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Mr Jeremy Powell
Technology Appraisal Project Manager
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MidCity Place, 71 High Holborn
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Dear Mr Powell:

RE: Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation; Comments on the Technology Assessment Report (TAR)

Schering-Plough welcomes the opportunity to comment on this report and its content. Following a thorough review of the assessment report by Southampton Health Technology Assessments Centre (SHTAC), this letter sets out Schering-Plough's comments: a summary of what we perceive to be the significant findings for peginterferon, followed by issues relating to the SHTAC Technology Assessment Group (TAG) analysis.

1. Key findings on peginterferon α-2b

Overall

The analysis conducted by the TAG suggest that peginterferon α– 2b (in combination with ribavirin) is clinically effective and cost effective in all three patient populations included in the NICE scope for this appraisal.

1.1 Shortened duration genotype 1

Peginterferon α-2b treatment for 24 weeks was found to have an increased rate of SVR compared to 48 week treatment (Berg et al, 2009). This causes shortened duration of treatment to dominate standard treatment in the cost-effectiveness analysis; however this result does not appear to be clinically intuitive. Schering-Plough is pleased to note that an additional scenario analysis was conducted by the TAG which suggests that peginterferon alfas are likely to be highly cost effective as long as there is no or a very small difference in efficacy between shorter treatment duration and standard treatment duration. Little difference in SVR rates are reported in Zeuzem et al (2006) which reports that SVR rates are not compromised when shorter duration treatment is used in certain patients:

> "An exception comprises HCV-1 infected patients with a low pretreatment HCV-RNA concentration (below 600,000 IU/mL) who become undetectable for serum HCVRNA already after 4 weeks of combination therapy.

In this subset of patients treatment for 24 weeks does not impair the sustained virologic response rate." Pg 102, Zeuzem, et al (2006)

1.2 Re-treatment

Peginterferon α-2b is highly cost effective in the re-treatment of patients who have previously failed treatment. In particular, using the early stopping rule of Early Virological Response (EVR) at 12 weeks is very cost effective for genotypes 1+4 and dominates no treatment for patients with 2+3 dominate no treatment with or without the EVR stopping rule. Peginterferon α-2b has the additional benefit for genotype 1 patients of being licensed for a re-treatment of 48 weeks rather than the 72 weeks required when taking peginterferon α-2a.

1.3 HIV co infection

Peginterferon alfa-2b is cost effective in treating for HCV/HIV co-infection. For genotypes 1 and 4 the ICER was £11,806 and for genotypes 2 and 3 the ICER was £2,161. Peginterferon treatment is also recommended by the British HIV Association (BHIVA), in their guidelines for the treatment of HIV-1 and hepatitis B or C co-infection (Brook et al, 2010).

2. Issues in the assessment report

2.1. Deterministic sensitivity analysis results for genotype 1 patients eligible for shortened treatment duration using peginterferon α-2b and ribavirin combination therapy.

Results in Table 50 (pg 119, assessment report) and Table 51 (pg 120, assessment report) do not concur with one another as they should. It appears that the assessment group may have reported the analysis of 48 weeks versus 24 week treatment duration shown in Table 51, while an analysis of 24 weeks versus 48 weeks is reported in Table 50. Schering-Plough requests that these analyses are clarified or amended in the report.

2.2 Scenario analysis in short term treatment duration genotype 1

The scenario analyses for the shortened treatment duration presented in Table 48, for peginterferon α-2a (pg 114, assessment report) and Table 52, for peginterferon α-2b (pg 121, assessment report) are not explained in enough detail. The ICERs differ slightly between the two tables, however in both tables the incremental costs and QALYs are identical. The results are difficult to interpret given the fact that the peginterferons have different SVRs in this patient subgroup, but this is not discussed further in the report. Schering-Plough requests that these analyses are clarified or amended in the report.

2.3 TAG model

The model provided by the TAG in Microsoft Excel was not referenced and it is not clear how some inputs are used in the model. Many variables are entered directly into formulas which made the model more difficult to validate. There are also a number of variables which appear not to have been considered in the probabilistic sensitivity analysis (PSA).

3. Detailed response on limitations identified in the TAR

3.1 Deterministic sensitivity analysis results for genotype 1 patients eligible for shortened treatment duration using peginterferon α-2b and ribavirin combination therapy.

Berg et al (2009) report that shortened treatment duration with peginterferon-α-2b was associated with a higher SVR rate than peginterferon-α-2b standard treatment. The implications for this are shown in the base case results, Table 51, where the incremental outcome in QALYs is positive, i.e. there are more QALYs associated with shortened treatment than standard treatment. The report states that there are cost savings of approximately £9000 due to the reduction in drug acquisition costs, and on-treatment monitoring costs. There are also additional cost savings due to the higher SVR rate which reduces the total cost of treating disease progression. In Table 50 (Base case cost-effectiveness for shortened treatment duration using peginterferon α-2b and ribavirin combination therapy in genotype 1 patients) incremental costs, incremental QALYs and the ICER are stated as the following, respectively, "-£8,996", "0.49" and "shortened duration dominates" when comparing shortened treatment duration to standard treatment.

Table 50 however states the same numbers but with opposite signs, the incremental cost is positive "£8,996", and the incremental QALY is negative, "-0.49" and the resultant ICER, "-£18,190". The deterministic sensitivity analysis which follows in the table continues the trend of positive incremental costs and negative incremental QALYs, with the resultant ICERs implying that shortened treatment with peginterferon α-2b lies in the south-west quadrant of the cost effectiveness plane. This is counter intuitive given the clinical trial results from Berg et al. Given the trends in other deterministic sensitivity analysis undertaken by SHTAC for the other subgroups it appears that the values in the incremental cost column in Table 51 are likely to be negative, while the values in the incremental QALY column are likely to be positive assuming the trend is consistent with other deterministic sensitivity analysis in the report. The table should read, given this assumption is correct, "Shortened duration dominates" throughout the ICER column.

3.2 Scenario analysis for shortened treatment genotype 1

Table 48 (pg 114, assessment report) and Table 52 (pg 121, assessment report) show slightly different ICER values but exactly the same incremental costs and incremental outcomes for genotype 1 patients. The data informing the scenario analysis is not explained and therefore the reason for the same incremental costs and QALYs between the two analyses is not clear. Given the assessment report explains that the two products, peginterferon α-2b and α-2a are pharmacologically different products, the efficacy data informing the base SVR rate should differ between the peginterferons, resulting in differences between the two products ICERs across the scenario analyses.

The fact that the same incremental costs and incremental QALYs are reported with slightly different ICER values could be due to differences in decimal places of the incremental cost and incremental QALY values; however this in itself does not explain why there are not more significant differences between the peginterferons. Differing baseline SVRs should be reflected by differing incremental costs and incremental QALYs between the two peginterferons. Schering-Plough requests that further clarification around this analysis is made available.

3.3 Excel Model provided by TAG

- **Formulas and referencing**

Throughout the model a large number of variables change depending on the scenario currently being considered. Many of these variables are hard-coded (i.e. entered directly) into formula, this makes it difficult to asses that the value used actually relates to the correct scenario. In addition, the model does not contain references.

