NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA300; Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people

This guidance was issued in November 2013.

The review date for this guidance is September 2016.

1. Recommendation

The guidance should be transferred to the 'static guidance list'.

2. Original remits

TA300 to review the clinical and cost effectiveness of peginterferon alfa in combination with ribavirin within their licensed indications for the treatment chronic hepatitis C in children and young people.

3. Current guidance

Peginterferon alfa in combination with ribavirin is recommended, within its marketing authorisation, as an option for treating chronic hepatitis C in children and young people.

This guidance updates and replaces:

Section 1.7, bullet 2 only, of NICE technology appraisal guidance 75 (TA75) 'Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C'

Part of section 1.6 of NICE technology appraisal guidance 106 (TA106) 'Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C'.

4. Rationale[1]

The marketing authorisation for peginterferon and ribavirin has not changed since the guidance was produced. There is availability of more evidence relating to long-term efficacy, safety, sub-groups and cost-effectiveness. However, this will not change current guidance as the evidence is supportive of current recommendations and it is acknowledged that further randomised controlled comparative studies are needed. The guideline planned for hepatitis C is currently paused until there is

[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

stability in the availability of treatments and the cost to the NHS of these drugs (as of 23rd September 2016). In conclusion, there is no new evidence that is likely to change the recommendations in TA300, so it would be appropriate to transfer this guidance to the static 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 Assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from November 2012 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

The literature search identified several new studies in children since the guidance was published in 2013. Of these 12 were relevant to the scope of the remit or to the recommendations in TA300. This included evidence of long-term efficacy and safety, evidence from meta-analyses, evidence of use in co-morbidities, use in specific genotypes and cost-effectiveness studies. Only a few studies were conducted in the UK. There has been no change to the marketing authorisations to any of the drugs and there are no newly licensed comparators in children since the guidance was published.

7.1 Efficacy and safety

In TA300 the committee was concerned the trials were poor quality and had a low number of participants. It was also concerned about the adverse events and long-term effects from treatment on children's growth. 9 studies were found that were either observational, follow-up studies or meta-analyses. They all covered children in the target age group (3 to 17 years), had small sample sizes (n=30 to 107) and studied sustained virological response (SVR) in a range of genotypes (from 1 to 4). But only one of these was conducted in the UK. All found the combination of peginterferon-alpha with ribavirin efficacious in genotypes 2 and 3, over 1 and 4. Rosen, I et al. 2013 found there may be a benefit for treatment with peginterferon-alpha 2a than 2b (although no statistical outcome differences were found between the two groups, n=30). Of note; Abdel-Hady et al, 2014 conducted an observational study in the UK and found treatment had no significant effect on the growth of children (n=74 across all 4 genotypes). There is conflicting results from an open-label follow-up study conduct with peginterferon 2b in children from Egypt, by Haber, B et al. 2016 which found growth was indeed affected

(n=54). All these studies are either observational or meta-analyses of observation studies. There is still a need for large RCTs and studies conducted in the UK for the long-term effect of peginterferon plus ribavirin in children. Most of the results are also conflicting so no new evidence here would change current guidance.

7.2 Co-morbidities

The original scope outlined that all groups (i.e. co-HIV) should be included in the analysis. Only 1 study is relevant to the target population. Mehrnoush, L et al. 2015, reported results from a case-controlled study for treatment in haemophilic children. It found, compared to treating adults, SVR was not any different according to HCV genotype but the efficacy may be higher in haemophilic children. There is not enough evidence for a change in guidance relating to this population.

7.3 Comparators other than best supportive care

The committee had concerns in TA300 that no comparisons were made to other treatments that may be used off-license in children. 1 systematic review with a meta-analysis was found by El Sherbini, A et al. 2015, which compared peginterferon-alpha against interferon-alpha monotherapies and as a combination therapy with ribavirin (n=934, but the age range in the analysis was wider than the guidance, between 2 and 19 years)). It found that SVR was slightly higher with combination treatment than monotherapies (genotypes 1, 2 and 3), and adverse events with the peginterferon-alpha combination was higher than the interferon combination. Peginterferon-alpha plus ribavirin had a higher SVR for genotype 1 (modest superiority, 50% vs 40%), 2 and 3 but was lower for genotype 4 compared to interferon-alpha plus ribavirin. The authors conclude that although the superiority of peginterferon-alpha for SVR was higher in genotypes 2 and 3, the significant adverse events and modest responses in genotypes 1 and 4, renders peginterferon-alpha plus ribavirin a sub-optimal therapy compared to interferon-alpha plus ribavirin. Authors conclude that clinical trials with direct comparisons to anti-viral drugs is needed in the future so the evidence presented here will not change current guidance.

