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Sent by Email

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23 March 2015

Dear Sir

Please find enclosed NHS England's response to the ACD consultation on the hepatitis C drug combination Ledipasvir–sofosbuvir.

The consultation response has been prepared by the specialised services commissioning team and incorporates comments from clinical members of the hepatitis subgroup of the Infectious Diseases Clinical Reference Group. These comments do not describe a consensus view from the clinical body as this has not been reached due to the variety of issues facing the decision-making around hepatitis C and we expect clinicians to respond to the appraisal consultation as individuals from their own organisation. The Infectious Diseases Clinical Reference Group, under the chairmanship of Peter Moss, will be able to provide any further direct advice to the NICE appraisal process through NHS England as requested.

The introduction of the oral treatments for hepatitis C is a major change in the management of this disease and NHS England is supporting the implementation of these treatments in a stepwise fashion with our previous early access scheme for decompensated cirrhosis, the second access scheme for all patients with cirrhosis soon to be available, and the formation of the work programme to establish access to oral drugs for patients with F3 liver fibrosis in conjunction with an effective program of surveillance for other patients and a focus on the specific needs of the complex patient groups with hepatitis C.

The potential publication of the NICE guidance as a single technology appraisal has led to a number of concerns that are described in the consultation response. This is a rapidly changing field of medicine with new evidence emerging and NHS England would want to implement through modifications of its early access scheme policies. All stakeholders who have advised NHS England have indicated the importance of forming a multiple technology appraisal evaluating the new suite of medications, their combinations, the previously available treatments and the potential for shorter treatment durations. It is understood that a multiple technology appraisal would be best achieved in approximately 18 months time when the full range of these new medications have been licensed.

In the meantime NHS England is confident that treatment strategies through commissioning policy can be formed to substantially reduce the burden of liver disease associated with hepatitis C.

The potential impact of not adopting the stepwise implementation approach described above needs to be considered explicitly in terms of both suboptimal treatment of those with hepatitis C and the impact on the ability of the NHS to meets its wider obligations. Using the prices described within the ACD and an estimated population of non-cirrhosis G1 & G4 subtypes of circa 34000, the potential budget impact of the ACD (in excess of planned access schemes) is circa £1,300M. NHS England is clear that affordability is not part of the consideration of the Technology Appraisal process. However, as the potential financial impact is so high, there is minimal room for uncertainties in the assumptions taken to reach a position.

Until a NICE multiple technology appraisal can be carried out, NHS England would support with their Access Scheme Programmes a NICE ‘Recommended with Research’ position for patients without cirrhosis. These schemes would harness substantial ‘real world’ data on the effectiveness of treatments and their combinations to deliver much greater value for money for the NHS than proceeding with a NICE recommendation through a single technology appraisal at this stage.

Yours sincerely

[redacted]

NHS England

NHS England Response to NICE ACD – Ledipasvir–sofosbuvir for treating chronic hepatitis C [ID 742]

Please find NHS England's response to the ACD – Ledipasvir–sofosbuvir for treating chronic hepatitis C (including responses from the Hepatitis C CRG subgroup).