For example, the drug costs have been calculated elsewhere (outlined in the AG report) and the absolute value of the cost of the treatments has been entered in to the model with no references. This makes it difficult to validate the model without going back to the report to check calculations made. The AG report was checked for treatment cost calculations and these appear to have been correctly estimated. However, they were not varied in the probabilistic sensitivity analysis. Given that the cost of the treatments can vary according to formulation and patient weight, perhaps this should be addressed in sensitivity analysis for completeness.

There appears to be an annual cost applied to patients in the SVR state (patients who transitioned from the compensated cirrhosis state) of £96, this is only applied in the AntiViralTreatment and ShortendDuration engines and not the BSC. This variable has little impact on the results but will bias the results of treatments against BSC. This cost does not appear to be addressed in the report therefore the reason for and impact of its inclusion is unclear.

- **Probabilistic Sensitivity Analysis (PSA)**

When considering the probabilistic sensitivity analysis (PSA) a number of parameters appear to have been omitted, these include the following:

- The starting age of the population
- The proportion of the population who are male
- The starting states of the population: Proportion with mild cirrhosis, moderate cirrhosis and compensated cirrhosis
- The probability of discontinuing treatment, prior to normal end of course
- The utility decrement due to adverse effects of treatment
- The relative risk of cirrhosis progression for HIV co-infected patients
- The relative risk of decompensation for HIV co-infected patients

The following transition probabilities are also omitted from the PSA:

- Decompensated cirrhosis to liver transplant
- HCC to liver transplant
- Compensated cirrhosis to death
- Liver transplant to death year 1
- Liver transplant to death year 2

And the following costs are also omitted from the PSA:

- Acquisition cost for peginterferon alfa (weekly)
- Acquisition cost for ribavirin (weekly)
- Cost on-treatment monitoring for patients who do not achieve EVR
- Cost on-treatment monitoring for patients who achieve EVR
- Initial costs of assessing patients' eligibility for treatment

Some of these variables are constant across all scenarios (Such as starting age and the proportion of males) and so the impact should be minimal however for completeness it is felt that they should be included in the PSA. The omission of these variables does not appear to be discussed in the report either in terms of justification or impact of exclusion. Schering-Plough requests that this is acknowledged by the assessment group as a limitation in the analysis.

4. Response to the critique of the Schering-Plough model

Responses to comments made in the assessment report are laid out below with the comments quoted and the response below.

4.1 Schering-Plough Model Assumptions

"The Schering-Plough model appears to under-estimate the SVR in each analysis, as a result of applying an unnecessary adjustment for treatment discontinuation, but appears to over-estimate the utility gain through treatment by not applying an adjustment for treatment discontinuation:"

> The Schering-Plough model applies a treatment discontinuation due to adverse events to ensure that patients who discontinue due to these reasons in the trial had been accounted for in the model. We did not apply this adjustment for utility because only those who achieved SVR will receive the utility value attached to this state. Therefore although we may have underestimated the SVR we feel we did not overestimate utility gain. The above adjustment will therefore favour the no treatment arm and is not likely to bias the model in favour of treatment.

> The Schering Plough model had a disutility of 0.13 applied to SVC and HCV health states. This was based on the overall mean difference in EQ-5D utility score for treated and control patients at 12 or 24 weeks following randomisation in the UK Mild Hepatitis C trial.{10654} The disutility associated with treatment was adjusted for duration of treatment, so that a lower utility decrement would apply for patients (who fail to demonstrate an EVR) stopping treatment at 12 weeks.

"There is an implicit assumption that patients achieve an SVR immediately after treatment is initiated and therefore accrue health benefits on entering the model. It might be more reasonable to assume that transitions occur mid-cycle (essentially applying half-cycle adjustment). This would mean adjusting cycle lengths (currently annual) to cope with treatments that are significantly less than 52 weeks, or calculating a weighted combination of the utility for the initial state and the utility for the appropriate SVR state (weighted according to what proportion of the cycle is spent in the initial health state and what proportion in the SVR state)."

> The application of half cycle corrections is debatable in health economics. In the Schering-Plough model, the specific reason for not applying a half cycle correction was because all of

the treatment effects were taken into account at different time periods in the first year. Following year one of the model all patients went through the same markov processes and therefore all the effects are incremental. Patients were assumed to begin moving between disease states at the end of the decision tree and then at the end of each cycle. This is likely to bias results in favour of no treatment as patients moving to a more severe disease state during the first cycle experience higher QoL and lower disease management costs associated with the original disease state for a longer period of time.

"The model collapses the SVR state into one and therefore does not track whether patients have achieved SVR from mild HCV, moderate HCV or compensated cirrhosis. It applies the same health state utility to patients achieving an SVR, irrespective of their stage of liver disease when treatment was initiated. This doesn't accord with utility data from the UK Mild Hepatitis C trial which reported a lower mean utility for patients achieving SVR from moderate liver disease than those achieving SVR from mild liver disease;"

The Schering-Plough model as it stands does not track whether patients have achieved SVR from mild or moderate HCV or from compensated cirrhosis. This is acknowledged as a limitation of the analysis and perhaps could have been further explored in sensitivity analysis. The available sensitivity analyses on other scenarios in the model suggest that this change would be unlikely to show that treatment is not cost effective compared with no treatment. This is supported by an additional analysis by the assessment group on the Schering-Plough model which showed that the highest ICER was £8,102 per QALY (an increase of £925 from the submitted base case) in the most difficult to treat patient group (HCV/HIV co infected patients genotypes 1&4), therefore treatment remains cost effective according to the usual thresholds considered by NICE.

"The model assumes that the SVR health state cost is applied for all cycles the patient remains in the SVR state. This differs from the assumption applied in our previous assessment report, where it was assumed that the SVR cost applied only for the year following treatment response."

A fixed annual management cost was applied to each patient who achieves SVR or clears the virus spontaneously as this allows for the ongoing monitoring of this patient cohort. As mentioned in the submission, this may overestimate the true cost of managing these patients, since the intensity of monitoring is likely to decrease over time for patients who remain HCV RNA-negative. It was acknowledged in the submission that some previous economic evaluations appear to have assumed that patients achieving SVR will require no further NHS resources attributable to hepatitis C. However the assumption used in the submission is a conservative one and likely to underestimate the cost effectiveness of treatment.

"The model appears to have underestimated the cost of ribavirin – Table 31 and Table 32 of the MS report weekly cost of ribavirin as £16.41 for re-treated patients and £13.13 for HCV/HIV co-infected patients. These are derived using an estimated average cost per 200mg tablet of ribavarin of approximately £3.28. However the figures used in the MS are the daily, not weekly cost."

This was an error in the analysis. The AG re-ran the model with updated costs. The implication of the error was to underestimate the ICER by approximately £1,500 for the HIV/HCV group and by approximately £2,500 in the re-treatment group (all genotypes).

