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Wednesday 10th February 2010

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BY E-MAIL

Dear Jeremy,

Technology assessment report: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (Part-review of TA75 and TA106)

Thank you for the opportunity to review and comment on the technology assessment report.

Please find below our comments on the analysis performed by the assessment group. We have raised a number of points for consideration by the appraisal committee which we feel requires further discussion at the appraisal committee meeting.

Yours Sincerely

[redacted]

Points for consideration

There are a number of differences between the clinical and economic analyses submitted by Roche or reviewed by the assessment group and the conclusions contained within the assessment group report. We believe that these should be highlighted and that it is critical that the Appraisal Committee is aware of areas where Roche considers the assessment group's interpretation of the evidence may not be entirely consistent with the evidence presented.

1. Assumed clinical effectiveness for pegylated interferon α-2a

Roche is unclear on the exact source of clinical data used in the cost effectiveness analysis by the Assessment Group as reflected in table 39 of the report.

Standard treatment duration v shorter treatment duration for **G4** patients:

The Assessment Group has only explored scenarios covering genotype 1, 2 and 3 patients. According to pegylated interferon α-2a's label extension, genotype 4 patients are also covered by the license. Treatment naive patients with genotype 1 with LVL and RVR or genotype 4 with RVR should be considered for the shorter treatment duration regimen. Therefore the cost effectiveness analysis should include this sub-population. The analysis has been included in the Roche submission and the data supporting the clinical effectiveness has been presented in table 36 of the submission. A reproduction of the table can be found below.

Table 1: SVR in the model comparisons

Com.	Population characteristics		SVR	Source
4	Naïve patients, genotype 2 or 3 with LVL and RVR.	16 weeks peginterferon alfa-2a and ribavirin combination	89%	NV17317, subgroup analysis (Roche data on file)
		24 weeks peginterferon alfa-2a and ribavirin combination	94%	NV17317, subgroup analysis (Roche data on file)
5	Naïve patients, genotype 1 or 4 with LVL and RVR.	24 weeks peginterferon alfa-2a and ribavirin combination	91%	Jensen et al. 2006, subgroup analysis (Roche data on file)
		48 weeks peginterferon alfa-2a and ribavirin combination	97%	Jensen et al. 2006, subgroup analysis (Roche data on file)
6	HIV-HCV co-infected patients	Peginterferon alfa-2a and ribavirin combination	40%	Torriani et al. 2004
		Interferon alpha and ribavirin combination	12%	Torriani et al. 2004

Standard treatment duration v shorter treatment duration for patients **G2 or G3** patients:

As part of the Roche submission a retrospective analysis of the ACCELERATE patients was presented. The SVR rates were also reported in table 36 of the

submission (above). It is unclear why the Assessment Group ignored the data provided by Roche in this analysis and instead utilised data from 2 smaller supportive studies that used an unlicensed ribavirin dosing regiment.

2. Predictability of Virological Response at Week 12 on Sustained Virological Response in naïve and treatment experienced patients

Early prediction of eventual treatment success on a basis of week 12 virological response is a classical tool to individualize therapy and to deliver more cost effective treatment even to the most difficult subpopulation of HCV patients.

Many clinical studies have investigated the role of EVR, achieved with Peg-IFN alfa 2a in predicting treatment outcomes in naïve patients. In one of the first publications Lee et al[1] examined the baseline viral load factors and the predictability value of early HCV RNA determinations in patients, treated with Peg-IFN alfa 2a. Detailed ROC curve analyses in the same study demonstrated that as early as week 12 we could predict a very low likelihood of SVR with a negative predictive value of 98% in patients who did not achieve HCV RNA levels<100copies/ml or a $2\log_{10}$ drop in HCV RNA compared to baseline. This treatment manoeuvre is known now as a week 12 stopping rule and its applicability to treatment experienced population is further verified in the REPEAT trial, the largest study in non-responders to previous treatment with Peg IFN so far.

The ability of virological responses at week 12 to predict sustained virological response was assessed according to the actual treatment period in all patients treated in the REPEAT study. Virological response at week 12 was evaluated both as **early virological response** using the standard definition (achieving a $\geq$ 2-$\log_{10}$ decrease from baseline in HCV RNA or undetectable or unquantifiable HCV RNA) or as **virological suppression** (undetectable HCV RNA defined as HCV RNA <50 IU/mL). Although the negative predictive values for sustained virological response were high using either early virological response at week 12 or viral suppression at week 12, the positive predictive values for sustained virological response were highest in patients who achieved more stringent criteria for virological suppression at week 12.

Between 11% and 24% of patients across the four treatment groups achieved virological suppression (HCV RNA < 50 IU/mL) at week 12. The negative predictability of not achieving virological suppression at week 12 for not having a sustained virological response ranged from 94% to 98% in the four treatment groups. These results are very similar to the previously published results for naïve patient population. Of the 719 patients who did not achieve virological suppression at week 12, only 32 patients (4%) achieved a sustained virological response at the end of follow-up. Thus, in the patient population studied, if a patient did not achieve virological suppression at week 12, the probability was

very low that the patient would achieve a sustained virological response. These findings led to a new definition of what degree of viral suppression at week 12 is desired in order to predict a final SVR in treatment experienced patients. According to Pegasys label patients who have detectable virus at week 12 should stop therapy, a recommendation that fully compliments additional SHTAC analyses of this patient population. [2]

The positive predictability after achieving virological suppression at week 12 for a sustained virological response was 53% and 68% in the two groups receiving 72 weeks of treatment (or 57% when the two 72 week groups are pooled), which was considerably higher than the positive predictability of 36% and 34% in the two groups receiving 48 weeks of treatment (or 35% when the two 48 week groups are pooled) (table 43 below)[3].