Has all of the relevant evidence been taken into account?
Yes all current evidence has been taken into account. However, NHS England understand that new data in specific patient groups is continuing to emerge and it would seem prudent to allow for a more extensive time period to enable NHS England to assess the emerging evidence under an evaluative process that can be managed centrally rather than dictated by statutory guidance. *Additional comments from the CRG:* The relevant Phase 2 and 3 trials are included. However other studies, and in particular those looking at 'real world' experience, have not been fully considered. New data were presented at AASLD 2014 (for example the SOLAR and SIRIUS studies) which include important information about the additional benefit of ribavirin in selected patients. These data suggest that for patients with advanced liver disease a total of 12 weeks of sofosbuvir/ledipasvir/ribavirin is equivalent to 24 weeks of therapy. An additional meta-analysis of all patients with cirrhosis treated with sofosbuvir/ledipasvir +/- ribavirin was presented by Dr Bouliere at the AASLD meeting in November and these data suggest that 12 weeks of sofosbuvir / ledipasvir / ribavirin is as effective as 24 weeks in this patient population. Taken together these data strongly suggest that 12 weeks therapy with ribavirin is sufficient for virtually all patients. The SOLAR results are described by NICE as being 'commercial in confidence', although they were actually presented publicly in November 2014. The NHS England commissioned Early Access Program data has been presented at confidential meetings and shows that 12 weeks sofosbuvir based therapies in patients with advanced cirrhosis leads to SVR4 rates of 90% in patients with G1 and 70-80% in G3. Hence we see no indication for extended duration therapies except in very restricted patient groups. There are considerable gaps in the available evidence base which make it difficult at present to fully evaluate the role of the sofosbuvir/ledipasvir combination (+/- ribavirin), especially in G3 and G4 infection, and in patients with advanced liver disease. Much of this information is just not available, and will require further evaluation of the drug combinations either in clinical trials (unlikely) or through observational studies of real life use. However for the G4 patients some extrapolation from existing data is possible. Results

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from treating with 12 weeks of sofosbuvir/ledipasvir (albeit in small numbers) gave nearly 100% SVR in a population that included a large proportion of cirrhotic and treatment failure patients. This, along with results with sofosbuvir/peg-interferon/ribavirin for G4, and EC50 data from in vitro studies, suggests that sofosbuvir/ledipasvir would be good for G4 and probably at the reduced duration.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

NHS England believes there are still a number of uncertainties relating to the evidence coupled with NICE only considering licensed dosing regimens. In particular, the course length needs further consideration given the emerging evidence around 12 week courses and SVR rates. Consideration needs to be given to the following issues:

1. Uncertainty in treatment effects and comparative effectiveness

The evidence base on these new treatment regimens is small, particularly in more severe patients (i.e. patients with cirrhosis), in less prevalent genotypes and in harder to reach subpopulations (e.g. people who inject drugs, co-infection with HIV). In the appraisal of ledispavir, for example, the NICE committee recognised the weaknesses in the evidence base given the lack of concurrent controls, small proportion of patients with cirrhosis and the limited evidence in patients with HCV genotype 3 and 4. Furthermore, the clinical studies are mainly non-randomised open-label studies without concurrent controls. These studies are at higher risk of bias and additional uncertainty from the lack of randomised control. Evidence from these studies should therefore be interpreted with caution.

The new treatments for chronic hepatitis C offer sustained virologic response (SVR) rates of approximately 90% although at a high cost. Both SVR rates and treatment cost have been shown to be key cost-effectiveness drivers. Consequently, for the assessment of added value, the focus should be on the comparison of the additional benefits of new treatments versus the benefits achieved by the current ones with their additional costs. The additional value can be affected by patient characteristics that influence SVR rates for existing regimens even where they do not impact on SVR rates for the newer regimens. The NICE appraisals of added value have been based on naïve indirect comparisons with existing treatment regimens. The evidence used within these appraisals to characterise the existing treatment regimens represents only a selected proportion of that available.

The uncertainty in the evidence base has implications for decision uncertainty. In other words, treatments that appear cost-effective under the current evidence may not be cost-effective as new evidence emerges. However, recommending treatments with uncertain evidence base may reduce the likelihood that new evidence is generated and may make it more difficult to change the recommendation in the future once new evidence emerges. In these situations, recommendations for only-in-research or

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approval-with-research may be more appropriate than a recommendation as an option.