SVR State Assumptions: "The effect of treatment is to induce an SVR in a proportion of patients, which is assumed to be a permanent cure. This agrees with previously published models in this patient population and is supported by long term follow up studies of patients achieving SVR on treatment. However recent publications have highlighted a risk of liver cancer in patients in patients who have undergone SVR – particularly in patients with compensated cirrhosis at baseline – which, while lower than for non-responding patients, is not completely eradicated. Since patients can enter the model in the compensated cirrhosis state (and receive treatment) excluding a transition from the SVR state (for patient who had developed cirrhosis at baseline) may overestimate the benefits from an SVR".(Pg 87)

This assumption was used based on the previous economic model by SHTAC. We did not assume a probability of liver cancer for patients who entered the model with compensated cirrhosis, as this had not been previously estimated. Given the fact that only 10% of new patients and 32% of existing patients have cirrhosis, adding a probability of liver cancer from SVR was not expected to significantly change the results.

Transitions between health states: "The transitions between health states came again from the Mild Hepatitis C trial {10654}, from the UK study of patients undergoing transplantation, and on a range of additional studies, referenced within the submission. It is unclear how these have been derived, and from which studies." (Pg 89)

In the submission the transition probabilities are listed along with the source of data used. These transition probabilities have been used in previous submissions for Hepatitis C, including the previous economic model by Southampton and are established transition probabilities for modeling the natural history of Hepatitis C.

4.2 Presentation of Schering-Plough model results

"When the EVR and SVR values from the more recent Laguno and colleagues 2009 RCT were applied, the manufacturers report ICERs of £6,140 per QALY in genotypes 1 and 4, £422 per QALY for genotypes 2 and 3 and £2,311 for all genotypes. It is not clear if both EVR and SVR have been adjusted here." (Pg 90, Assessment report)

The Schering-Plough submission stated " The costs and QALYs were also recalculated using the EVR and SVR statistics from Laguno 2008; this gave ICERs of £6,140/QALY for genotypes 1 or 4, £422/QALY for genotypes 2 or 3 and £2,311 for all genotypes." This information was also available in the economic model (response page) where alternative data sources can be used).

Only SVR rates were available in the Laguno 2004 studies and therefore the analysis focused on results using only these data. Laguno 2009 had EVR and SVR response rates and this study was therefore used to derive results in a scenario analysis on SVR rates in

the HIV co-infected subgroup of patients. Both the SVR and EVR rates were adjusted as shown in the tables below.

Both the EVR and SVR were adjusted in this analysis according to the trial data.

Base case

Response rates (Laguno 2004)

Genotype	SVR
G1&4	38%
G2&3	53%

Scenario analysis results based on the following data

Response rates (Laguno 2009)

	EVR	SVR
G1&4	57%	28%
G2&3	83%	62%

"A sensitivity analysis was performed on distribution of genotype at baseline. The treatment response of genotypes 1 and 4, and then 2 and 3, are applied to all patients. The treatment response of genotypes 1 and 4 applied to the entire cohort resulted in an ICER of £7,176 per QALY, and that of genotypes 2 and 3 resulted in an ICER of £782, in the re-treatment group. In the HCV/HIV co-infected group the ICERs became £1,637 and £403. The ICERs are the same as those presented in the base case analysis, and it is unclear what has been added to this analysis by the reporting of this scenario."(Pg 90, Assessment report)

This analysis produces the same results as in the base case which is to be expected as it is simply running the model for each of the groups of genotypes as presented in the base case analysis. The analysis indicates that the model is robust.

"The presentation of the PSA appears generally to be in accordance with NICE methodological guidance, 68 but does not report mean costs and outcome for the PSAs." (Pg 91, Assessment Report)

The mean costs and outcomes for the results reported in the submission are presented in Appendix 1. Table 1.1 presents the values for HIV/HCV patients while Table 1.2 presents the values for re-treatment patients.

"The written submission contains an appendix which lists the parameters included in the PSA, their mean value, standard error and the choice of distribution, but not the parameterization of the distribution."(Pg 91, Assessment report)

The parameterizations are presented in a table in the Appendix 2.

4.3 Literature searches

"The MS does not report whether a systematic search was undertaken for economic evaluations of peginterferon α-2b or other treatments for chronic HCV in the patient populations covered by the scope, nor does it report any detail on the development and validation (including any details of clinical validation) of the model adopted for the MS." (Pg 80, Assessment Report)

Schering-Plough developed the model, which was validated internally to be based on previous work by the SHTAC on behalf of NICE and the economic evaluation alongside the Mild Hepatitis C trial. This was stated in the submission. A brief literature search was carried out in order to identify economic evaluations relevant to the UK setting. This search was carried out in the Cochrane library (NHS EED and HTA databases) and identified no further economic evaluations relevant to the UK since the publications of the assessment group models of hepatitis C. Therefore the model methodology previously established by the AG was considered the most robust and appropriate to use in the submission.

A brief literature search was carried out on NHSEED and HTA databases (via Cochrane) to identify economic evaluations relevant to the UK to ensure that no further model methodologies had been used since the previous TAs.

The following search terms were used

(hepatitis C OR HCV) AND (economic OR pharmacoeconomic OR cost-effectiv* OR cost-utility OR cost-benefit OR cost-consequence OR decision analysis OR markov OR decision tree OR monte carlo OR models, economic OR models, econometric OR economics)

The main inclusion criteria were the following: UK study, Economic evaluation ,HCV or HCV/HIV coinfection

This search resulted in 297 hits in NHSEED and 26 hits from the HTA database. Of these, 5 relevant papers were identified.

Of the 5 studies identified:

- 3 were HTA reports detailing methods and results used in the NICE appraisals (Shepherd 2004, Wright 2006 and Shepherd 2007)
- 2 were other journal publications following on from the NICE technology appraisals (Grieve 2006 and Shepherd 2005)
- 3 of the studies outlined treatment in mild hepatitis C (Grieve 2006, Wright 2006 and Shepherd 2007) and the other 2 studies looked at moderate/severe hepatitis C (Shepherd 2004 and Shepherd 2005)
- All of the studies had funding provided by NHS programmes

Although this is a brief search which has limitations, effort was made to ensure that there were no additional economic evaluations which were missing.

"The health state utilities have been derived from the UK Mild Hepatitis C trial{10654}, and a study of the cost-effectiveness of liver transplantation. There is no systematic search for these values reported in the submission." (Pg 82, Assessment Report)

The utilities were derived from the previous assessment group model for the reasons stated above (established utilities considered robust and appropriate).

4.4 Clinical data used in re-treatment: EPIC data

"The MS does not discuss the relevance of data from the EPIC3 study,[94] with inclusion criteria that patients had prior failure (either nonresponse or relapse) on previous combination therapy with ribavirin and (non-pegylated or pegylated) interferon. The study does not appear strictly to meet the scope for the appraisal which identifies the population considered for re-treatment to be those previously treated with peginterferon alfa and ribavirin." (Pg 88)

Data from all the patients in the EPIC trial was used in the analysis of re-treatment in patients. This was clearly a limitation in the analysis. However, a sensitivity analysis was conducted around the reasons for requiring re-treatment on SVR, in addition a deterministic analysis on EVR and SVR showing that peg 2b remains cost-effective compared with no treatment over a range of treatment response rates.

