National Institute for Health and Clinical Excellence

Multiple Technology Appraisal (MTA)

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

Response to consultee and commentator comments on the draft scope (no consultation on draft remit required)

Section	Consultees	Comments	Action
Background information	Southampton Health Technology Assessments Centre (SHTAC)	No comments.	No action required.
	Royal College of Pathologists (RCP)	No comments.	No action required.
	Royal College of Paediatrics and Child Health (RCPCH)	All new patients now are either new migrants or children with vertical transmission.	Comment noted.
	Roche Products	No comments.	
	Healthcare Improvement Scotland (HIS)	In children, the vast majority of cases occur as a result of mother to child transmission at the time of birth, not percutaneous exposure. Asymptomatic children are currently considered for treatment if they have favourable genotype, and are likely to adhere. Successful treatment before child-bearing age removes the risk of transmission to infants born (risk of 5% from PCR positive woman).	Comment noted. The background in the scope has been updated to reflect this new information.

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	MSD	The draft scope states that 439 people between the ages of 15 and 24 were newly diagnosed with HCV in England in 2010. We would like to note that the majority of these patients would have been aged 18 or over, therefore are not relevant for this appraisal. Figure 11 in the Health Protection Agency (HPA) Report on Hepatitis C in the UK, 2011[1], illustrates that the majority of these 439 diagnosed patients were aged between 20 and 24 years. The draft scope does not include an estimate of HCV diagnoses among patients aged under 15 years. The Health Protection Report (Volume 5, Issue 29) states that 26 patients aged under 1 year and 21 patients aged between 1 and 14 were diagnosed with HCV in 2010[2]. The draft scope states that an estimated 0.4% of the HCV infected adult population would have chronic infection. We would disagree with this statement, as the HPA Report on Hepatitis C in the UK, published in 2011[1], estimates that 74% of HCV infected adults will develop chronic disease. This estimate is based on a systematic review conducted by Micallef et al[3], which reported that 26% of HCV infected patients cleared the hepatitis C infection spontaneously.	Comment noted. The background has been updated to reflect information on children and young people and references to adults have been removed.

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The technology/ intervention	SHTAC	With the NICE TA200 guidance in mind, will shortened treatment durations of the Peginterferon interventions according to genotype be considered or will the interventions include standard treatment durations (i.e. 48 weeks for genotypes 1,4 and 24 weeks for genotypes 2,3)?	Comment noted. The scope has been updated to reflect people with criteria where shortened courses of peginterferon alfa-2a and alfa-2b in combination with ribavirin are warranted. Further, NICE guidance will be issued in accordance with the marketing authorisation for peginterferon alfa-2a and alfa-2b.
	RCP	No comments.	No action required.
	RCPCH	The only treatment used currently will be with combination therapy with either form of interferon and ribavirin.	Comment noted. NICE guidance will be issued in accordance with the marketing authorisation for peginterferon alfa-2a and alfa-2b.
	Roche Products	The Roche phase III clinical trial (NV17424) recruited children from ages 5-17 years, and Roche is filing for a label in line with this age range, not children 3-17 years old.	Comment noted. The description of Peginterferon alfa-2a has been updated to reflect the anticipated marketing authorisation for this drug.
	HIS	No comments.	No action required.
	MSD	No comments.	No action required.

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Population	SHTAC	Please could you clarify whether the population group will include: (a) Children with mild, moderate and severe HCV? (b) Children who are treatment-naïve and those who have been previously treated, or just the former? (c) Children who are co-infected with hepatitis B or HIV?	Comment noted. The population scope has been updated to reflect people with criteria where shortened courses of peginterferon alfa-2a and alfa-2b in combination with ribavirin are warranted, and to include people with HIV co-infection and those who are treatment naive or have experienced a relapse or have not responded to prior therapy.
	RCP	It may be appropriate to specify the HIV status of the target group i.e. to make separate recommendations for those children who are, or are not, co-infected with HIV.	Comment noted. See above.
	RCPCH	Yes. Treatment by genotype and whether children are naive to treatment or have not responded or relapsed.	Comment noted. See above.
	Roche Products	Roche's phase III clinical trial studied patients aged 5-17. Therefore, consideration should be taken as to whether or not children aged 3 and 4 years will be different from studied age group.	Comment noted. NICE guidance will be issued in accordance with the marketing authorisation for peginterferon alfa-2a.
	HIS	Genotypes 2 and 3 should be considered separately from less favourable genotypes.	Comment noted. NICE guidance will be issued in accordance with the marketing authorisation for peginterferon alfa-2a and alfa-2b.
	MSD	No comments.	No action required.

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Comparators	SHTAC	Please could you provide clarification on whether the comparators will be: (a) Peg α-2a vs Peg α-2b? and/or (b) Peg + RBV vs Peg monotherapy? Also whether any other drugs currently used for adults will be considered as comparators (e.g. non-pegylated interferon, boceprevir, telaprevir)? Further details on the definition of supportive care would be useful.	Comment noted. The clinical and cost effectiveness of peginterferon alfa- 2a and alfa-2b will be compared with routine clinical practice in the UK, and will in line with its UK marketing authorisation. To inform what constitutes best supportive care, a working definition has been included in the 'other considerations' of the scope.
	RCP	No comments	No action required.
	RCPCH	Recruitment is now beginning for clinical trials with boceprevir and telaprevir, but no data available yet.	Comment noted. NICE recognises that these drugs, while currently being investigated in a paediatric population, are not licensed in this population and are not currently used in routine UK clinical practice. Best supportive care is the comparator for this appraisal.
	Roche Products	There is data in the literature to support non-pegylated interferon as a treatment; however Roche is unaware of its use in the NHS. Roche is unaware of any head-to-head data to describe any treatment option as 'best alternative care'.	Comment noted. See above.
	HIS	IFN alpha 2a monotherapy should not be considered as a therapeutic option, as there is evidence of inferiority.	Comment noted. The intervention section of the scope has been updated to reflect this new information.