2. Development of the evidence base

The small sample sizes for particular patient groups may have implications for external validity. For example, the SVR rate for ledispavir+sofosbuvir (LED+SOF) over 12 and 24 weeks in cirrhotic people with HCV genotype 1 was obtained from the ION-1 study. In this study, 34 patients with chronic hepatitis C genotype 1 and cirrhosis received LED+SOF over 12 weeks, of which 32 (94.1%) achieved SVR. Had the trial recruited an additional patient with those characteristics, and that additional patient had not achieved SVR, the SVR rate would have reduced to 91.4%, a drop of 2.7%. Had an additional 5 patients been recruited who did not achieve SVR, the SVR rate would have reduced to 82.1%. Reductions in SVR rates are likely to affect the cost-effectiveness of the new treatments.

Ongoing studies are likely to strengthen the evidence base in the near future: ELECTRON-2 is an ongoing study on LED+SOF for patients with HCV genotype 1, 3 or 6 and SOLAR-1 is an ongoing study for patients with HCV genotype 1 or 4.

The access scheme commissioned by NHS England is currently accruing data on the effects of these new treatment regimens in populations not covered by the clinical trials, such as patients with decompensated cirrhosis. These data on SVR rates with 12 week regimens in a patient group with severe disease may be valuable in assessing prioritisation of access to new treatment regimens.

3. The static nature of the cost-effectiveness models

The cost-effectiveness models utilised in the ACD did not include reinfections or onward transmission. Excluding reinfection is likely to overestimate the benefits and underestimate the costs of more effective treatments since re-infected individuals require new treatment. Excluding onward transmission may underestimate the benefits of more effective treatments. The impact of excluding reinfection and onward transmission is likely to be larger and depends on the prevalence of the disease and on the probability of risky behaviours by the patient population.

A further source of uncertainty in this is the nature of the patient population that is currently treated versus the patient population that could be treated with the newer, shorter, non-interferon based regimens. While reinfection rates and onward transmission effects may be small in patients with cirrhosis, the impact of excluding these factors may increase if treatment is expanded to more hard to treat populations and/or to earlier stages of disease.

4. The omission of relevant treatment strategies: watchful waiting and treatment sequences

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Watchful waiting and treatment sequences have not been evaluated in the most recent NICE STAs nor in the current ACD. Watchful waiting consists of monitoring the patient until the disease progresses to a more severe stage then treat. Watchful waiting may represent current practice. This strategy may be cost-effective for patients with mild disease and low likelihood of onward transmission. Treatment sequences include strategies where patients are treated with a cheaper less effective regimen (e.g. Pegylated Interferon and Ribivirin) and patients who do not achieve SVR are re-treated with a more expensive more effective regimen. A treatment sequencing strategy may be more cost-effective than a 'treat all' strategy since it is likely to achieve similar health benefits at much lower cost.

5. The opportunity costs of high cost medications affecting large populations

NHS England understands that the cost of a 8 week course of LED+SOF is £25,987 and a 12 week course is £38,980. Most up-to-date figures estimate a total chronic hepatitis C population at almost 160,000 in England (approximately 102,000 mild, 46,000 moderate and 6,000 compensated cirrhotic patients). Assuming that around half of patients have genotype 1 or 4, treating only the cirrhotic patients with a 12 week course of SOF+LED represents a cost of £121 million. Overall, NHS England has a budget of circa £98 billion for 2015/16, and approximately 10% is allocated to medicines. Therefore, treating only the compensated cirrhotic patients with genotype 1 or 4 with LED+SOF represents 1.3% of the total NHS budget for medicines. Extending treatment to all patients with moderate disease with genotype 1 or 4 increases the budget impact to 10.3% of the total NHS budget for medicines. The displaced interventions are likely to offer more than 1 QALY per £20,000 spent. Therefore, offering these new drugs to **all** eligible patients is likely to result in a net loss of health.

6. The capacity constraints to offer treatment to all eligible patients

NHS England have already highlighted issues around capacity in feedback relating to TA330: Sofosbuvir for treating chronic hepatitis C. NHS England believe these issues still remain despite feedback from clinicians that say otherwise.