Schering-Plough has carried out additional analysis using the model submitted to the assessment group, which uses the one third of patients from the EPIC trial who had previously had treatment in peginterferon only. The analysis is re run with the correct ribavirin cost applied.

The results for the re run analysis are as follows:

Deterministic results

Subgroup analyses - Previous treatment with pegylated interferons (including 2a & 2b) based on all 100 Re-treatment patients

Non Discounted	**No treatment**	**Peg2b + RIB**
Total Cost	£3,613,204	£4,212,193
Cost per patient	£36,132	£42,122
QALYs	1,554	1,695
QALYs per patient	15.54	16.95
Cost-effectiveness compared to no treatment		**£4,272**
Discounted	**No treatment**	**Peg2b + RIB**
Total Cost	£2,212,978	£2,948,874
Cost per patient	£22,130	£29,489
QALYs	997	1,068
QALYs per patient	9.97	10.68
Cost-effectiveness compared to no treatment		**£10,415**

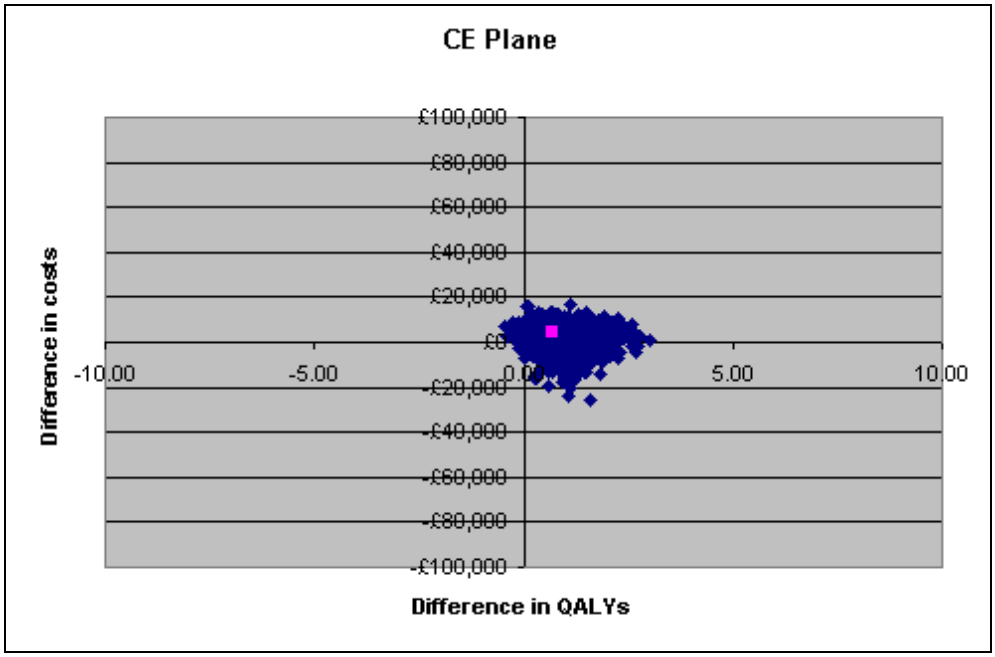
The ICER of £10,415 for patients' retreated following peginterferon only for all patients is higher than the ICER of £6,731 (with corrected ribavirin costs, see Appendix 3) for patients who previously received interferon or peginterferon.

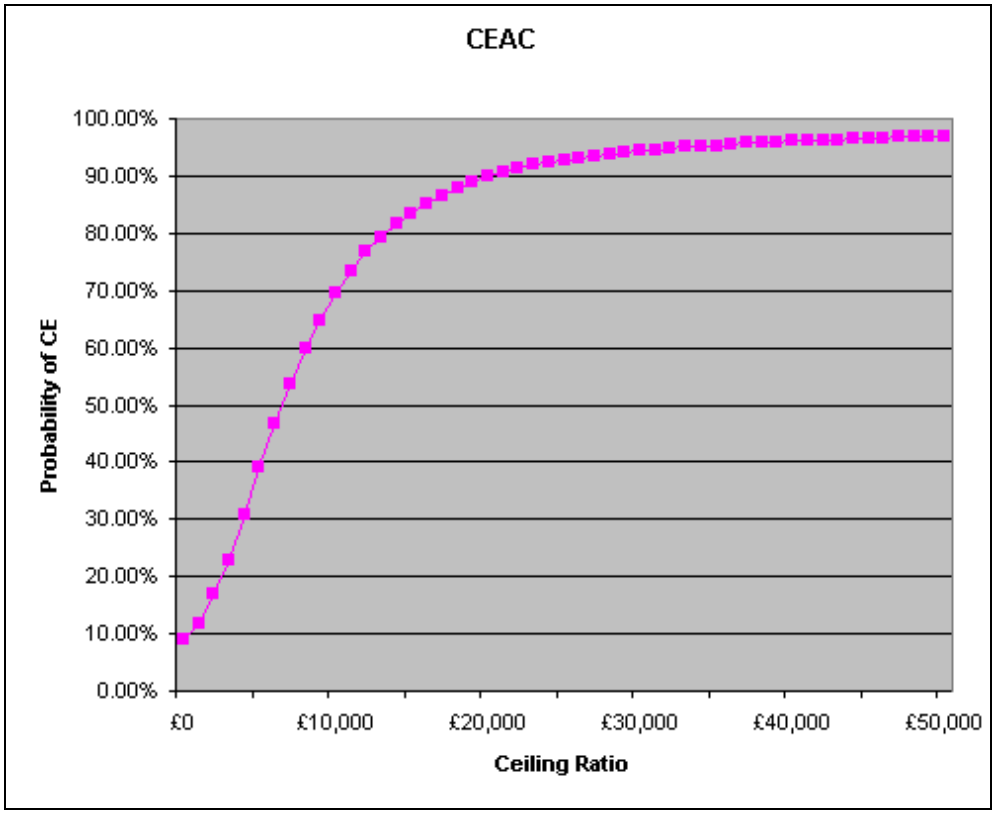
Probabilistic results

Probabilistic results for the subgroup analysis.

Re-treated patients – All: Peg2b+RIB vs. No treatment.
Subgroup analysis looking at previous treatment with pegylated interferons (including 2a & 2b)

	Diff Cost	Diff QoL	ICER
Mean	£3,998	0.71	£5,654





Probability of CE at £20,000: 89.80%
Probability of CE at £30,000: 94.30%

50% of simulations are cost-effective at £6,422

The ICERs are slightly higher than the ICERs reported in the submission; however peginterferon α-2b is still cost effective in the re-treatment group of patients who have previously received peginterferon. The data informing the ICERs is also generalisable to the UK patient population in this treatment group, as outlined below.

