NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE

Review of TA330; Sofosbuvir for treating chronic hepatitis C, and TA331; Simeprevir for treating genotype 1 or 4 chronic hepatitis C

Both TA330 and TA331 were issued in February 2015.

The review date for these appraisals is within 1 year of publication.

1. Recommendations

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

TA330

To appraise the clinical and cost effectiveness of sofosbuvir within its licensed indication for treating chronic hepatitis C.

TA331

To appraise the clinical and cost effectiveness of simeprevir within its licensed indication for treating genotype 1 or 4 chronic hepatitis C.

3. Current guidance

TA330

1.1 Sofosbuvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1.

Table 1 Sofosbuvir for treating adults with chronic hepatitis C

	Sofosbuvir in combination with peginterferon alfa and ribavirin		**Sofosbuvir in combination with ribavirin**	
Genotype	**Treatment history**	**Recommendation**	**Treatment history**	**Recommendation**
Adults with genotype 1 HCV	All	Recommended	All	Not recommended
Adults with genotype 2 HCV	All	Not licensed for this population	Treatment-naive	Only recommended for people who are intolerant to or ineligible for interferon
			Treatment-experienced	Recommended
Adults with genotype 3 HCV	Treatment-naive	Only recommended for people with cirrhosis	Treatment-naive	Only recommended for people with cirrhosis who are intolerant to or ineligible for interferon
	Treatment-experienced	Recommended	Treatment-experienced	Only recommended for people with cirrhosis who are intolerant to or ineligible for interferon
Adults with genotype 4, 5 or 6 HCV	All	Only recommended for people with cirrhosis	All	Not recommended
HCV – hepatitis C virus Treatment-naive – the person has not had treatment for chronic hepatitis C Treatment-experienced – the person's hepatitis C has not adequately responded to interferon-based treatment				

1.2 People currently receiving treatment initiated within the NHS with sofosbuvir that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

TA331

1.1 Simeprevir, in combination with peginterferon alfa and ribavirin, is recommended within its marketing authorisation as an option for treating genotype 1 and 4 chronic hepatitis C in adults.

4. Rationale[1]

The new clinical evidence regarding sofosbuvir and simeprevir for treating hepatitis C that has become available since the publication of TA330 and TA331 supports the existing recommendations. In addition, NICE has recommended a number of newer, interferon-free technologies for the treatment of chronic hepatitis C, which are starting to replace the use of treatment combinations that include interferon and ribavirin in clinical practice. Further treatment options for treating chronic hepatitis C are also coming through the technology appraisal work programme.

As such, a review of the guidance is not warranted and it is appropriate to transfer TA330 and TA331 to the static guidance list.

5. Implications for other guidance producing programmes

The guideline planned for hepatitis C continues to be paused until there is stability in the availability of treatments and the cost to the NHS of these drugs (update as of 23rd September 2016).

6. New evidence

The search strategy from the original ERG reports was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from October 2013 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

TA330; Sofosbuvir for treating chronic hepatitis C

At the time of the company's submission in the appraisal of sofosbuvir, there was limited data for some populations, particularly in people with genotype 1 HCV who have been treated previously and in people with genotype 3 HCV. Since then, there has been some additional data published that supports the recommendations made by NICE.

BOSON (n=592), which has recently completed, is a randomised study evaluating the safety and efficacy of sofosbuvir plus ribavirin for 16 or 24 weeks compared with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. The study included people who are treatment-naïve or treatment-experienced with genotype 3 HCV with and without cirrhosis. The results of this study support the evidence already

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

considered during the appraisal and would not be expected to alter the recommendations in the guidance.

There are 17 publications containing (non-UK) real-world data on the use of sofosbuvir based regimens which support the clinical trial data considered during the appraisal. In addition, there are numerous conference reports following up the pivotal studies for sofosbuvir (FISSION, FUSION, POSITRON, NEUTRINO, PHOTON-1, VALENCE and LONESTAR). Each of these studies reported similar sustained virological response rates to those considered by the appraisal committee in TA330.

The list price of sofosbuvir has not changed since TA330.

In summary, there is no evidence that is likely to lead to a change in the existing recommendations in TA330.

TA331; Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C

The evidence identified for simeprevir included 9 systematic reviews, 13 'real-life' case studies and numerous conference reports following-up the pivotal studies for simeprevir (ATTAIN, ASPIRE, C212, RESTORE, QUEST-1 and 2, PROMISE). All of these studies reported similar sustained virological response rates to those already observed and included in the appraisal of simeprevir. The price of simeprevir has not changed.

In summary, there is no evidence that is likely to lead to a change in the existing recommendations in TA331.

