Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Final protocol, 27th June 2012

1. Title of the project:

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people.

2. Name of TAR team and 'lead'

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3. Plain English Summary

The hepatitis C virus (HCV) in children and young people is most commonly acquired via 'vertical' transmission where the virus is passed down from an HCV-infected mother to her child in the weeks before and after childbirth. HCV is a slowly progressing disease and develops over a number of years, often decades. However, a small proportion of children with chronic HCV will develop significant liver disease during childhood. For many people there can be few obvious signs and symptoms of infection, although quality of life may be affected.

Drug treatment is available for adults with chronic HCV, and typically involves taking a combination of peginterferon (injected beneath the skin usually once per week) and ribavirin (taken orally each day) for between 6 and 12 months. For children, the best course of therapy is less clear but it has been suggested that they should be treated using the same principles applied to the treatment of adults. The National Institute for Health and Clinical Excellence (NICE) have previously recommended the use of peginterferon and ribavirin combination therapy in adults in the UK. The marketing authorisations for the two available brands of peginterferon have either been extended to allow children and young people to also receive treatment, or will be extended shortly. It is important for NICE to update its guidance to the health service to reflect any changes in the drug licences.

The aim of this project is to systematically review the available studies to enable NICE to make evidence-informed policy recommendations for the treatment of HCV in children and young people. In addition, an overall estimate will be made of the benefit to patients in relation to how much treatment costs, taking into account any effect on patients' quality of life. This will allow NICE to determine whether treatment represents an efficient use of health service money.

4. Decision problem

The aim of this health technology assessment is to review the clinical effectiveness and cost-effectiveness of peginterferon alfa (alfa-2a and alfa-2b) in combination with ribavirin within the licensed indications for the treatment of chronic hepatitis C in children and young people.

There have been a number of technology appraisals by NICE of peginterferon and ribavirin for the treatment of adults with chronic hepatitis C, addressing mild (TA106[1]) and moderate to severe (TA75[2]) HCV, with the most recent appraisal in 2010 focusing on specific patient subgroups that were affected by licence extensions (TA200[3]). All of these appraisals were supported by independent assessment reports conducted by SHTAC.[4-6]

Since publication of these three technology appraisals, an additional extension to the licence for peginterferon alfa-2b has been granted, and an extension for peginterferon alfa-2a is undergoing consideration, to include those under the age of 18 years. This health technology assessment relates specifically to the treatment of children and young people.

4.1 Background

Hepatitis C

Hepatitis C is a disease of the liver arising from the blood-borne hepatitis C virus (HCV). It is a slowly progressing disease which has two main phases of infection: acute and chronic. The period immediately after HCV infection is the acute phase. In adults, the virus will be cleared spontaneously during this phase in approximately 20% of cases, with the remaining 80% developing chronic infection. Chronic HCV is defined as infection persisting for more than six months. Chronic HCV is the focus of this assessment.

HCV is a ribonucleic acid (RNA) virus which has six genetic variations, known as genotypes. There are six major HCV genotypes (i.e. genotype 1, 2, 3, etc.), and within these there are several sub-types (labelled a, b, c, etc.). The prevalence of the genotypes varies considerably between countries, with the most prevalent groups in England and Wales being genotypes 1 and 3 (representing at least 90% of infections).[7-9] Of these, genotype 3a is the most common with a prevalence of 39%, followed by

genotype 1a with a prevalence of 22%.[9] Response to treatment is strongly influenced by HCV genotype (see below).

Chronic HCV can be categorised as mild, moderate or severe according to the extent of damage to the liver. This is based on both the level of fibrosis (scarring) in the liver and the degree of inflammation and destruction of liver cells (necroinflammation). For many people with chronic HCV, symptoms are mild and non-specific (e.g. fatigue, flu-like symptoms, itching and nausea),[10-12] and many children are entirely asymptomatic. For some people however, chronic infection with HCV can have a more significant impact with corresponding reductions in quality of life which can be unrelated to the extent of liver damage.[13] These include the social burden associated with stigma and also care-giver stress.[12] Symptoms may also occur later in the disease when liver damage has progressed.

