NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Peginterferon α-2a (Pegasys®) and Ribavirin for the Treatment of Paediatric Chronic Hepatitis C

MTA Submission

1st October 2012

Executive Summary

Relevant product and indication details

Product	**Pegylated interferon α-2a (PEG-IFN α-2a) (Pegasys®)**
Current licensed indication(s)	**Chronic hepatitis B**: PEG-IFN α-2a is indicated for the treatment of HBeAg-positive or HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis (see sections 4.4 and 5.1). **Chronic hepatitis C:** PEG-IFN α-2a is indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4). The optimal way to use PEG-IFN α-2a in patients with chronic hepatitis C is in combination with ribavirin. The combination of PEG-IFN α-2a and ribavirin is indicated in naïve patients and patients who have failed previous treatment with interferon alpha (pegylated or non-pegylated) alone or in combination therapy with ribavirin. Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin.
Proposed wording for license extension in children, submitted to EMA	PEG-IFN α-2a is indicated in a combination regimen with ribavirin for the treatment of children 5 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, 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. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case-by-case basis.
Available formulations	135 micrograms solution for injection in pre-filled syringe 180 micrograms solution for injection in pre-filled syringe 135 micrograms solution for injection in pre-filled pen 180 micrograms solution for injection in pre-filled pen
Proposed formulation extension for use in children	90 micrograms solution for injection in pre-filled syringe

Background

Chronic hepatitis C (CHC) is a disease caused by the hepatitis C virus (HCV) which eventually leads to the development of liver complications. It is typically a slow

progressing disease which may take several years to develop those liver complications, however in some the complications may develop much faster.

In children with CHC, data suggests that pegylated interferon (PEG-IFN) treatment may also be efficacious. PEG-IFN α-2b (ViraferonPeg ®, Merck Sharp and Dohme) is currently licensed for the treatment of paediatric CHC. Roche has filed for a license extension with the European Medicines Agency (EMA) for the use of PEG-IFN α-2a (Pegasys®) in combination with ribavirin (RBV) , in children aged 5 years and older as well as adolescents, for the treatment of previously untreated CHC.

Optimal therapy for children with chronic HCV is not clearly defined due to a lack of efficacy data in children. Currently, all children over 3 years of age are considered for treatment with PEG-IFN, regardless of histological severity. In patients with mild fibrosis, the decision to treat is generally based on genotype and likelihood of response to treatment.

It has been observed that HCV-infected children have a greater chance than adults of spontaneously clearing the infection and are also unlikely to experience significant immediate liver damage[1]. However, consideration must be given to delaying the start of treatment particularly because interferon treatments have consistent observable side-effects such as flu-like symptoms and inhibiting growth. Therefore in this submission, a case is presented for the cost-effectiveness of treatment of paediatric CHC with PEG-IFN α-2a+RBV combination versus delayed treatment ("watchful waiting") or no treatment.

Efficacy – pivotal trial (PEDS-C)

The license extension proposal is based on findings from a randomized, double-blind study (PEDS-C) which assessed the efficacy and safety of PEG-IFN α-2a+RBV combination therapy compared with PEG-IFN α-2a monotherapy, in previously-untreated children aged 5 to 17 years who had CHC and who tested positive for hepatitis C (HCV) viral RNA at the time of study recruitment. The primary endpoint was SVR. Overall study results show that more patients receiving PEG-IFN α-2a+RBV combination therapy attained SVR compared to those patients receiving PEG-IFN α-2a monotherapy. Based on this data, PEG-IFN α-2a+RBV combination is considered the treatment of choice for paediatric CHC.

The PEDS-C study found that treatment with PEG-IFN α-2a+RBV combination therapy was significantly more efficacious compared with PEG-IFN α-2a monotherapy in terms of SVR (49% for combination versus 20% for monotherapy; p=0.002). Additional efficacy parameters such as viral response over time, maintenance of end of treatment (EOT) viral response, relapse from EOT viral response, and changes from baseline in $\log_{10}$ HCV RNA values over time mirrored the finding that combination therapy is more efficacious in combating HCV than monotherapy. The findings (shown in Table 1 and Figure 1) also align with what has been observed in the adult CHC population.