7. Implementation of 'recommended as option' guidance

The STA process is designed to evaluate a technology vs its current relevant comparators. However, as the current relevant comparators change over time as new therapies emerge, a sequence of STAs risks excluding relevant comparators. For example, the most recently issued technology appraisal on SOF+LED did not include daclastavir-based regimens in their comparisons and vice-versa despite being appraised almost concurrently. In addition, there are older NICE STAs on pegylated interferon and ribivirin (PR), Boceprevir (BOC) and Telaprevir (TVR) that have not been withdrawn and are still valid. For example, patients with HCV genotype 1 have PR, BOC+PR, TVR+PR, SMV+PR, SOF+PR and LED+SOF as NICE recommended options. Given

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the difference in costs and effectiveness, it is unclear which treatment should be prioritised for implementation.

8. Investment in increasing uptake of cheaper treatments vs investment in expensive treatments

Another important consideration is the role of PR in the current treatment pathway. Many patients are reluctant to take PR due to the risk of side effects. However, most side effects are mild to moderate in severity and can be managed without reducing the dose or discontinuing the therapy. Therefore, a potentially relevant alternative is to invest in increasing the uptake of cheaper PR-based regimens with a treatment sequencing approach to treatment (see Issue 4 for a discussion), in which patients are treated first with PR and only treatment failures are treated with more expensive alternatives. The value of investing in an implementation activity that increases the uptake of PR-based regimens vs investing in more expensive treatments could be evaluated in a value of implementation framework. This may again vary by HCV genotype as response rates to PR may be higher for patients with genotype 3 (not relevant to this ACD) disease compared to genotype 1.

Additional comments from the CRG:

The included evidence has been adequately summarised. However some of the conclusions and recommendations are open to further discussion. Sofosbuvir/ledipasvir (+/- ribavirin) is a significant step forward in HCV treatment compared to interferon-based therapy, especially for genotype 1 and 4 patients. Along with a number of other oral anti-viral combinations it gives the opportunity for more effective, better tolerated treatment, with a high cure rate across most patient populations.

There remain unanswered questions about the combination. Despite a lack of evidence from the manufacturer's trial programme many clinicians believe (based on real world experience) that the addition of ribavirin is beneficial, especially in certain patient sub-groups. It is not clear whether sofosbuvir/ledipasvir is a better treatment for G1 and G4 patients than other potential comparator regimens such as sofosbuvir/simeprevir, or ombitasvir/paritaprevir/dasabuvir. Certainly there may be better options for G3, although there is a paucity of data on sofosbuvir/ledipasvir/ribavirin in G3 patients (presumably because the manufacturer is developing a G3 specific combination for future use). Optimum length of treatment course in 'difficult to treat' groups remains uncertain. There are also a number of other drug regimens in development (and likely to be available in the fairly near future) which may be comparable to or better than sofosbuvir/ledipasvir.

It is clear from the clinical trial evidence that for many patient groups sofosbuvir/ledipasvir is an excellent treatment. However for others, who fell outside the relatively restrictive clinical trial programme, it is difficult given the currently available data to say with certainty how and in whom the sofosbuvir/ledipasvir combination should be used.