Current clinical practice

A consensus meeting on Treatment Regimes for HCV Infection was held on 3 March 2015 by the British Association for the Study of the Liver, British Infection Society, British Society of Gastroenterology, British Viral Hepatitis Group and included leading HCV clinicians, nurses and virologists. The goal of the meeting was to determine a consensus of treatment recommendations taking into account the available evidence, the marketing authorisations and existing NICE guidance.

Genotype 1

The group recommended the use of simeprevir plus peginterferon alfa and ribavirin or sofosbuvir plus peginterferon alfa and ribavirin to treat people with genotype 1 HCV with no evidence of cirrhosis or fibrosis only if oral direct acting antiviral regimens are not funded for this patient group by the NHS.

Since then, NICE has recommended ledipasvir-sofosbuvir, daclatasvir, ombitasvir-paritaprevir-ritonavir (with dasabuvir) and elbasvir-grazoprevir as treatment options for people with genotype 1 HCV in TA363, TA364, TA365 and TA413, respectively. The final appraisal determination issued in December 2016 also provisionally recommends sofosbuvir-velpatasvir for genotype 1 HCV [ID921].

Genotype 4

Simeprevir plus peginterferon alfa and ribavirin

The group recommended the use of simeprevir plus peginterferon alfa and ribavirin to treat people with genotype 4 HCV for people with no evidence of cirrhosis or fibrosis, although the preferred treatment is for therapy with all oral direct acting antiviral regimens (ombitasvir-paritaprevir-ritonavir or ledipasvir-sofosbuvir).

Sofosbuvir plus peginterferon alfa and ribavirin

The group recommended the use of sofosbuvir plus peginterferon alfa and ribavirin to treat people with genotype 4 HCV for people with no evidence of cirrhosis or fibrosis, although the preferred treatment is for therapy with all oral direct acting antiviral regimens (ombitasvir-paritaprevir-ritonavir or ledipasvir-sofosbuvir).

In TA365, NICE recommends 12 weeks treatment with ombitasvir-paritaprevir-ritonavir plus ribavirin for people without cirrhosis (regardless of having never been treated or treated previously). TA365 and TA363 recommends 12 weeks of treatment with ombitasvir-paritaprevir-ritonavir plus ribavirin and ledipasvir-sofosbuvir for people genotype 4 hepatitis C who have cirrhosis[2]. TA413 recommends elbasvir-grazoprevir for 12 weeks. The final appraisal determination issued in December 2016 also provisionally recommends sofosbuvir-velpatasvir for genotype 4 HCV [ID921].

Genotype 2

Intolerant or ineligible for treatment with interferon or previously treated

The group recommended sofosbuvir plus ribavirin for people with genotype 2 HCV who have never been treated before who are intolerant or ineligible for treatment with interferon and for people who have been previously treated with peginterferon alfa and ribavirin, in line with NICE TA330.

The final appraisal determination issued in December 2016 provisionally recommends sofosbuvir-velpatasvir for genotype 2 HCV for people who cannot tolerate interferon or it is not suitable for them, and for previously treated disease [ID921].

Never treated before, eligible for interferon

For people with genotype 2 HCV who have never been treated before who are eligible for treatment with interferon, the group recommended peginterferon alfa and ribavirin for 12 to 16 weeks of treatment unless they have cirrhosis, in which case, they recommended sofosbuvir plus ribavirin, in line with TA330.

[2] For people with compensated cirrhosis who have been previously treated, ledipasvir-sofosbuvir is only recommended is certain criteria are met. See NICE TA363 for more details.

The final appraisal determination issued in December 2016 provisionally recommends sofosbuvir-velpatasvir for genotype 2 HCV with compensated cirrhosis [ID921].

Genotype 3

Sofosbuvir plus peginterferon alfa and ribavirin

The group recommended this in treatment experienced people, only recommended in people with cirrhosis who have never been treated before.

Sofosbuvir plus ribavirin

The group recommended this only in people with cirrhosis who are intolerant or ineligible for interferon treatment.

Also, newer treatments have a better adverse effects profile compared to treatments which include peginterferon alfa. The British Association for the Study of the Liver "Final recommendations for new HCV drugs" can be found here (https://www.basl.org.uk/index.cfm/news/list/cid/8).

The final appraisal determination issued in December 2016 provisionally recommends sofosbuvir-velpatasvir for genotype 3 HCV [ID921].

Conclusion

The new clinical evidence that has become available since the publication of TA330 and TA331 is supportive of the original recommendations. In addition, new, all oral, direct acting antiviral treatments for hepatitis C that are highly effective at shorter treatment durations, and have since been recommended by NICE as treatment options for HCV (see published guidance list in appendix , are starting to replace the use of treatment combinations that include interferon and ribavirin in clinical practice. A review of the guidance is therefore not considered to add value to the NHS, and TA330 and TA331 should be transferred to the static guidance list.