Analysis of the EPIC data suggests that the peginterferon previously used in treatment influences the SVR rate in re-treatment as shown in the table below (Poynard et al, 2008). The implication on the ICERS being that re-treatment is likely to be much more cost effective using peginterferon α-2b rather than peginterferon α-2a in patients such as G2/3 F2 patients who were previously treated with peginterferon α-2b.

SVR RATES	Prior Nonresponders			Prior Relapsers		
	Peg-2b n = 280	Peg-2a n = 196	IFN alfa n = 903	Peg-2b n = 180	Peg-2a n = 164	IFN alfa n = 300
All patients	7%	6%	18%	32%	34%	43%
G1 F2	8%	4%	18%	37%	27%	42%
G1 F3	4%	2%	16%	29%	10%	28%
G1 F4	5%	2%	8%	18%	20%	26%
G2/3 F2	57%	50%	68%	75%	50%	76%
G2/3 F3	50%	33%	39%	63%	62%	67%
G2/3 F4	0%	33%	40%	36%	58%	59%
G4 F2	--	50%	33%	--	2/2	100%
G4 F3	0%	--	0%	--	0%	100%
G4 F4	0%	--	14%	50%	100%	75%

(Poynard et al, 2008)

EPIC study characteristics (Poynard et al, 2009):

- Prospective, international, multicentre, open-label, single-arm, multi-phase clinical program involving 133 sites in the US, Canada, Europe, Latin America, Taiwan, and Australia
- 84% of patients were Caucasian
- Mean age was 49
- Mean weight 81kg
- Male 71%
- Genotype 1 80% of patients, genotype 3 13% of patients

93 % of patients in the EPIC trial were infected with genotypes 1 and 3, this is comparable to the reported statistic of 'more than 90%' by the assessment for patients in England and Wales diagnosed. There are also more men in the study than women which is representative of the UK hepatitis C patient population.

"The main treatment effect applied in the model is the SVR for treated patients. For patients who failed to respond to or relapsed following previous interferon therapy the SVRs were taken from

the EPIC3 study which is an open-label, single-arm study. The SVR for best supportive care was assumed to be zero for patients with moderate chronic HCV or compensated cirrhosis, but a low spontaneous SVR probability was applied for patients with mild chronic HCV. The spontaneous SVR probability is applied to both the treatment and best supportive care cohorts. The spontaneous clearance of HCV is not discussed in the MS and the value (and derivation) of the transition probability is not included in Table 35 of the MS, which lists the transition probabilities in the model." (Pg 88)

> This was an omission. Within the analysis, it was assumed that patients achieving SVR or spontaneously clearing HCV RNA would remain in the viral clearance disease state for the rest of their lives with a constant quality of life and health care costs based on those observed in the Mild Hepatitis C study.
>
> A transition probability of 0.2% for spontaneous viral clearance from mild HCV was applied based on Yousuf et al (1992). This value was varied in probabilistic sensitivity analysis from 0.0% to 0.4%.

4.5 Shorter Treatment Duration

"No assessment is presented on the cost-effectiveness of shortened versus standard treatment duration. The reason for this omission is not discussed by the manufacturer though it maybe due to peginterferon α-2b only being licensed for shorter treatment durations in genotype 1 (as opposed to genotypes 2, 3 or 4*)"(* Pg 80, Assessment report)

Section 4.2 of the SPC states:

> "In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1)…..
>
> **….Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1." (Peginterferon α-2b, SPC)
>
> Schering-Plough did not submit evidence for the shortened treatment subgroup. However the license indicates that genotypes 4 should be treated the same as genotype 1 patients, implying that shorter treatment duration applies to both genotypes 1 and 4.

Once again, we are grateful for the opportunity to comment on the TAR and look forward to continued dialogue with NICE regarding the issues raised in this response.

Schering-Plough requests that the issues regarding the assessment report are considered by the assessment group. Given the data presented by the assessment group, indicating that peginterferons are clinically and cost effective, Schering-Plough expects NICE guidance to

recommend the use of peginterferons in all three treatment groups looked at in within this appraisal.

Sincerely,

[redacted]

[redacted]
Schering-Plough

References

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Viraferon Peg SPC:
http://emc.medicines.org.uk/medicine/10321/SPC/ViraferonPeg+Pen+50%2c+80%2c+100%2c+120+or+150+micrograms++powder+and+solvent+for+solution+for+injection+in+pre-filled+pen/

Appendix

Appendix 1: PSA mean values

Table 1.1 HCV/HIV co-infected patients

Treatment group, comparator, source	Diff Cost	Diff QoL	ICER
G1&4: Peg2b+RIB vs. No Treatment, Laguno, 2004	£597	2.04	£293
G2&3: Peg2b+RIB vs. No Treatment, Laguno, 2004	-£2,015	2.88	Dominant
All: Peg2b+RIB vs. No Treatment, Laguno, 2004	£1,118	1.70	£658
G1&4: Peg2b+RIB vs. No Treatment, Laguno, 2009	£3,298	0.90	£3,683
G2&3: Peg2b+RIB vs. No Treatment, Laguno, 2009	-£2,527	3.04	Dominant
All: Peg2b+RIB vs. No Treatment, Laguno, 2009	£1,118	1.70	£658

Table 1.2: Re-treated patients

Treatment group, comparator, source	Diff Cost	Diff QoL	ICER
G1&4: Peg2b+RIB vs. No treatment. EPIC	£3,275	0.70	£4,711
G2&3: Peg2b+RIB vs. No treatment. EPIC	-£1,707	2.77	Dominant
All: Peg2b+RIB vs. No treatment. EPIC	£2,467	1.03	£2,389
G1&4: Peg2b+RIB vs. No treatment. Scotto, 2008	£6,746	0.52	£12,977
G2&3: Peg2b+RIB vs. No treatment. Scotto, 2008	£1,432	2.15	£666
All: Peg2b+RIB vs. No treatment. Scotto, 2008	£5,706	0.84	£6,803

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Appendix 2: Parameterization of the distributions used in PSA

Model variables

Epidemiology

Variable	Default value	Reference	Lower value	Upper value	S.E.	Distribution	Alpha	Beta
% pts with mild disease at baseline	33.30%	Assumption	0.00%	100.00%	0.26	Gamma	1.70	0.20
% pts with moderate/severe disease at baseline	33.30%	Assumption	0.00%	100.00%	0.26	Gamma	1.70	0.20
% pts with cirrhosis disease at baseline	33.40%	Assumption	0.00%	100.00%	0.26	Gamma	1.71	0.19
Pt group: Co-inf - G1&4	62.64%	Laguno, 2009	55.46%	69.83%	0.04	Beta	109.00	65.00
Pt group: Co-inf - G1&4 (Laguno, 2004)	63.00%	Laguno, 2004	53.32%	72.68%	0.05	Beta	59.85	35.15
Pt group: Re-Tx - G1&4	80.42%	Scotto, 2008	73.92%	86.92%	0.03	Beta	115.00	28.00
Pt group: Re-Tx - G1&4 (EPIC)	83.74%	EPIC. CSR, Table 14	81.77%	85.72%	0.01	Beta	1,123.00	218.00
Pt group: Co-inf - Weight	68.29	Laguno, 2009	45.71	90.88	11.52	Gamma	35.13	1.94
Pt group: Co-inf - Age	40.65	Laguno, 2009	30.42	50.87	5.22	Gamma	60.69	0.67
Pt group: Co-inf - % Male	72.53%	Laguno, 2009	66.17%	78.89%	0.03	Beta	126.20	47.80