7.4 Cost-effectiveness studies

There are concerns over the cost for drugs to treat hepatitis C to the NHS and as such the guideline has been suspended until a time this has been resolved. A recent paper released by the centre of health economics in York has tried to resolve some of this uncertainty. The model revealed that the newer costlier drugs should be reserved for second line after peginterferon-alpha. This still maintained similar cures rate (90%). This is strong case to keep current guidance unchanged, although it is not clear if the population for the analysis included children. This study is good representation of the effort made to resolve the substantial uncertainty around treatment costs to the

NHS. Once this is resolved, it may restart the clinical guideline which can update and incorporate current guidance.

8. Adoption and Impact

No submission was received from the Adoption and Impact team.

9. Equality issues

In the original guidance no adjustments were made but it was suggested that young people who misuse drugs, recent immigrants and asylum seekers who are children should be considered in this appraisal. However, because NICE does not exclude any specific groups of children and young people in this appraisal, this suggestion did not need further action.

GE paper sign off: Helen Knight, Associate Director, 18/11/2016

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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
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

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

Hepatitis B and C testing: people at risk of infection (2012) NICE guideline PH43

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

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 (2013) NICE technology appraisal guidance 75

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

Hepatitis C (chronic) - sofosbuvir and velpatasvir (2017) NICE technology appraisal guidance 430

Suspended/terminated

Hepatitis C NICE guideline. Publication date to be confirmed.

NICE has decided that the development of a hepatitis C clinical guideline should continue to be paused until there is stability in the availability of treatments and the cost to the NHS of the drugs (September 2016).

Faldaprevir for treating genotype 1 chronic hepatitis C [ID670] NICE technology appraisal guidance. Publication date to be confirmed.

Boehringer Ingelheim has informed us that it has decided not to proceed as it considers that there are now several new treatment options available for patients and that there is no longer an unmet medical need that would be filled with this regimen (July 2014).

Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Peginterferon alfa-2a (Pegasys, Roche Products) in combination with ribavirin has a UK marketing authorisation for the treatment of children and adolescents 5 years of age and older with chronic hepatitis C, who test positive for serum hepatitis C virus (HCV) ribonucleic acid (RNA) and who have not previously received any treatment. The price of peginterferon alfa-2a is £107.76 for a 135-microgram prefilled syringe or pen and £124.40 for a 180-microgram prefilled syringe or pen (excluding VAT; 'British national formulary' [BNF] edition 65).	**Current indication** Pegasys in combination with ribavirin is indicated for the treatment of chronic hepatitis C in treatment-naïve children and adolescents 5 years of age and older who are positive for serum HCV-RNA. When deciding to initiate treatment in childhood, it is important to consider growth inhibition induced by combination therapy. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis. Source: SPC (June 2016) **Indication** [redacted] Source: Roche letter to NICE (21 Sept 2016) **Patent** Pegasys patent expires [redacted] Source: SPS (log in required) **Cost - Pegasys**

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
	£107.76 - 135 micrograms 1 pre-filled injection £497.60 - 180 micrograms 4 pre-filled injections Source: BNF (September 2016)
Peginterferon alfa-2b (ViraferonPeg, Merck Sharp and Dohme [MSD]) in combination with ribavirin has a UK marketing authorisation for the treatment of children aged 3 years and older and adolescents who have chronic hepatitis C without hepatic decompensation, who test positive for serum HCV RNA and who have not previously received any treatment. The price of peginterferon alfa-2b is £1.33 per microgram and it is available in 50-, 80-, 100-, 120- and 150-microgram pens costing £66.46, £106.34, £132.92, £159.51 and £199.38 respectively (BNF edition 65).	**Current indication** ViraferonPeg is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, previously untreated, without liver decompensation, and who are positive for HCV-RNA. When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition that may be irreversible in some patients. The decision to treat should be made on a case by case basis. Source: SPC (Sept 2015) **Indication** [redacted] Source: MSD letter to NICE (26 Sept 2016) **Patent** Expired 16 April 2010 Source: SPS (log in required) **Cost - ViraferonPeg**

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
	£66.46 - 50 microgram 1 pre-filled injection £106.34 - 80 microgram 1 pre-filled injection £132.92 - 100 microgram 1 pre-filled injection £159.51 - 120 microgram 1 pre-filled injection £199.38 - 150 microgram 1 pre-filled injection Source: BNF (September 2016)
Ribavirin (manufactured as Copegus by Roche Products) has a marketing authorisation in combination with peginterferon alfa-2a or interferon alfa-2a for treating chronic hepatitis C; the marketing authorisation for Copegus does not include specific recommendations for use in children and young people.	**Current indication** Copegus is indicated in combination with other medicinal products, for the treatment of chronic hepatitis C (CHC). Source: SPC (February 2015) Rebetol is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults. Rebetol is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) for paediatric patients (children 3 years of age and older and adolescents) not previously treated and without liver decompensation. Source: SPC (November 2015) **Current indication** [redacted] Source: MSD letter to NICE (26 Sept 2016) **eMIT indicative prices (NHS average prices ex. VAT)** £46.46 – 200mg 42 tablets