8. Implementation

No submission was received from Implementation.

9. Equality issues

TA330 Sofosbuvir for treating chronic hepatitis C

The Committee considered comments received during consultation which highlighted a potential equality issue from not recommending sofosbuvir for genotypes 4, 5 and 6 stating that there was a higher prevalence of ethnic minorities, people with haemophilia and HIV co-infection particularly in people with genotype 4. Taking into consideration the potential equality issues raised about genotypes 4, 5 and 6 HCV, the high unmet need and the lack of treatment options for people with cirrhosis, the Committee considered it was reasonable to conclude that sofosbuvir plus

peginterferon alfa and ribavirin for treating people with genotype 4, 5 or 6 treatment-naive HCV who have cirrhosis was a cost-effective use of NHS resources.

TA331 Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C

The Committee considered comments received during responses to the appraisal consultation document that recommending simeprevir plus peginterferon alfa and ribavirin only for people with genotype 1 HCV and not for genotype 4 HCV could indirectly discriminate against people from minority ethnic groups. This is because the proportion of people from minority ethnic groups is higher in genotype 4 HCV than in genotype 1. However, having decided that simeprevir plus peginterferon alfa and ribavirin could be considered a cost-effective use of NHS resources in people with genotype 4 HCV, the Committee concluded that no further consideration of this potential equality issue was necessary to meet NICE's obligation to promote equality of access of treatment.

During the scoping phase of this appraisal, comments were received about the specific challenges faced by patients who have hepatitis C and use intravenous drugs, have thalassaemia or have haemophilia. These challenges include adherence to treatment, re-infection risk, consultation attendance, previous treatment failure and higher risk of anaemia. These issues cannot be addressed through the technology appraisal process, and the recommendations do not differentiate between any groups of patients.

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Elbasvir–grazoprevir for treating chronic hepatitis C (2016) NICE technology appraisal guidance 413.

NICE pathway: liver conditions (last updated July 2015)

Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C (2015) NICE technology appraisal guidance 365.

Daclatasvir for treating chronic hepatitis C (2015) NICE technology appraisal guidance 364.

Ledipasvir–sofosbuvir for treating chronic hepatitis C (2015) NICE technology appraisal guidance 363.

Simeprevir in combination with sofosbuvir for treating genotype 1 or 4 chronic hepatitis C (terminated appraisal) (2015) NICE technology appraisal guidance 361.

Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C (2015) NICE technology appraisal guidance 331.

Sofosbuvir for treating chronic hepatitis C (2015) NICE technology appraisal guidance 330.

Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people (2013) NICE technology appraisal guidance 300. Review date: September 2016.

Boceprevir for the treatment of genotype 1 chronic hepatitis C (2012) NICE technology appraisal guidance 253.

Telaprevir for the treatment of genotype 1 chronic hepatitis C (2012) NICE technology appraisal guidance 252.

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (2010) NICE technology appraisal guidance 200.

Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C (2006) NICE technology appraisal guidance 106.

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C (2004) NICE technology appraisal guidance 75.

In progress

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]. NICE technology appraisal guidance. Publication expected January 2017.

Referred - QSs and CGs

Hepatitis C: diagnosis and management of hepatitis C. NICE guideline. Status: paused in January 2014 pending recent/upcoming technology appraisals and recommenced scoping in October 2015.

Suspended/terminated

Faldaprevir for treating genotype 1 chronic hepatitis C. NICE technology appraisal guidance. Status: discontinued in July 2014 as the manufacturer is no longer pursuing a license for this indication [ID670].

Details of changes to the indications of the technology

Technology Appraisal	Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
TA330	Sofosbuvir (Sovaldi, Gilead Sciences) has a UK marketing authorisation for use 'in combination with other medicinal products for treating chronic hepatitis C in adults'. The cost of sofosbuvir is £11,660.98 per 28 tablet pack of 400mg tablets (excluding VAT, 'British national formulary' [BNF] May 2014). The cost of a 12 week course of treatment is £34,982.94 and a 24 week course is £69,965.88 (both excluding VAT), not including the cost for ribavirin and peginterferon alfa	Unchanged Sources: SPC (January 2016) Unchanged BNF (March 2016)
TA331	Simeprevir (Olysio, Janssen) has a marketing authorisation in the UK for use in combination with other medicinal products for treating adults with genotype 1 or 4 chronic hepatitis C, including people with or without cirrhosis, and people who also have HIV. Simeprevir costs £1866.50 per pack of 7x150 mg tablets (excluding VAT, MIMS online, accessed July 2014). A course of simeprevir (for 12 weeks) plus peginterferon alfa and ribavirin (both for 24 weeks) costs £27,220. A course of simeprevir (for 12 weeks) plus peginterferon alfa and ribavirin (both for 48 weeks) costs £32,155.	Indicated in combination with other medicinal products for the treatment of chronic hepatitis C in adult patients Source: SPC (January 2016) Unchanged BNF (March 2016)