Table 1. Key secondary endpoint results

	PEG-IFN α-2a+RBV Combination therapy (n = 55)	PEG-IFN α-2a+PBO Monotherapy (n = 57)	*p* value
Viral response at wk 24	36/55 (65%)	23/57 (39%)	0.0092
EOT viral response (actual treatment duration)	39/55 (71%)	23/57 (39%)	0.0013
EOT viral response (scheduled treatment duration)	35/55 (64%)	22/57 (37%)	0.0056
Maintenance of EOT viral response	77%	55%	
Relapse from EOT viral response	23%	43%	

NOTES: PBO, placebo; EOT, end of treatment

Subgroup analyses found that SVR was lower among patients who had a high baseline HCV RNA measurement, or who carried the more difficult-to-treat (genotype 1) strain of HCV. In addition, a trend was identified showing that patients who had normal alanine aminotransferase (ALT) levels at baseline were more likely to achieve an SVR than those with elevated ALT levels.

Additional subgroup analyses were explored in HCV-HIV coinfected patients, and in a retreatment population. Due to the small numbers of paediatric patients within these subgroups, the analyses were based on extrapolation studies which draw paediatric data from other sources, in combination with relevant adult data. The extrapolation analyses found that adult HIV-HCV co-infection efficacy data could reasonably be inferred to apply to adolescents; they also found that retreatment with PEG-IFN α-2a+RBV was a viable option in children previously treated with sub-optimal IFN regimens (i.e. IFN ± RBV) or those with severe, progressive liver disease.

Various parameters measuring growth in children (weight, height, BMI and body composition) were also used as secondary endpoints. These found a consistent impact of PEG-IFN α-2a (regardless of RBV exposure) on growth during the treatment period. Considering the patient group who received the typical treatment duration of 48 weeks, growth (measured in terms of age-adjusted z-scores) in bodyweight and BMI was inhibited during exposure to PEG-IFN and gradually returned to the population average after the treatment stopped. Height-for-age z-scores remained below the population average 100 weeks after treatment, although this final measurement was not statistically significant. A graphical summary of age-adjusted z-scores is shown below.

Safety

In the PEDS-C study, influenza-like, headache and gastrointestinal symptoms occurred in almost all children. Treatment with PEG-IFN α-2a led to significant declines in total white blood cell counts, absolute neutrophil counts and haemoglobin levels, however these all returned to baseline values when therapy was stopped. Declines in white blood cell and neutrophil counts and haemoglobin levels were greater in patients treated with PEG-IFN α-2a plus RBV combination therapy than in patients receiving PEG-IFN α-2a monotherapy.

Overall, 27% of subjects required dose reduction for neutropenia, although neutropenia was not associated with increased rates of infection. Dose reductions of PEG-IFN α-2a or RBV were common, but appeared to have little effect on SVR rates in either group. Adherence was excellent overall, with more than 95% of subjects

adhering to 90% of the prescribed doses of PEG-IFN α-2a+RBV or PEG-IFN α-2a + placebo.

Non-RCT evidence

Additional non-RCT studies were identified through a literature search, providing additional efficacy and safety data in this population. Data from these studies have been used in addition to the PEDS-C data to support the economic analyses in this submission. In particular the study by Sokal and colleagues demonstrated that for patients infected with the less difficult-to-treat genotype 2/3 strain of HCV, 24 weeks of treatment with PEG-IFN α-2a+RBV was sufficient to achieve the same rates of SVR as seen for this patient group in PEDS-C[2]. This finding was used to inform the inclusion of an additional arm in our economic model which explored the cost-effectiveness of treating genotype 2/3 HCV infected patients for 24 weeks only as opposed to the 48 weeks' treatment given in PEDS-C.

Economic model

A cost effectiveness model was developed to evaluate PEG-IFN α-2a+RBV compared to best supportive care (i.e. no treatment) in the treatment of paediatric CHC. This economic model is similar to previous models used to evaluate hepatitis C technologies in adult populations. A Markov model chain was employed to evaluate costs and effects. Patient characteristics in the model were set up to reflect the population in the PEDS-C study, and a 30 year time horizon was used. A lifetime horizon would ordinarily be considered most appropriate; however, it is difficult to predict what the care pathway might look like for paediatric patients who are unsuccessful on initial treatment. Given existing NICE guidance in the area of hepatitis C, it is likely that these patients will be offered re-treatment, but it is uncertain at what point. This is beyond the scope of the current evaluation. An additional 'arm' was evaluated based on results from the Sokal and colleagues study**,** wherein patients infected with HCV genotypes 2 or 3 received only 24 weeks of PEG-IFN α-2a+RBV therapy[2]. Accordingly, the model was developed such that it produced results separately for:

- genotypes 2 and 3
- genotypes 1, 4 and 5

Model inputs

The base-case analysis considers treatment-naïve patients as reflected in clinical trials of PEG-IFN α-2a+RBV[2-5]. The cohort is assumed to enter the model at a starting age of 11 years old, based on the weighted average in the clinical trial and studies from the literature. Some children enter the model with mild CHC and some with moderate CHC (88% and 12%, respectively), where mild and moderate refer to the level of fibrosis based on their ISHAK score.

Treatment efficacy was defined by SVR, and the estimates for PEG-IFN α-2a+RBV were based on data from the PEDS-C study and studies from the literature. A weighted SVR based on population size from each study was used to estimate overall efficacy. Response criteria and stopping rules were defined according to the rules in the PEDS-C study. SVR rates for the genotype 2 and 3 24-week therapy arm were sourced from Sokal and colleagues[2].

The model assumes a UK National Health Services (NHS) and personal social services (PSS) cost perspective and its design adheres to the NICE economic evaluation reference case and has been accepted in previous NICE health technology assessments (HTA) for the adult CHC population. Drug costs were calculated based on unit prices listed in the British National Formulary[6] . Doses were calculated according to the dosage regimen in PEDS-C and age-related mean height/weight from the Health Survey for England 2010 [7].

Due to the lack of available quality of life data for paediatric patients with CHC, EQ-5D derived utility weights were adapted from previous NICE health technology assessments for adults with CHC[8-12]. Health state utilities were adjusted according to a multiplier derived from the adult CHC population in the literature and applied to the paediatric cohort baseline demographics.

Economic model results

A summary of the total costs, outcomes (as life years gained and QALYs gained) and incremental cost effectiveness ratio (ICER) can be found in Table 2.

Table 2. Base case cost-effectiveness of PEG-IFN α-2a+RBV combination therapy in patients with chronic HCV

Treatment	Cost (£)	Outcome (Life Years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotype 1, 4 and 5				
No Treatment	£8,199	18.47	14.20	
PEG-IFN α-2a+RBV	£12,170	18.56	15.21	
Incremental	£3,971	0.09	1.01	£3,915
Genotype 2 and 3				
No Treatment	£8,199	18.47	14.20	
PEG-IFN α-2a+RBV (for 24 weeks)	£6,336	18.61	15.77	
PEG-IFN α-2a+RBV (for 48 weeks)	£11,010	18.60	15.61	
Incremental analysis for Genotype 2 and 3				
PEG-IFN α-2a+RBV (24 weeks) versus no treatment	-£1,864	0.14	1.57	Dominates no treatment
PEG-IFN α-2a+RBV (48 weeks) versus 24 weeks	£4,675	-0.01	-0.16	Dominated by 24 weeks

Treatment with PEG-IFN α-2a+RBV improved expected health outcomes (by 1.01 and 1.57 QALYs for genotype 1, 4 and 5 and genotypes 2 and 3, respectively) and increased or decreased costs over the 30 year time horizon (by £3,971 and -£1,864 for genotype 1, 4 and 5 and genotypes 2 and 3, respectively). The reduction in future supportive care costs associated with disease progression across genotypes sufficiently offsets the additional costs of antiviral treatment given a willingness to pay threshold of £20,000/QALY gained. The incremental cost effectiveness ratio (ICER) for PEG-IFN α-2a+RBV versus no treatment for genotype 1, 4 and 5 was £3,915/QALY and the ICER for PEG-IFN alfa-2a+RBV for genotype 2 and 3 patients dominates no treatment.

Sensitivity Analyses

In a series of one-way sensitivity analyses, varying key baseline prognostic variables, the cost effectiveness of PEG-IFN α-2a+RBV is relatively insensitive to changes in

these variables. The model was most sensitive to five parameters: time horizon, rate of disease progression, probability of SVR with treatment, distribution of liver disease severity at model entry, and annual cost of achieving SVR. However estimated ICERs were all under the £20,000/QALY at the most conservative of these parameter estimates.