Aetiology

HCV is acquired primarily through exposure to contaminated blood. In adults in the UK the most common source of infection is through the sharing of injecting equipment in intravenous drug misuse. This accounts for around 90% of cases.[9] Other sources of HCV infection include needle stick injury, tattooing and body piercing, and from treatment with contaminated blood products (prior to blood screening in 1991). The risk of sexual transmission is thought to be low.[9]

In children, mother-to-child ('vertical') transmission is the primary reason for HCV infection, with perinatal transmission being the most important route, and to a lesser extent, intrauterine transmission.[14] The rate of perinatal transmission from an HCV infected mother to her child ranges from 2% to 5%.[12;15] Breast feeding does not appear to increase the risk of HCV transmission, even though HCV RNA may be detected in breast milk and colostrum. A number of factors may change the risk of mother-to-child transmission. There is an increased risk of transmission depending on the level of maternal viral load and whether the mother is also co-infected with human immunodeficiency virus (HIV).[16] A systematic review of 77 studies published in 2001 showed that the rate of mother-to-child transmission was in the region of 5% from women without HIV infection and 22.1% from women with HIV infection.[17]

Epidemiology

Estimates based on laboratory surveillance by the Health Protection Agency (HPA)[18] in the UK suggest that around 216,000 individuals were chronically infected with HCV in 2011. The prevalence of HCV in children of all ages is unclear. The HPA report estimated that 26 children aged ≤ 1 year, 21 young people aged 1 to 14 years and 439 people between the ages of 15 and 24 years were newly diagnosed with HCV in England in 2010. Many of the latter will be acquired through injecting drug

use which often begins in late adolescence and early adulthood.[18]

Published population-based studies range in their estimates, in part owing to many studies having small, and in some cases, unrepresentative samples (e.g. antenatal screening can be selective), and thus vertical transmission may be undetected in some. Estimates generally suggest that the prevalence of HCV in children in developed countries are in the region of 0.1% to 0.4%.[12;14;19] In some populations this may exceed 10% (for example in some regions of Saudi Arabia and Africa).[12] Estimates of regional prevalence rates in pregnant women in the UK range from 0.19% to 0.43%.[14] Studies have shown that genotypes 1, 2 and 3 are the most clinically relevant groups in children with HCV, whilst genotype 4 is less prevalent.[12]

Progression and prognosis

The natural history of HCV acquired during childhood is not completely understood. In vertical transmission, estimates suggest somewhere between 2.4% and 55% of children will spontaneously clear the infection, with the cumulative probability of progression to chronic HCV being approximately 80%.[12;14] Caution is required in the interpretation of these data however, as most of the studies that these estimates come from have small numbers of children, with different ages at acquisition of HCV and different co-morbidities.[14] Spontaneous viral clearance is thought to be dependent on genotype, with children infected with genotype 3 having a higher likelihood of clearance than those with genotype 1.[12]

Fibrosis of the liver is slowly progressive, and thus severity of HCV relates to the duration of infection. As a result, progression to advanced disease is less likely in children than in adults.[19] A recent systematic review[15] evaluated the outcomes of untreated HCV in children from population based screening studies. Results from 25 studies including 733 people infected with HCV as children showed that of the 180 (25%) who underwent a liver biopsy as adults, 4% (1% of the total) had liver cirrhosis with no other individuals developing a severe adverse outcome. The authors conclude that the majority of people with disease acquired during childhood have a mild degree of hepatitis and fibrosis during childhood. No clear risk factors for severe adverse outcomes were identified in the studies reviewed. The review conclusions were limited by the relatively short follow-up periods in most of the studies included.[15]

Other studies suggest that the rate of advanced liver fibrosis or cirrhosis seen on liver biopsy in children with chronic HCV infection is approximately 4% to 6%,[12;19] with 4-5 children undergoing liver transplantation each year in the United States for end-stage liver disease.[19]

Current treatment options

Optimal therapy for children with chronic HCV is not clearly defined due to the lack of efficacy data in children.[14;19] Published NICE technology appraisals on the treatment of chronic HCV recommend treatment for any severity of disease but relate only to adults.[1-3] The 2006 SIGN guidelines on the management of hepatitis C recommend that children with moderate or severe HCV should be considered for treatment with peginterferon and ribavirin, whilst the benefits of treatment for those with mild HCV should be weighed against the risk of treatment side effects.[20] In current clinical practice in the UK, all children over 3 years of age are considered for treatment, with selection not based on histological severity. In those with mild disease, which is the majority, the decision to treat is based on genotype and the likelihood of response. Those with genotypes that respond more favourably to treatment (genotypes 2 or 3) are more likely to receive treatment, whilst those with genotypes 1 or 4 often prefer a 'watchful waiting' approach. This generally consists of six monthly reviews and monitoring of viral load and disease progression, and ultrasound scans every 1-2 years. Treatment of the minority who have severe disease is always considered more urgent, and treatment is more likely to be recommended. It is recommended that children diagnosed with HCV are referred to, and managed in conjunction with, a paediatric hepatologist at one of the three specialised paediatric hepatology centres in the UK.[14] Shared care pathways are well established in the UK, with treatment and overall care delivered outside the three specialist centres at joint clinics.