Pt group: Co-inf - Weight (Laguno, 2004)	62.00	Laguno, 2004	39.42	84.58	11.52‡	Gamma	28.96	2.14
Pt group: Co-inf - Age (Laguno, 2004)	40.00	Laguno, 2004	29.77	50.23	5.22‡	Gamma	58.77	0.68
Pt group: Co-inf - % Male (Laguno, 2004)	63.00%	Laguno, 2004	53.62%	72.38%	0.05	Beta	59.85	35.15
Pt group: Re-Tx - Weight	79.79	Scotto, 2008	50.45	109.13	14.97‡	Gamma	28.41	2.81
Pt group: Re-Tx - Age	46.85	Scotto, 2008	28.28	65.41	9.47	Gamma	24.46	1.92
Pt group: Re-Tx - % Male	57.34%	Scotto, 2008	49.24%	65.45%	0.04	Beta	82.00	61.00
Pt group: Re-Tx - Weight (EPIC)	80.67	EPIC. CSR, Table 14	51.33	110.01	14.97	Gamma	29.04	2.78
Pt group: Re-Tx - Age (EPIC)	49.00	EPIC. CSR, Table 14	33.28	64.72	8.02	Gamma	37.33	1.31
Pt group: Re-Tx - % Male (EPIC)	70.84%	EPIC. CSR, Table 14	68.41%	73.28%	0.01	Beta	950.00	391.00

Values in Red are estimated from the provided S.E.

Values in Blue are estimated using the lower and upper CI

‡ Data not available so S.E. assumed to be equivalent to Laguno, 2009

Efficacy

Variable	Default value	Reference	Lower value	Upper value	S.E.	Distribution	Alpha	Beta
Co-Inf: EVR, G1&4 - PegInt2a	71.00%	Laguno, 2009	59.70%	82.30%	0.06	Beta	44.02	17.98
Co-Inf: EVR, G2&3 - PegInt2a	96.00%	Laguno, 2009	89.10%	100.00%	0.04	Beta	29.76	1.24
Co-Inf: EVR, G1&4 - PegInt2b	32.00%	Laguno, 2009. SVR reported at 72 weeks	17.85%	46.15%	0.07	Beta	15.04	31.96
Co-Inf: EVR, G2&3 - PegInt2b	71.00%	Laguno, 2009. SVR reported at 72 weeks	58.37%	83.63%	0.06	Beta	24.14	9.86
Co-Inf: SVR, G1&4 - PegInt2a	57.00%	Laguno, 2009.	45.39%	68.61%	0.06	Beta	35.34	26.66
Co-Inf: SVR, G2&3 - PegInt2a	83.00%	Laguno, 2009.	67.03%	98.97%	0.08	Beta	25.73	5.27

Co-Inf: SVR, G1&4 - PegInt2b	28.00%	Laguno, 2009. SVR reported at 72 weeks	15.16%	40.84%	0.07	Beta	13.16	33.84
Co-Inf: SVR, G2&3 - PegInt2b	62.00%	Laguno, 2009. SVR reported at 72 weeks	45.68%	78.32%	0.08	Beta	21.08	12.92
Co-Inf: SVR, All - PegInt2b (Laguno, 2004)	38.00%	Laguno, 2004. SVR reported at 72 weeks	21.44%	54.56%	0.08	Beta	12.54	20.46
Co-Inf: SVR, All - PegInt2b (Laguno, 2004)	53.00%	Laguno, 2004. SVR reported at 72 weeks	30.56%	75.44%	0.11	Beta	12.54	20.46
Re-Tx: SVR, G1&4 - PegInt2a	15.79%	Scotto, 2008 SVR reported at 72 weeks	6.32%	25.26%	0.05	Beta	9.00	48.00
Re-Tx: SVR, G2&3 - PegInt2a	35.71%	Scotto, 2008 SVR reported at 72 weeks	10.61%	60.81%	0.13	Beta	5.00	9.00
Re-Tx: SVR, G1&4 - PegInt2b	12.07%	Scotto, 2008 SVR reported at 72 weeks	3.69%	20.45%	0.04	Beta	7.00	51.00
Re-Tx: SVR, G2&3 - PegInt2b	42.86%	Scotto, 2008 SVR reported at 72 weeks	16.67%	69.05%	0.13	Beta	6.00	8.00
Re-Tx: EVR, G1&4 - PegInt2b (EPIC)	29.76%	EPIC Data, CSR table 19&21	27.08%	32.44%	0.01	Beta	333.60	787.40
Re-Tx: EVR, G2&3 - PegInt2b (EPIC)	79.13%	EPIC Data, CSR table 19&21	73.58%	84.68%	0.03	Beta	163.00	43.00
Re-Tx: SVR, G1&4 - PegInt2b (EPIC)	48.65%	EPIC Data, CSR table 19&21	43.29%	54.01%	0.03	Beta	162.49	171.51
Re-Tx: SVR, G2&3 - PegInt2b (EPIC)	69.95%	EPIC Data, CSR table 19&21	64.20%	78.10%	0.04	Beta	114.01	48.99

Values in Red are estimated from the provided S.E

Discontinuation rates

Variable	Default value	Reference	Lower value	Upper value	S.E.	Distribution	Alpha	Beta
Disc rate: Co-inf - PegInt 2a	13.98%	Laguno, 2009 Discontinuation due to AE only	6.17%	21.79%	0.04	Beta	13.42	82.58

Disc rate: Co-inf - PegInt 2b	9.30%	Laguno, 2009 Discontinuation due to AE only	1.50%	17.10%	0.04	Beta	8.00	78.00
Disc rate: Co-inf - PegInt 2b (Laguno, 2004)	17.31%	Laguno, 2004 Overall discontinuation	7.03%	27.59%	0.05	Beta	9.00	43.00
Disc rate: Re-Tx - PegInt 2a	14.08%	Scotto, 2008 Discontinuation due to AE only	5.99%	22.18%	0.04	Beta	10.00	61.00
Disc rate: Re-Tx - PegInt 2b	11.11%	Scotto, 2008 Discontinuation due to AE only	3.85%	18.37%	0.04	Beta	8.00	64.00
Disc rate: Re-Tx - PegInt 2b (EPIC)	6.64%	EPIC STUDY: Table 31 CSR Discontinuation due to AE only	5.30%	7.97%	0.01	Beta	89.00	1,252.00