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	MSD	No comments.	No action required.
Outcomes	SHTAC	These are consistent with those included in the previous appraisals.	Comment noted.
	RCP	No comments.	Comment noted.
	RCPCH	Pre treatment histology is collected routinely, but not post treatment Mortality not relevant for children Growth pre and post 5 yrs treatment is required (see accompanying ESPGHAN/EMA guidelines)	Comment noted. The scope section on outcomes has been updated to include growth inhibition – pre and post treatment. Mortality is retained in the list of outcomes as required for the modelling which will adopt a life-time horizon.
	Roche Products	No comments.	No action required.
	HIS	Very few children will undergo serial biopsy therefore histological improvement will rarely be a useful outcome measure.	Comment noted.
	MSD	No comments.	No action required.
Economic analysis	SHTAC	This is consistent with the scope of the previous NICE appraisals of hepatitis C treatment.	Comment noted. No action required.
	RCP	No comments.	
	RCPCH	Need to consider the reduction in healthcare cost by preventing the life time risk of chronic liver disease as children respond better than adults to combination treatment (see abstract on UK treatment).	Comment noted. Reduction in healthcare costs will be included in the economic model.

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	Roche Products	Roche will consider a 30 year time horizon as the base case.	Comment noted. NICE methods guide 2008 (5.2.13) note that a time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.
	MSD	No comments.	No action required.
Equality and Diversity	SHTAC	No comments.	No action required.
	RCP	No comments.	No action required.
	RCPCH	Ensure recent migrants and asylum seeker children are included Also young drug abusers.	Comment noted. NICE is not excluding any specific groups of children and young people in this appraisal.
	Roche Products	No comments.	

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Innovation	MSD	Yes, we would consider the technologies peginterferon alfa-2a and -2b to be innovative. Successful treatment of chronic hepatitis C can prevent children from going on to develop liver damage and cirrhosis, thus avoiding the potential consequences of hepatocellular carcinoma and the need for liver transplant. Peginterferon alfa-2a and -2b are also dosed once weekly, compared to the thrice weekly dosing of interferon alfa, thus reducing the burden of the treatment for patients. The dosing of peginterferon alfa-2b is based on patients' body surface area. Viraferonpeg is available in pens of different strengths, and the dose administered by each pen can be altered. This allows flexibility, in particular if the patient's dose needs altering.	Comment noted.
Other considerations	SHTAC	None.	
	RCP	No comment.	
	RCPCH	No comment.	
	Roche Products	No comment.	
	HIS	see above: genotype consideration is very important	
Questions for consultation	RCPCH	Combination therapy is considered standard of care See ESPGHAN guidelines Supportive therapy should include management at specialised centres/trained nurses/out reach clinics, telephone help line QoL is difficult to collect for children under 7yrs	Comment noted. To inform what constitutes best supportive care, a working definition has been included in the 'other considerations' of the scope.

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	Roche Products	This is not a new technology and the same class of drug has been used in adult and paediatric populations. It is not a 'step change' in the management of paediatric hepatitis C, however it will make a potential significant and substantial impact on health-related benefits by providing children and their caretakers with an alternative treatment option for Hepatitis C. A summary of Roche's clinical trial data for Pegasys in combination with ribavirin in paediatric hepatitis C is publicly available via paper published in Gastroenterology by Schwarz and colleagues, 2011. Supportive care will be assumed to be no treatment, and patients will follow the natural progression of disease for this group.	Comment noted.
	HIS	This technology has the potential to make a significant difference to infected children, currently managed with monitoring only. Those who achieve SVR will not need long term medical care, will not be at risk of liver disease or of transmitting the virus, and will no longer be stigmatised by the condition Important to consider the prevention of transmission of infection and the potential cost savings resulting from prevented cases. Epidemiological data collected by HPS and HPA should be able to provide an estimate of size of this effect. Supportive case consists merely of monitoring by blood tests and ultrasound scans for evidence of liver disease, with no means to affect progression. >95% children will have chronic infection – Adverse side effects monitored should include effect on growth.	Comment noted. The impact of these drugs on growth is being considered as an adverse event, and is explicitly listed in the outcomes section of the scope.

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Additional comments on the draft scope.	Department of Health	The scope and questions posed are highly specialised but seem appropriate. We would have pointed out the lower limit of three years is because of licensing. Although the experts in this field will know this, the non- medics interested in this scope may not.	Comment noted.
	Roche Products	Our preliminary literature review returned no clinical trial data on MSD's ViraferonPeg so Roche will not be able to conduct any indirect head-to-head comparison of the two pegylated interferons.	Comment noted.
	MSD	We believe that successful treatment of chronic hepatitis C in children will have an impact on the carers of the children, commonly their parents, and this would not be captured by the QALY calculation. Rodrigue et al[1] reported that hepatitis C among children is associated with increased caregiver stress, and a study conducted in Australia[2] indicated substantial quality of life benefits for parents/caregivers as a result of the child achieving SVR. As these benefits do not directly relate to the patients, they would not be included in the QALY. In addition, a carer other than a parent may be required for a child with chronic hepatitis C and the costs associated with this would not be captured by the QALY calculation.	Comment noted.