4.2 Definition of the intervention

The intervention under review is dual therapy with peginterferon and ribavirin. The peginterferons are cytokines whose mechanism of action is to assist the immune response by inhibiting viral replication. Two forms are available: peginterferon alfa-2a (Pegasys, Roche Products Ltd.) and peginterferon alfa-2b (ViraferonPeg, Merck Sharp & Dohme Ltd). Ribavirin (RBV) is a synthetic nucleoside analogue which is available in two primary forms - Copegus (Roche Products Ltd.) and Rebetol (Merck Sharp & Dohme Ltd.) - as well as a number of generic forms - Ribavirin BioPartners (BioPartners GmbH), Ribavirin Mylan (Generics UK) and Ribavirin Teva (Teva Pharma B.V.). Copegus is indicated for combination therapy only with peginterferon alfa-2a, whilst Rebetol is indicated for combination therapy only with peginterferon alfa-2b.

Peginterferon alfa-2a was originally licensed in June 2002 and an extension to the license to allow treatment in children and young people is expected shortly. In clinical practice, the dose used for children is 180mcg/1.73m^2 body surface area, once weekly, administered subcutaneously. Peginterferon alfa-2b was originally licensed in May 2000 with the most recent extension to the license for use in children granted in February 2012. The recommended dose for children is 60mcg/m^2

body surface area, once weekly, administered subcutaneously. Treatment duration is recommended at 24 or 48 weeks dependent on genotype.

The two primary forms of ribavirin, Copegus (Roche Products) and Rebetol (Merck Sharp & Dohme), were licensed in November 2002 and May 1999 (oral solution, January 2005) respectively. The recommended dose of ribavirin is dependent on body weight and is 15 mg/kg/day for children and adolescents weighing <47 kg. It is taken orally each day in two divided doses as an oral solution.

For peginterferon alfa-2b, the recent therapeutic indication is the treatment of children and adolescents aged three years and older with chronic hepatitis C, without liver decompensation, who are positive for serum HCV RNA and who have not previously been treated. The license for peginterferon alfa-2a is anticipated to be indicated for children and adolescents aged five years and older. The marketing authorisation for peginterferon alfa-2b does not permit peginterferon monotherapy in this age group and treatment must be given in combination with ribavirin. It is expected to be the same for peginterferon alfa-2a.

Full details of the indications, dosages and duration of treatment are given in the Summary of Product Characteristics.[21-24]

4.3 Place of the intervention in the treatment pathway

Treatment of chronic HCV is aimed at eradicating the virus and preventing related complications. Accordingly, the main goal of treatment is to clear HCV and achieve a sustained virological response (SVR), defined as undetectable HCV RNA in the serum at least six months after treatment ends. Successful treatment reduces the rate of progression of liver fibrosis and related complications and improves quality of life for patients. For adults, combination therapy with peginterferon alfa and ribavirin is recommended as first-line treatment for chronic HCV patients,[3] but there is currently no NICE guidance for the treatment of hepatitis C in patients younger than 18 years. In clinical practice in the UK, all children with chronic HCV over the age of 3 years are considered for treatment with peginterferon and ribavirin as first-line treatment.

4.4 Relevant comparators

The comparators for this review will comprise no active treatment, i.e. best supportive care (BSC), also referred to as ‘watchful waiting’. BSC treatment is variable and includes treatment without any form of interferon therapy, symptomatic treatment, monitoring of viral load and disease progression by blood tests and ultrasound scans, and can include treatment in specialised paediatric hepatology centres. The interventions will also be compared with each other within their licensed indications, i.e. peginterferon alfa-2a + ribavirin versus peginterferon alfa-2b + ribavirin. Combination therapy will

not be compared with peginterferon monotherapy due to restrictions in the marketing authorisation (see section 4.2).

4.5 Population and relevant sub-groups

The patient populations for this review are limited to those that are, or are likely to be, affected by the recent licence extensions for the peginterferons which are children and young people aged 3-17 years with chronic hepatitis C. People with mild, moderate or severe HCV are included, as are those who are co-infected with HCV/HIV. The population includes people who are treatment naïve as well as those who have been previously treated and did not respond, or who responded but relapsed (although previously-treated people are not included in the marketing authorisation for peginterferon alfa-2b). Potential subgroups can be described according to the presence of factors associated with a sustained virological response (e.g. genotype). Assessment of the effectiveness of peginterferon alfa and ribavirin for any identified subgroup will be limited by the available data and the appropriateness of subgroup analyses (defined *a priori*, evidence that is statistically powered) within any identified trials.

