is contraindicated in patients with decompensated cirrhosis and therefore this combination cannot be used in the setting described in this policy statement. Other than the sof-vel combination discussed here there are no safe therapies that can be used in patients with decompensated cirrhosis

In addition to the studies identified above, NHS England has also identified the studies listed below as important in informing the clinical commissioning position and criteria:

Publication 4 (Curry et al 2015)

Phase 3 open label study in patients with decompensated cirrhosis showing safety and tolerability of the sof-vel regimen for either 12 weeks (with ribavirin) or 24 weeks (without ribavirin). Overall response rates were 94% for 12 weeks (N=98) and 86% for 24 weeks (N=92).

The strength of the study was the inclusion of patients with decompensated cirrhosis. The weakness was the exclusion of patients previously treated with all oral medications.

In summary, the evidence presented supports by extrapolation the principle of effectiveness of sof-vel (and ribavirin) for 24 weeks for the retreatment of individuals with chronic hepatitis C infection and advanced or decompensated cirrhosis (all genotypes) with the objective of achieving sustained virological response 12 weeks after the end of treatment whereby hepatitis C is undetectable (SVR12).

4 Commissioning Position

Rationale for an urgent clinical commissioning policy statement

The use of sof-vel for 24 weeks to retreat adults with chronic HCV and advanced or decompensated cirrhosis, whose first direct acting antiviral treatment has failed to achieve SVR, is of such significant clinical importance that an urgent clinical commissioning policy statement has been adopted. The time taken to develop a full clinical commissioning policy proposition for relative prioritisation and implementation would not meet the immediate need for patients, clinicians and the NHS to have clarity about whether an intervention is or is not routinely commissioned.

In addition, there are overriding patient safety or other clinical issues that require an immediate clinical commissioning position to be implemented.

The eligible individuals – patients with advanced and decompensated cirrhosis – are at risk of death within 12 months.

Clinical commissioning position

Based on a limited scoping of the evidence, NHS England has concluded that there is sufficient evidence to support the routine commissioning of this treatment for the indications and clinical criteria listed.

Clinical commissioning criteria

Patient eligibility criteria:

- adult patients with chronic hepatitis C (all genotypes) AND
- advanced or decompensated cirrhosis (as defined below) AND
- who have previously received a direct acting antiviral treatment which failed to achieve a SVR as measured at the SVR 12 week post treatment completion test AND
- where the ODN has confirmed that failure to achieve SVR was not due to poor adherence or HCV reinfection AND
- where previous treatment of G3 infection involving 24 weeks of sofosbuvir/daclatasvir that failed or where previous treatment of G1 infection involving 24 weeks of sofosbuvir/ledispasvir that failed, then patient eligibility (based on ability to benefit) will be confirmed via referral to the Hepatitis C appeals panel

Intervention considerations:

- Sofosbuvir/velpatasvir is licenced for use in patients with decompensated cirrhosis when used in combination with ribavirin. The licenced duration is 12 weeks. This policy statement recommends off-label use of sofosbuvir/velpatasvir in combination with ribavirin.

Dosing:

- 24 weeks treatment of sofosbuvir/velpatasvir, with the addition of ribavirin if required based on clinical assessment of patient's clinical condition. The addition of ribavirin aims to further strengthen the regimen.

Treatment starting criteria:

- Patient under the care of an ODN for HCV, their details are entered into the HCV registry and the on-line prior approval form has been appropriately completed
- Patient meets the criteria for retreatment and where the plausible objectives are to prevent avoidable death in the next 12 months AND achieve SVR12
- Patient's viral load is measured at weeks 2, 4, 8, 12, 18 and 24 during treatment
- Viral load is measured 12 weeks after the end of treatment to determine that SVR has been achieved.

Treatment stopping criteria:

- An increase in viral load from on-treatment nadir of greater than 1 log is indicative of virological breakthrough and treatment will be discontinued. Discontinuation avoids futile therapy and minimises the development of drug resistance.
- For patients who breakthrough on therapy or do not respond to the retreatment proposed in this policy statement there are currently no other proven therapeutic options

Exclusion criteria:

- Patients with cirrhosis or fibrosis whose condition is not consistent with the description of advanced or decompensated cirrhosis
- Patients who are unable to take sofosbuvir/velpatasvir +/- ribavirin due to contraindications or other clinical reason identified by their treating clinician
- Patients who have not had a first course of DAA
- Patients who require retreatment due to poor adherence or reinfection

- Retreatment of eligible patients using a regimen other than sofosbuvir/velpatasvir +/- ribavirin
- Patients whose previous treatment of G3 infection involved 24 weeks of sofosbuvir/daclatasvir that failed or whose previous treatment of G1 infection involved 24 weeks of sofosbuvir/ledipasvir that failed, where further treatment is not supported by the Hep C appeals panel.

Definition of advanced or decompensated cirrhosis:

- Evidence of present or previous decompensated cirrhosis with an episode of ascites, variceal bleeding, or encephalopathy; OR
- Child Pugh Score ≥ or = 7; OR
- The patient is at significant risk of death or irreversible damage. For example, patient is currently listed for liver transplantation; OR
- The patient has biochemical or haematological indicators of advanced cirrhosis and/or significant portal hypertension eg albumin < 35, platelets < 50.
- Viral sequencing

HCV Research UK has made resources available to provide full viral sequencing on all patients enrolled in the HCV Research programme and these data will be used to determine whether there are any pre-treatment viral sequences that predict treatment failure. Where the viral sequencing of particular patient characteristics predicts treatment failure, HCV Research UK will feedback to ODN clinical leads and NHS England via an urgent clinical update for cascade to treating clinicians. It is recommended that all patients are enrolled in order to benefit from this.

<u>Clinical commissioning policy development plan</u>

It has been assessed that the development of a full clinical commissioning policy is not needed at this time. The rationale is that two new treatments which are due to receive marketing authorisation in the summer of 2017 are being assessed by NICE through the Technology Appraisal Programme and this is expected to include a recommendation on the use of the products for

retreatment. The due date for these assessments is early 2018. This will then inform the commissioning position for other patients whose first DAA treatment fails to achieve cure.

Should the subsequent published clinical commissioning policy be revised to 'not routinely commissioned', patients started on treatment under this policy statement will continue to have access to it provided they and the clinician responsible for their care continue to believe that it is the right treatment for them.

5 Mechanism for funding

NHS England will reimburse activity undertaken within the terms of this policy statement, as follows:

- The patient is under the care of one of NHS England's approved 22 Operational Delivery Networks
- The appropriate prior approval form has been fully and correctly completed by the treating clinician and submitted confirming patient eligibility. This includes referral to the Hepatitis C Appeals Panel for specified patients who failed previous 24 weeks treatments
- The approved treatment has been provided for the duration identified and discontinued where it is demonstrated that the treatment is failing to achieve a virological response
- Patient information has been recorded on the HCV registry
- Where the SVR at the end of treatment has been recorded

6 Date of policy statement approval and review

This urgent clinical commissioning policy statement is effective from September 2017.

A clinical commissioning policy is not planned to be developed at this stage. If a clinician, supported by peers, seeks a reappraisal by the Clinical Panel then a new 'Preliminary Policy Proposition' should be submitted. For guidance email england.specialisedcommissioning@nhs.net.

7 References

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