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
	£52.10 – 200mg 112 tablets £119.00 – 200mg 168 tablets £114.79 – 400mg 56 tablets £69.28 – 200mg 84 capsules £75.93 – 200mg 140 capsules £123.38 – 200mg 168 capsules **Cost - Copegus (Roche)** £233.58 - 200mg 112 tablets £350.37 - 200mg 168 tablets £233.58 - 400mg 56 tablets **Cost - Rebetol (MSD)** £160.69 - 200mg 84 capsules £267.81 - 200mg 140 capsules £321.38 - 200mg 168 capsules £67.08 40mg oral solution **Cost - ribavirin (AAH Pharmaceuticals)** £92.50 - 200mg 42 tablets £246.65 – 200mg 112 tablets £369.98 - 200mg 168 tablets £160.69 - 200mg 84 capsules £267.81 - 200mg 140 capsules £321.38 - 200mg 168 capsules **Cost - ribavirin (Teva)** £92.50 - 200mg 42 tablets £246.55 - 200mg 112 tablets £369.98 - 200mg 168 tablets

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
	£160.69 - 200mg 84 capsules £267.81 - 200mg 140 capsules £321.38 - 200mg 168 capsules Source: BNF (September 2016)

Details of new products

Drug (company)	Details (phase of development, expected launch date)	Post topic selection
Sofosbuvir-GS-9857-velpatasvir (Gilead)	Marketing authorisation expected [redacted]	Sofosbuvir-GS-9857-velpatasvir for treating chronic hepatitis C [ID1055]
Glecaprevir with pibrentasvir (Abbvie)	Launch expected [redacted]	Glecaprevir with pibrentasvir for treating chronic hepatitis C [ID1085]

Registered and unpublished trials

Trial name and registration number	Details
Assessment of the Safety, Efficacy, Tolerability and Pharmacokinetics of PEG-Intron Plus REBETOL in Pediatric Patients With Chronic Hepatitis C NCT00761735	Purpose: 5-year long term follow-up study in pediatric participants who were treated with at least one dose of peginterferon alfa-2b (PEG-IFN) and ribavirin (RBV) and who completed the follow-up in the P02538 Part 1 study (NCT00104052). No study drug therapy will be administered during the P02538 Part 2 study Enrollment: 94 Status: completed January 2013 Study results: available online (Wirth et al. 2010 was included in the ERG Assessment Report)

Relevant services covered by NHS England specialised commissioning

NHS England (2015) Clinical commissioning policy statement: Treatment of chronic hepatitis C in patients with cirrhosis. Reference: NHS England B07/P/a

NHS England (2015) Operational delivery networks for hepatitis C care in adults. Service specification: F04 S f

Additional information

British Association for Sexual Health and HIV - BASHH (2016) United Kingdom national guideline on the management of the viral hepatitis A, B and C 2015

British Association for the Study of the Liver (February 2016) Treatment recommendations for the management of patients with chronic HCV Infection

European Association for the Study of the Liver (2015) EASL recommendations on treatment of hepatitis C 2015

Scottish Intercollegiate Guideline Network (2013) Management of hepatitis C (SIGN 133)

World Health Organisation (2016) Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection

References

Rosen, I et al (2013). **Pegylated interferon alfa and ribavirin for children with chronic hepatitis C**. *World journal of gastroenterology,* 19(7): 1098-103.

Abdel-Hady M et al. (2014) **Treatment of chronic viral hepatitis C in children and adolescents: UK experience**. *Archives of Disease in Childhood: Education and Practice Edition,* 99(3): 505-510

Haber, B et al. (2016). **Long-term Follow-up of Children Treated With Peginterferon and Ribavirin for Hepatitis C Virus Infection**. *Journal of pediatric gastroenterology and nutrition*

Mehrnoush, L et al. (2015). **High Response Rate to Pegylated Interferon Alpha and Ribavirin Combination Therapy in Hemophilic Children with Chronic Hepatitis C; A Case-Control Study**. *Pediatric hematology and oncology,* 32(6): 399-405.

El Sherbini, A et al. (2015). **Systematic review with meta-analysis: comparison between therapeutic regimens for paediatric chronic hepatitis C**. *Alimentary pharmacology & therapeutics,* 42(1): 12-9

Faria, R et al (2016). **Improving Value for Money from Drug Treatment of Hepatitis C.** Centre of health economics publications. Accessed October 2016.