Values in Red are estimated from the provided S.E

Transitional probabilities

Variable	Default value	Reference	Lower value	Upper value	S.E.	Distribution	Alpha	Beta
TP: Mild => VC/SVR	0.20%	Bennett 1997, Morisco 1998	0.00%	0.40%	0.00	Gamma	3.84	0.00
TP: Mild => Mild	97.30%	Default state	95.50%	98.28%	0.01	Gamma	NA	NA
TP: Mild => Mod/Sev	2.50%	Wright 2006, Grieve 2005	1.72%	4.10%	0.01	Gamma	16.90	0.00
TP: Mod/Sev => Mod/Sev	96.20%	Default state	92.50%	98.95%	0.02	Gamma	NA	NA
TP: Mod/Sev => Cirr	3.70%	Wright 2006, Grieve 2005	1.00%	7.30%	0.02	Gamma	5.30	0.01
TP: Mod/Sev => HCC	0.10%	Bennett 1997	0.05%	0.20%	0.00	Gamma	6.83	0.00
TP: Cirr => Cirr	92.66%	Default state	90.82%	97.68%	0.02	Gamma	NA	NA
TP: Cirr => D Cirr	3.90%	Grieve 2005, Fattovich 1997	1.60%	4.50%	0.01	Gamma	27.79	0.00
TP: Cirr => HCC	1.44%	Fattovich 1997	0.72%	1.68%	0.00	Gamma	34.66	0.00
TP: Cirr => Liver death	2.00%	Fattovich 1997	0.00%	3.00%	0.01	Gamma	6.83	0.00
TP: D Cirr => D Cirr	83.36%	Default state	18.75%	88.28%	0.18	Gamma	NA	NA
TP: D Cirr => HCC	1.44%	Fattovich 1997	0.72%	3.00%	0.01	Gamma	6.14	0.00
TP: D Cirr => Tx	2.20%	Wright 2006, Siebert 2003	1.00%	3.25%	0.01	Gamma	14.69	0.00
TP: D Cirr => Liver death	13.00%	Grieve 2005, Fattovich 1997	10.00%	75.00%	0.17	Gamma	0.61	0.21
TP: HCC => HCC	42.00%	Default state	11.00%	57.00%	0.12	Gamma	NA	NA
TP: HCC => Tx	2.00%	Grieve 2005, Siebert 2003	0.00%	3.00%	0.01	Gamma	6.83	0.00
TP: HCC => Liver death	56.00%	Boring 1993, Sonnenberg 2003	43.00%	86.00%	0.11	Gamma	26.06	0.02
TP: Tx => Post Tx	85.00%	Default state	79.00%	88.00%	0.02	Gamma	NA	NA
TP: Tx => Liver death	15.00%	Wright 2006	12.00%	21.00%	0.02	Gamma	42.68	0.00
TP: Post Tx => Post Tx	94.30%	Default state	94.00%	97.00%	0.01	Gamma	NA	NA
TP: Post Tx => Liver death	5.70%	Bennett 1997, Detre 1996, Asher 1994, Kilpe	3.00%	6.00%	0.01	Gamma	55.47	0.00

		1994						

Values in Blue are estimated using the lower and upper CI

Drug Costs

Variable	Default value	Reference	Lower value	Upper value	S.E.	Distribution	Alpha	Beta
Copegus (200mg/42caps): Tab size	200	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (200mg/112caps): Tab size	200	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (200mg/168caps): Tab size	200	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (400mg/56caps): Tab size	400	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (200mg/42caps): Caps / pack	42	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (200mg/112caps): Caps / pack	112	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (200mg/168caps): Caps / pack	168	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (400mg/56caps): Caps / pack	56	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (200mg/42caps): Pack cost	£116	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (200mg/112caps): Pack cost	£308	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (200mg/168caps): Pack cost	£462	BNF, March 2009	NA	NA	NA	NA	NA	NA
Copegus (400mg/56caps): Pack cost	£308	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol (200mg/84caps): Tab size	200	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol (200mg/140caps): Tab size	200	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol (200mg/168caps): Tab size	200	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol (200mg/84caps): Caps / pack	84	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol (200mg/140caps): Caps / pack	140	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol (200mg/168caps): Caps / pack	168	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol (200mg/84caps): Pack cost	£276	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol (200mg/140caps): Pack cost	£459	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol (200mg/168caps): Pack cost	£551	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol: Solution - ml/bottle	100	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol: Solution - mg/ml	40	BNF, March 2009	NA	NA	NA	NA	NA	NA
Rebatol: Solution pack cost	£70	BNF, March 2009	NA	NA	NA	NA	NA	NA
Pegasys (135µg prefilled syringe): µg/pen	135	BNF, March 2009	NA	NA	NA	NA	NA	NA
Pegasys (180µg prefilled syringe): µg/pen	180	BNF, March 2009	NA	NA	NA	NA	NA	NA
Pegasys (135µg prefilled syringe): Pack cost	£114	BNF, March 2009	NA	NA	NA	NA	NA	NA
Pegasys (180µg prefilled syringe): Pack cost	£132	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Powder - 50µg bottle): µg/bottle	50	BNF, March 2009	NA	NA	NA	NA	NA	NA

Variable	Default value	Reference	Lower value	Upper value	S.E.	Distribution	Alpha	Beta
ViraferonPeg (Powder - 80µg bottle): µg/bottle	80	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Powder - 100µg bottle): µg/bottle	100	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Powder - 120µg bottle): µg/bottle	120	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Powder - 150µg bottle): µg/bottle	150	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Powder - 50µg bottle): Pack cost	£63	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Powder - 80µg bottle): Pack cost	£100	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Powder - 100µg bottle): Pack cost	£126	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Powder - 120µg bottle): Pack cost	£151	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Powder - 150µg bottle): Pack cost	£188	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 50µg pen): µg/pen	50	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 80µg pen): µg/pen	80	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 100µg pen): µg/pen	100	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 120µg pen): µg/pen	120	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 150µg pen): µg/pen	150	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 50µg pen): Pack cost	£69	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 80µg pen): Pack cost	£118	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 100µg pen): Pack cost	£138	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 120µg pen): Pack cost	£166	BNF, March 2009	NA	NA	NA	NA	NA	NA
ViraferonPeg (Prefilled pen - 150µg pen): Pack cost	£207	BNF, March 2009	NA	NA	NA	NA	NA	NA