Table 2: Predictive Values of the Virological Responses at Week 12 on Sustained Virological Response According to the Actual Treatment Period, All Patients Treated

		PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 Weeks (N=317)		PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 48 Weeks (N=156)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 72 Weeks (N=156)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 Weeks (N=313)	
		SVR	Non-SVR	SVR	Non-SVR	SVR	Non-SVR	SVR	Non-SVR
HCV RNA undetectable or unquantifiable or >=2 log-10 drop at week 12	Yes	51	145	10	81	20	56	26	104
	No	0	96	0	54	1	70	1	161
	Week 12 response	62%		58%		49%		42%	
	PPV	26%		11%		26%		20%	
	NPV	100%		100%		99%		>99%	
HCV RNA undetectable at week 12	Yes	40	35	8	14	17	8	12	23
	No	11	206	2	121	4	118	15	242
	Week 12 response	24%		14%		16%		11%	
	PPV	53%		36%		68%		34%	
	NPV	95%		98%		97%		94%	

Note: Sustained virological response is defined as a single last HCV RNA measurement that is not detectable (<50 IU/mL) >= follow-up week 20 (>= study day of last dose of study medication + 140).
The time windows for early virological response and virological response at week 12 are the last assessment between study day 72 and 99.
PPV=Positive predictive value, NPV=Negative predictive value
Patients with missing HCV RNA samples at week 12 are excluded for calculation of NPV.

Thus, achieving virological suppression at week 12 during re-treatment with PEG-IFN alfa-2a and ribavirin combination therapy provided these non-responders patients with more than a 50% chance of achieving a sustained virological response with 72 weeks of treatment. However, as shown in table 2 the probability of achieving a sustained virological response after 72 weeks of treatment was over 50% only if virological suppression was achieved at week 12. If less stringent criteria is used (HCV RNA is unquantifiable but detectable at week 12), the probability of achieving a sustained virological response is only 6% to 25%.

Table 3: Positive Predictive Values of Various Degrees of Virological Responses at Week 12 on Sustained Virological Response According to the Actual Treatment Period, All Patients Treated

	PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 72 Weeks (N=317)		PEG-IFN alfa-2a 360/180 ug Ribavirin 1000/1200 mg 48 Weeks (N=156)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 72 Weeks (N=156)		PEG-IFN alfa-2a 180 ug Ribavirin 1000/1200 mg 48 Weeks (N=313)	
	N	SVR	N	SVR	N	SVR	N	SVR
All Patients	317	52 (16%)	156	11 (7%)	156	22 (14%)	313	27 (9%)
HCV RNA Response at Week 12 (a)								
Undetectable	75	40 (53%)	22	8 (36%)	25	17 (68%)	35	12 (34%)
Detectable but not quantifiable	66	9 (14%)	35	2 (6%)	14	1 (7%)	44	11 (25%)
Quantifiable >=2 log drop from baseline	55	2 (4%)	34	0 (0%)	37	2 (5%)	51	3 (6%)
Quantifiable 1-2 log drop from baseline	43	0 (0%)	28	0 (0%)	32	1 (3%)	68	0 (0%)
Quantifiable not >=1 log drop from baseline	47	0 (0%)	22	0 (0%)	36	0 (0%)	81	1 (1%)
Missing or not assessable (b)	31	1 (3%)	15	1 (7%)	12	1 (8%)	34	0 (0%)

Note: Baseline HCV RNA: Last valid quantitative HCV RNA result at or before baseline (<=study day 1).
(a) HCV RNA at week 12: Last valid HCV RNA result in week 12 time window (>=study day 72 and <=study day 99).
(b)No HCV RNA result at week 12 or no baseline HCV RNA result and HCV RNA at week 12 neither 'undetectable' nor 'detectable but not quantifiable'.

In conclusion patients in group C, that received treatment with a labelled dose and duration of Peg-IFN alfa 2a and ribavirin have a positive predictive value of 68% and negative predictive value of 97% to reach SVR at the end of 72 weeks of treatment using the newly identified criteria of viral suppression at week 12.

Stopping rules for the retreatment of patients and implication to cost effectiveness

The Assessment Group has considered 3 analyses for the retreatment of non-responding G1 and non-G1 patients; no withdrawal, including withdrawal due to AEs and withdrawal according to stopping rules. The results are presented in tables 54, 55 and 56 of the AG report.

As already explained, from these 3 tables Roche believe that only table 56 can form the basis of the cost effectiveness of pegylated interferon alfa-2a in this indication as it is the only one assuming a stopping rule. Roche believe that upon positive NICE guidance eligible patients for retreatment will only receive the full length of the retreatment if they have undetectable virus in week 12. According to the SPC (section 4.2) treatment experienced patients who have detectable virus at week 12 should stop therapy.

The implications of assuming this stopping rule in the cost effectiveness analysis are best represented by table 56 of the AG report. The results from the AG analysis are consistent with the Roche analysis for retreatment of G1 and non-G1 non-responders as demonstrated in the table below showing that pegylated interferon alfa-2a is a highly cost effective option in the retreatment of non-responding patients.

	Roche submission ICER in cost per QALY	AG analysis ICER in cost per QALY
G1 non-responders	**£3,334.44**	**£9,169**
Non-G1 non-responders	**£809.49**	**£2,294**

References:

1. Lee-Samuel-S, et al (2002). Prognostic factors and early predictability of sustained viral response with peginterferon alfa-2a (40KD). *Journal of Hepatology , vol. 37, no. 4, p. 500-506*
2. Pegasys SmPC
3. REPEAT FSR