5. Report methods for the synthesis of evidence of clinical effectiveness

A review of the evidence for clinical-effectiveness and cost-effectiveness will be undertaken systematically following the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care.[25]

5.1 Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify all relevant studies investigating the two forms of peginterferon alfa with ribavirin in children with HCV. Separate studies will be conducted to identify studies of clinical effectiveness, cost-effectiveness, health-related quality of life and epidemiology.

The following electronic databases will be searched: The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials, NHS CRD (University of York) - Database of Abstracts of Reviews of Effects (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); PreMedline In-Process & Other Non-Indexed Citations (Ovid); Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) & Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); NIHR-Clinical Research Network Portfolio; Clinical Trials.gov and Current Controlled Trials. Relevant hepatitis C symposia will also be searched.

Bibliographies of related papers will be assessed for relevant studies. The manufacturers' submissions to NICE will be assessed for any additional studies that meet the inclusion criteria. Experts will be contacted to identify additional published and unpublished evidence.

Literature searches will be carried out from database inception to the present. For the cost-effectiveness assessment, searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see section 6) and may include a wide range of study types (including non-randomised studies). All searches will be updated when the draft report is under review, prior to submission of the final report.

5.2 Inclusion and exclusion criteria

The following criteria are those stipulated in the final scope issued by NICE.

5.2.1 Population

Children and young people aged 3 to 17 years (peginterferon alfa-2b), or 5 to 17 years (peginterferon alfa-2a), with chronic hepatitis C, without liver decompensation and who are positive for HCV RNA. All groups will be considered, including:

- People with HIV co-infection
- People with all grades of severity of chronic hepatitis C (mild, moderate and severe)
- People who are treatment naïve or, if appropriate, people who have been previously treated but who relapsed or did not respond.

5.2.2 Interventions

- Peginterferon alfa-2a in combination with ribavirin
- Peginterferon alfa-2b in combination with ribavirin

5.2.3 Comparators

- Best supportive care (e.g. symptomatic treatment, monitoring, treatment without any form of interferon therapy)
- The interventions will be compared with each other within their licensed indications, i.e. peginterferon alfa-2a + ribavirin versus peginterferon alfa-2b + ribavirin

5.2.4 Outcomes

Studies must report sustained virological response (SVR, defined as undetectable HCV RNA at least six months after treatment cessation). Studies may also include one or more of the following:

- virological response to treatment (e.g. during treatment, end of treatment)
- biochemical response (e.g. ALT)
- liver inflammation and fibrosis
- mortality
- adverse effects of treatment, including effects on growth
- health-related quality of life (HRQoL)

5.2.5 Types of studies

- Randomised controlled trials (RCTs) will be included. Where no RCTs of relevance are identified non-randomised controlled trials will be considered for inclusion. Studies without a control group will only be considered for inclusion in the absence of any controlled studies.
- Studies published in the last five years (i.e. since 2007) as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken.
- For the systematic review of cost-effectiveness, studies will only be included if they report the results of full economic evaluations (cost-utility analyses, cost-effectiveness analyses [reporting cost per life year gained], cost-benefit analyses or cost-consequence analyses).
- Systematic reviews will only be used as a source of references.
- Case series, case studies, narrative reviews, editorials and opinions will not be included.
- Only studies published in the English language will be included.

5.3 Screening and data extraction process

5.3.1 Reference screening

The titles and abstracts of studies identified by the search strategy will be assessed for potential eligibility using the inclusion/exclusion criteria detailed above. This will be performed independently by two reviewers. Full papers of studies that appear potentially relevant will be requested for further assessment, and these will be screened by one reviewer and checked by a second. Any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

5.3.2 Data extraction

Data will be extracted by one reviewer using a standardised data extraction form. Extracted data will be checked by a second reviewer. Discrepancies will be resolved by discussion, with recourse to a third reviewer when necessary.

5.4 Quality assessment strategy

The quality of the clinical effectiveness studies will be assessed according to criteria based on that used by the CRD (University of York).[25] The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus, and if necessary a third reviewer will be consulted. Quality assessment of the cost-effectiveness studies is detailed in section 6.1.