Dosing

Variable	Default value	Reference	Lower value	Upper value	S.E.	Distribution	Alpha	Beta
PEGIFN 2a: Dose (<75 kg - G1&4)	180	Pegasys, SPC	NA	NA	NA	NA	NA	NA
PEGIFN 2a: Dose (75+ kg - G1&4)	180	Pegasys, SPC	NA	NA	NA	NA	NA	NA
PEGIFN 2a: Dose (<75 kg - G2&3)	180	Pegasys, SPC	NA	NA	NA	NA	NA	NA
PEGIFN 2a: Dose (75+ kg - G2&3)	180	Pegasys, SPC	NA	NA	NA	NA	NA	NA
Copegus: Dose (<75 kg - G1&4) - ReTx	1000	Copegus, SPC	NA	NA	NA	NA	NA	NA
Copegus: Dose (75+ kg - G1&4) - ReTx	800	Copegus, SPC	NA	NA	NA	NA	NA	NA
Copegus: Dose (<75 kg - G2&3) - ReTx	1200	Copegus, SPC	NA	NA	NA	NA	NA	NA
Copegus: Dose (75+ kg - G2&3) - ReTx	800	Copegus, SPC	NA	NA	NA	NA	NA	NA
Copegus: Dose (<75 kg - G1&4) - Co-Inf	800	Copegus, SPC	NA	NA	NA	NA	NA	NA
Copegus: Dose (75+ kg - G1&4) - Co-Inf	800	Copegus, SPC	NA	NA	NA	NA	NA	NA
Copegus: Dose (<75 kg - G2&3) - Co-Inf	800	Copegus, SPC	NA	NA	NA	NA	NA	NA
Copegus: Dose (75+ kg - G2&3) - Co-Inf	800	Copegus, SPC	NA	NA	NA	NA	NA	NA
PEGIFN 2b: Dose (<40kg)	50	ViraferonPeg, SPC	NA	NA	NA	NA	NA	NA
PEGIFN 2b: Dose (40-64kg)	80	ViraferonPeg, SPC	NA	NA	NA	NA	NA	NA
PEGIFN 2b: Dose (65-75kg)	100	ViraferonPeg, SPC	NA	NA	NA	NA	NA	NA
PEGIFN 2b: Dose (76-85kg)	120	ViraferonPeg, SPC	NA	NA	NA	NA	NA	NA
PEGIFN 2b: Dose (>86kg)	150	ViraferonPeg, SPC	NA	NA	NA	NA	NA	NA
Rebetol: Dose (<40kg)	800	Rebetol, SPC	NA	NA	NA	NA	NA	NA
Rebetol: Dose (40-64kg)	800	Rebetol, SPC	NA	NA	NA	NA	NA	NA
Rebetol: Dose (65-75kg)	800	Rebetol, SPC	NA	NA	NA	NA	NA	NA
Rebetol: Dose (76-85kg)	1000	Rebetol, SPC	NA	NA	NA	NA	NA	NA
Rebetol: Dose (>86kg)	1200	Rebetol, SPC	NA	NA	NA	NA	NA	NA

Disease state costs

Variable	Default value	Reference	Lower value	Upper value	S.E.	Distribution	Alpha	Beta
Cost: VC/SVR	£311.36	Grieve 2005	£216.53	£465.60	193.00	Gamma	2.60	119.63
Cost: Mild	£165.90	Grieve 2005	£111.47	£251.99	170.00	Gamma	0.95	174.20
Cost: Mod/Sev	£861.94	Grieve 2005	£747.86	£1,140.52	1029.00	Gamma	0.70	1,228.43
Cost: Cirr	£1,368.05	Grieve 2005	£901.93	£2,095.24	2479.00	Gamma	0.30	4,492.12
Cost: D Cirr	£10,964.83	Grieve 2005	£8,089.23	£15,932.88	9610.00	Gamma	1.30	8,422.57
Cost: HCC	£9,769.89	Grieve 2005	£5,772.76	£15,631.44	8541.00	Gamma	1.31	7,466.68
Cost: Tx	£44,953.12	Grieve 2005	£24,597.58	£73,792.74	0.00	Gamma	12.83	3,503.71
Cost: Post Tx	£1,664.98	Grieve 2005	£907.52	£2,740.18	2906.00	Gamma	0.33	5,072.03
Cost: Liver death	£0.00	Assumption	£0.00	£0.00	0.00	None		

Utilities

Variable	De-fault value	Reference	Lower value	Upper value	S.E.	Dis-tribution	Alpha	Beta
Utility: VC/SVR	0.82	Grieve 2005	0.74	0.90	0.21	Beta	19.68	4.32
Utility: Mild	0.77	Grieve 2005	0.74	0.80	0.22	Beta	142.45	42.55
Utility: Mod/Sev	0.66	Grieve 2005	0.60	0.72	0.25	Beta	46.86	24.14
Utility: Cirr	0.55	Grieve 2005	0.44	0.66	0.34	Beta	22.00	18.00
Utility: D Cirr	0.45	Grieve 2005	0.39	0.51	0.24	Beta	28.80	35.20
Utility: HCC	0.45	Grieve 2005	0.39	0.51	0.24	Beta	28.80	35.20
Utility: Tx	0.45	Grieve 2005	0.39	0.51	0.24	Beta	28.80	35.20
Utility: Post Tx	0.67	Grieve 2005	0.34	1.00	0.00	Beta	0.00	0.00
Utility: Liver death	0.00	Grieve 2005	0.00	0.00	0.00	None		
QoL in Tx pts: Utility	0.66	Mean EQ-5D score among adults with mild hepatitis C receiving Viraferon plus ribavirin in the NHS HTA study	0.59	1.00	0.10	Beta	12.88	6.63
QoL in Tx pts: Disutility	0.13	Based on the mean change when mild hepatitis C pts receieved Viraferon plus ribavirin in adults participating in the NHS HTA study who completed EQ-5D	0.00	0.16	0.04	Beta	8.70	58.19

Values in Blue are estimated using the lower and upper CI

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Appendix 3

EPIC re-treatment group (previously treated on both peginterferon and interferon) with the corrected ribavirin costs. These are now comparable to the additional analysis conducted on the EPIC retretment population.

Retreatment – EPIC CSR

This is based on the 84 Retreatment Genotype 1 & 4 patients (EPIC)

Non Discounted	**No treatment**	**Peg2b + RIB**
Total Cost	£3,026,140	£3,515,765
Cost per patient	£36,136	£41,983
QALYs	1,302	1,417
QALYs per patient	15.55	16.93
Cost-effectiveness compared to no treatment		**£4,235**
Discounted	**No treatment**	**Peg2b + RIB**
Total Cost	£1,853,416	£2,455,845
Cost per patient	£22,132	£29,326
QALYs	835	894
QALYs per patient	9.97	10.67
Cost-effectiveness compared to no treatment		**£10,335**

This is based on the 16 Retreatment Genotype 2 & 3 patients (EPIC)

Non Discounted	**No treatment**	**Peg2b + RIB**
Total Cost	£587,443	£602,733
Cost per patient	£36,136	£37,076
QALYs	253	340
Cost-effectiveness compared to no treatment		**£174**
Discounted	**No treatment**	**Peg2b + RIB**
Total Cost	£359,790	£458,795
Cost per patient	£22,132	£28,222
QALYs	162	207
QALYs per patient	9.97	12.75
Cost-effectiveness compared to no treatment		**£2,195**

This is based on all 100 Retreatment patients (EPIC)

Non Discounted	**No treatment**	**Peg2b + RIB**

Total Cost	£3,613,583	£4,118,498
Cost per patient	£36,136	£41,185
QALYs	1,555	1,758
QALYs per patient	15.55	17.58
Cost-effectiveness compared to no treatment		**£2,484**
Discounted	**No treatment**	**Peg2b + RIB**
Total Cost	£2,213,206	£2,914,640
Cost per patient	£22,132	£29,146
QALYs	997	1,101
QALYs per patient	9.97	11.01
Cost-effectiveness compared to no treatment		**£6,784**