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date)
Asunaprevir/Beclabuvir/Daclatasvir (Bristol-Myers Squibb)	Phase 3 clinical trials [redacted]
Danoprevir (Roche)	Phase 2 clinical trials [redacted]
Emricasan (Conatus)	Phase 2 clinical trials [redacted]
Glecaprevir (AbbVie)	Phase 3 clinical trials [redacted]
GS-5816 (Gilead)	Phase 2 clinical trials [redacted]
GS-9857 (Gilead)	Phase 2 clinical trials [redacted]
MK-3682/elbasvir/grazoprevir	Phase 2 clinical trials [redacted]
Ombitasvir/paritaprevir/ritonavir/dasabuvir (Abbvie)	Filed in EU [redacted]
Sovaprevir (Achillion)	Phase 2 clinical trials [redacted]
Tenofovir alafenamide (Gilead)	Phase 3 clinical trials [redacted]
Tenofovir disoproxil fumarate (Viread)	Phase 3 clinical trials [redacted]

Registered and unpublished trials

Trial name and registration number	Details
A Phase 3, Safety and Efficacy Study of Boceprevir/Peginterferon Alfa-2a/Ribavirin in Chronic HCV Genotype 1 IL28B CC Subjects P07755 NCT01544920	Status: completed Randomized, Open Label, Parallel Assignment Enrollment: 737 Start date: May 2012 Expected completion date: May 2015
Observational multicenter study in ex-people who inject drugs (ex-pwids) to evaluate efficacy, safety, and adherence to telaprevir in combination with pegylated interferon alfa and ribavirin in genotype 1 chronic hepatitis C patients INTEGRATE NCT01980290	Status: completed Prospective cohort study Enrollment: 50 Start date: May 2013 Expected completion date: February 2015

Relevant services covered by NHS England specialised commissioning

> "NHS England commissions …a range of drugs including protease inhibitors and anti-virals for patients with hepatitis C" (p156).

Source: (January 2014) Manual for Prescribed Specialised Services. Chapter 65. Highly specialist services for adults with infectious diseases (B07 – Infectious Diseases)

NHS England has established a Hepatobiliary and Pancreas Clinical Reference Group.

NHS England (June 2015) Clinical Commissioning Policy Statement: treatment of chronic Hepatitis C in patients with cirrhosis (B07/P/a).

NHS England (2015) Operational Delivery Networks for Hepatitis C Care in Adults.

NHS England (2013) 2013/14 NHS standard contract for specialised services for infectious diseases (adult) section b part 1 - service specifications (B07/S/a).

Additional information

Biospace (21 January 2015) Merck & Co. (MRK) to Stop Selling Once-Hot Hep C Drug Victrelis.

British Association for the Study of the Liver (2015) Final recommendations for new HCV drugs.

British Association for Sexual Health and HIV (2016) United Kingdom national guideline for the management of the viral hepatitides A, B and C 2015.

British Association for the Study of the Liver, and others (2014) 2014 UK consensus guidelines hepatitis C management and direct-acting anti-viral therapy.

European Association for the Study of the Liver (2015) EASL clinical practice guidelines: recommendations on treatment of hepatitis C 2015.

Medicines and Healthcare Products Regulatory Agency (17 Nov 2014) Boceprevir (Victrelis) and telaprevir (Incivo): predictive factors for sepsis, worsening liver function, and mortality. *Drug Safety Update*, 8(4): s1.

Public Health England (2015) Hepatitis C in the UK: 2015 report.

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Scottish Intercollegiate Guidelines Network (2013) Management of Hepatitis C – a national clinical guideline: SIGN 133. Review date: 2016.

Vertex (11 August 2014) Subject: Discontinuation of INCIVEK® (telaprevir) tablets in the United States. Dear Healthcare provider letter.

Welsh Assembly Government (2015) Together for Health – Liver Disease Delivery Plan. A Delivery Plan for NHS Wales and its Partners to 2020.

World Health Organisation (2014) Guidelines for the screening, care and treatment of persons with hepatitis C infection.

World Gastroenterology Organisation Global Guidelines (2013) Diagnosis, management and prevention of hepatitis C.

Appendix 3 – references

References for TA330; Sofosbuvir for treating chronic hepatitis C

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