5.5 Methods of data analysis/synthesis of clinical-effectiveness data

Clinical effectiveness data will be synthesised through a narrative review with tabulation of the results of included studies. Where data are of sufficient quality and homogeneity, a meta-analysis of the clinical effectiveness studies will be performed to estimate a summary measure of effect on relevant outcomes. If a meta-analysis is appropriate, it will be performed using Cochrane Review Manager (RevMan 5) software and heterogeneity explored. Where data allow, clinical- and cost-effectiveness will be assessed according to HCV genotype.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Identification and systematic reviewing of published cost-effectiveness studies

The sources outlined above in section 5 will be used to identify studies of the cost-effectiveness of peginterferon alfa-2a and -2b in combination with ribavirin in children with hepatitis C. The aim of the review is to identify studies that are relevant to the UK NHS. The inclusion and exclusion criteria for the systematic review of published cost-effectiveness studies will be identical to that applied in the systematic review of clinical effectiveness, differing only in study design (outlined in section 5.2.5). The quality of the included economic evaluations will be assessed using a critical appraisal checklist based upon those proposed by Drummond and colleagues[26] and Philips and colleagues.[27] The data from these studies will be tabulated and discussed in a narrative review. Any economic evaluation included in sponsor submissions to NICE will be assessed using the same quality criteria as for published economic evaluations, but will be reported separately.

6.2 Methods for estimating quality of life

Where presented, HRQoL data will be extracted from studies included in the systematic review of clinical effectiveness, the systematic review of cost-effectiveness or the sponsor submission. In addition, a systematic literature search will be conducted specifically for publications reporting HRQoL or health state utility for children with HCV, including the impact of peginterferon alfa-2a or -2b on these children. Studies will be synthesized through a narrative review with tabulation of results of included studies. Where available, HRQoL data will be used in our economic model. In the absence of evidence that meets our quality criteria, the model may use indirect evidence of quality of life from

alternative sources, for example HRQoL from adults with HCV. There are methodological challenges with measuring health state utilities in children, for example the use of parents' valuations as proxies, and these issues will be explored by discussion within the team.

6.3 Economic Modelling

The Markov model developed by SHTAC for a previous NICE assessment of treatment for mild chronic hepatitis C[6] will be reviewed to assess its applicability to children within the scope of the current review. If the model structure is considered appropriate, the model parameters will be further reviewed to determine whether more relevant data are available for disease progression, health state utility or resource use/cost for children with HCV. The perspective for the analysis will be that of the NHS and Personal Social Services, with costs and outcomes discounted at 3.5%. The time horizon for our analysis will initially be governed by the outcomes reported, and the follow-up data available from included clinical trials. We will investigate the feasibility of extrapolating treatment effects beyond the clinical trials in order to model a lifetime horizon. Incremental cost-effectiveness of the interventions will be estimated in terms of cost per quality-adjusted life year (QALY) gained, as well as the cost per life year gained if data permit.

The simulated population will be defined on the basis of the published evidence about the characteristics of children in the UK with chronic HCV, within the scope of the current review. This will include children with HIV co-infection, or who have been previously treated where good quality clinical effectiveness evidence is available.

Parameter values for the model will be obtained from relevant research literature, including our own systematic review of clinical effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group, we may use data from sponsor submissions to NICE or clinical experts' opinion. Searches for additional information regarding model parameters, patient preferences and other topics will be conducted as required. All updated parameter estimates will be derived from the best available published literature, NHS sources (including the Finance Department at Southampton University Hospitals Trust) and industry submissions, where applicable. Sources for, and methods of, deriving parameter values will be stated clearly.

Adverse effects will be accounted for in the model if these are clearly reported by the trials included in our systematic review of clinical effectiveness. These will be included as an extra cost and, where possible, disutility.

Uncertainty will be explored through both one way sensitivity analyses and scenario analysis. A probabilistic sensitivity analysis (PSA) will be undertaken if the both the data and modelling approach

permit this. The outputs of any PSA will be presented using plots of the cost–effectiveness plane and cost-effectiveness acceptability curves.

7. Handling the company submission(s)

All data submitted by the manufacturers will be considered if received by the TAR team no later than 3rd October 2012. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's guidance on presentation,[28] will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Methods adopted and incremental cost-effectiveness ratios (ICERs) estimated from models supporting the company submission will be compared with published economic evaluations of peginterferon and ribavirin for children included in the assessment report together with the results from the Assessment Group's analysis. Reasons for any large discrepancies in estimated ICERs will be explored and, where possible, explained.

Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name, e.g. in brackets).

8. Competing interests of authors

There are no competing interests.

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