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Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
For the reasons stated above NHS England do not believe the recommendations are in the best interest of the NHS at this time. *Additional comments from the CRG:* This regimen is likely to be the first all oral HCV treatment recommended by NICE for the majority of G1 and G4 patients. Availability of these drugs would therefore be welcomed as a very significant improvement on interferon based therapy for such patients. However there may be alternative treatment regimens of comparable efficacy for G1 and G4, and sofosbuvir/ledipasvir is clearly not the ideal treatment for other genotypes. There are potential risks which accompany immediate recommendation of this regimen as proposed in the ACD for all patients with G1 infection, especially given that many patients with hepatitis C infection have mild asymptomatic disease (and will remain in this state for many years to come). • The ACD defines a large population of patients who may be suitable for treatment with sofosbuvir/ledipasvir. This includes patients with cirrhosis and advanced fibrosis, who are in urgent need of treatment, as well as many others who do not have significant liver disease or symptomatic infection. Commissioning should aim to safeguard and ensure early access to treatment for the former group of patients. Due to both constraints of both finance and capacity this would require prioritisation of treatment for certain groups of patients. • The place of sofosbuvir/ledipasvir in the treatment of some HCV groups is inadequately defined by the published literature. It would be better if the drugs could be used in a controlled and evaluated fashion in order to better define their role in the treatment of these patients. • The impact of widespread prescribing of an easy to use medication whose success is contingent upon meticulous adherence is not yet clear. Given the inclusion of NS5A inhibitors in most emerging treatment regimes it is probable that development of NS5A resistance (which has been reported in association with suboptimal dosing) will significantly reduce future treatment options and the emergence of ‘untreatable, multi-drug resistant HCV’ is a matter of concern. Data on treatment of ‘real world’ patient cohorts will be required to assess the risks of viral resistance and strategies to combat them will be required as access to therapy is increased. Therefore although it would be very helpful to have sofosbuvir/ledipasvir (with or without ribavirin) as a NHS-funded treatment option, general availability in an unrestricted manner may not be the best way for NHS England to use these drugs.

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The Clinical Reference Group has supported NHS England to put in place a second Early Access Programme to make highly effective oral treatment available during 2015-16 (and starting in the first quarter of the year) for all eligible diagnosed patients with cirrhosis. Planning is underway for NHS England to consider the formation of a third Access Programme for advanced fibrosis (F3), patients with progressive fibrosis as evidenced by changes in Fibroscan scores (or other validated invasive or non-invasive markers) and other patients who, in the opinion of an expert panel, require urgent therapy.

Based on the understanding that well tolerated and effective oral therapies will be made available during 2015-16 to a significant proportion of patients with hepatitis C (as listed above), and to all those judged to be in urgent clinical need, the CRG would support making these therapies available through alternative approaches to the proposed NICE recommendation for the use of sofosbuvir/ledipasvir as set out in the ACD. In particular, given the many unanswered questions described above, we would support the use through NHS England policies of different oral regimens (including sofosbuvir/ledipasvir) as part of a 'Commissioning through Evaluation' programme, as long as this met the stated requirement for making treatment accessible to those patients who need it. Drug treatment for hepatitis C could be commissioned on an evaluative basis for a fixed two year period, with robust data collection and analysis included as an integral part of the programme delivered by regional treatment networks. This would allow thorough evaluation of available therapies ahead of a more long term commissioning strategy.

Any other comments

NHS England is aware that current practice is evolving as new therapies emerge and older therapies are discontinued. Boceprevir and telaprevir, which are recommended by NICE for genotype 1 infections in combination with PR (pegylated interferon alpha and ribavirin), have been withdrawn from the US market and their availability in the UK over the longer term is to be determined.

Daclastavir (BMS) is under appraisal by NICE and guidance is expected in May-June 2015. A four-drug therapy regimen for genotype 1 or genotype 4 patients, ombistavir+ paritaprevir+ritonavir with or without dasabuvir (Abbvie), has recently been approved by the European Medicines Agency (EMA) and will be appraised by NICE later this year with an anticiapated publication date of September. Another interferon-free regimen, grazoprevir+elbasvir (MSD), is likely to be submitted for regulatory approval this year.

Therefore, NICE guidance is being issued in moving ground, where new technologies and more evidence is constantly emerging. The implication is that a strategy to wait until all these technologies have been licensed may avoid committing resources to technologies that may be quickly superseded. The health impact of delaying access to more effective medicines is likely to vary with disease severity, as patients with more severe liver damage may be at risk of irreversible health loss.

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It is for this reason coupled with the uncertainties highlighted above that NHS England wish to propose an evaluative process to take place over the next five years. This process will help determine which drug or combination of drugs offers the best value to the NHS within specific hepatitis C populations.

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