In a probabilistic sensitivity analysis, PEG-IFN α-2a+RBV combination therapy for paediatric patients with genotype 1, 4 and 5 had a 91.6% probability of being cost-effective (compared to no treatment) at a willingness-to-pay threshold of £20,000/QALY and a 93.7% probability of being cost-effective at a willingness-to-pay threshold of £30,000/QALY.

For patients with genotypes 2 and 3, the probability of 24-week combination therapy being cost-effective compared to no treatment is 97.2% at a £20,000/QALY and 96.9% at a £30,000/QALY gained threshold. The probability of 48 weeks of combination therapy being cost-effective compared to no treatment is 94.1% and 95% at £20,000/QALY and £30,000/QALY thresholds, respectively. When directly compared, 24 weeks of treatment was found to be more cost-effective than 48 weeks of treatment in 94% of simulations at a threshold of £20,000/QALY and 91% of simulations at a threshold of £30,000/QALY.

Subgroup Analyses

The scoping document for this appraisal suggests subgroup analyses on HIV co-infection, varying degrees of HCV infection, and previous treatment failures.

A previous extrapolation analysis on the pivotal RCT was conducted to study the HIV co-infected subgroups and it was determined that co-infected children would respond at least as well, if not better, than the adult HIV co-infected population. However due to the low number of patients, it was not possible to conduct a robust analysis and therefore a formal analysis was not carried out.

Varying degrees of CHC were assessed by changing the starting levels of infection in a deterministic sensitivity analysis. The analysis determined that treating patients who start at more severe levels of CHC are more cost effective as compared to patients who start out in mild health states. All ICERs dominate no treatment across all genotypes even when patients of moderate and severe health states are treated.

A subgroup analysis was conducted on patients who previously failed PEG-IFN α-2a monotherapy and were retreated with combination PEG-IFN α-2a+RBV. Final results suggest that retreatment may be cost effective with an ICER of £16,118 compared to no treatment. However, the probabilistic sensitivity analysis suggests there is a 53% probability that the estimated value is below £20,000/QALY threshold.

One additional scenario analysis was conducted to evaluate whether it is cost-effective to treat patients earlier versus ‘watchful waiting’ where treatment would be initiated once patients reach 18 years old, at which point they would be treated under adult guidelines. The analysis suggests that watchful waiting is cost effective compared to no treatment, however early treatment dominates watchful waiting.

Conclusion

The health economic model suggests that PEG-IFN α-2a+RBV is a cost effective option for the treatment of paediatric CHC compared to best supportive care for the treatment of genotype 1, 4 and 5 patients (ICER of £3,914/QALY) and genotype 2 and 3 (ICER dominates). The ICERs are well within NICE’s willingness to pay

threshold of approximately £20,000/QALY. Probabilistic sensitivity analyses suggest that there is a 91.6% probability that the ICER for the treatment of genotype 1,4 and 5 patients with PEG-IFN α-2a+RBV compared to best supportive care is below £20,000/QALY, and for genotypes 2 and 3 there is a 97.2% probability it is below £20,000/QALY.

A limitation of this model is the method of evidence generation since formal systematic reviews were not carried out to gather data. However, based on the known limited amount of data and small size of the patient population, the most valuable studies were likely identified and included in the analysis through the targeted literature review. An additional limitation is the simplifying assumption that the comparator arm receives no treatment for the duration of the model. This is partially due to the understood heterogeneity of physicians decisions to treat. Further longitudinal data should be collected to better understand if there are any consistent themes in decisions to treat during a patient's lifetime. The model attempts to clarify this in the watchful waiting subgroup analysis where all patients commence treatment at the age of 18.

Attempts to analyse subgroups helped clarify treatment possibilities for children with CHC. Currently there are not enough data (perhaps due to the low incidence) to inform a subgroup analysis of HIV co-infected patients in the UK. Deterministic sensitivity analyses which vary the starting level of severity of paediatric CHC suggest that it is cost effective to treat patients at all levels of CHC severity. A subgroup analysis on genotype 1 patients who had previously failed treatment suggests that there may be a need for additional data to determine if it is cost effective to retreat paediatric patients or wait until they have reached adult age to retreat. More information may be needed or the decision to treat patients may need to be considered on an individual basis.