Paul Catchpole, Ph.D
Healthcare Management Director

Thursday 9th March 2006

Alana Miller
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
LONDON
WC1V 6NA

BY E-MAIL

Dear Alana,

HEALTH TECHNOLOGY APPRAISAL – Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C

Thank you very much for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above technology appraisal.

Overall, Roche welcomes the Appraisal Committee's provisional views endorsing pegylated interferon alfa-2a (Pegasys) for the treatment of mild hepatitis C.

We have a number of points of feedback which relate to the broader application of the evidence base and to the specific licensed indication of each pegylated interferon again both in regard to the proposed guidance.

These points are set out below:

1. "Whether you consider that all of the relevant evidence has been taken into account"

a) Licensed indications of pegylated interferons

The specifics of the licensed indications of the two pegylated interferons have not wholly been taken into account when formulating the draft guidance. An important distinguishing factor exists between the two respective licensed indications.

The licensed indication for pegylated interferon alfa-2a permits the treatment of patients with normal and elevated ALT levels. However, the licensed indication for pegylated interferon alfa-2b only permits the treatment of those patients with elevated ALT.

A proportion of normal ALT patients will have mild disease; therefore to recommend pegylated interferon alfa-2b as a treatment option for all mild patients, is endorsing a use which is outside of license. The guidance should therefore make explicit that pegylated interferon alfa-2b should only be recommended for use in mild patients with elevated ALT only.

b) Recommendation of watchful waiting strategy

Paragraph 1.3 of the guidance states that:

"the decision as to whether a person with mild CHC should be treated immediately rather than waiting until the disease has reached a moderate stage (watchful waiting) should be made by the person after fully informed consultation with the responsible clinician".

This appears to provide an implicit recommendation within the guidance to "watch and wait" without a clear definition of the circumstances under which this is considered the optimal treatment choice. The recommendation appears to contradict the available evidence base which demonstrates that the decision to treat early with pegylated interferon compared to the decision to "watch and wait" is cost effective (section 4.6.2 of the ACD). Consequently the statement perhaps gives the impression that the option to "watch and wait" is being recommended within the guidance, in addition to the option to treat with pegylated interferon.

c) Pegylated interferon as an "option" for treatment of mild CHC

It is not clear to us why pegylated interferon is only being recommended as an option when section 4.2.7.3 of the ACD states that compared to conventional interferon pegylated interferon is cost effective. In addition, compared to the option to watch and wait prior to treatment within the moderate/severe setting, pegylated interferon is also cost effective. Consequently Roche suggests that pegylated interferon is recommended for the treatment of mild CHC and not stated as an "option" within the final guidance.

2. "Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate"

a) Progression rates from mild to moderate/severe CHC

Section 2.2 appears to provide slightly conflicting messages over the rate of progression of this disease describing the rate as "slow yet variable". Also the sentence that states: "30% of those infected develop cirrhosis within 20-30 years" should be clarified to state that this is from the time of infection and not diagnosis.

In general, the guidance perhaps appears to cast an unnecessary level of uncertainty over CHC progression and its potential impact upon the cost effectiveness of treating mild CHC patients. Sensitivity analysis performed on the cost effectiveness results within the Assessment Report (P.126-127) illustrated that the rate of progression from mild to moderate disease was not a sensitive parameter upon the final ICER. Roche has not identified any evidence base that demonstrates:

- evidence of lower rates of progression from mild to moderate disease compared to those presented in the assessment report;

- threshold level of progression rates that would lead to the treatment of mild patients with pegylated interferon's not being cost effective.

Consequently, sections 4.2.1, 4.3.9 and 4.3.10 should be amended because presently the evidence of slower progression rates and the potential impact of this on the cost effectiveness of treatment is extremely weak and only serves to undermine the relatively high degree of certainty around the cost effectiveness of these treatments.

b) Off-license assessment of pegylated interferon alfa-2b dose

In section 4.1.8 the description of "low dose pegylated interferon alfa-2b" plus ribavirin that achieved an SVR of 51% is an "off-licence" dosing schedule and is inappropriate to evaluate the efficacy of pegylated interferon alfa-2b.

c) Cost per QALYs listed

It is unclear within section 4.2.7.2 whether the cost per QALYs listed are reflective of the early stopping rules recommended in section 1.4 to 1.7 of the guidance. We would suggest the definitive cost per QALYs listed within the guidance should be consistent and representative of these.

3. "Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS"

In the light of our feedback above, Roche considers that at present the provisional recommendations of the Appraisal Committee do not wholly represent a sound basis for the preparation of guidance to the NHS. In particular, we would respectfully request that the Appraisal Committee give consideration to the licensed indications issue raised and also the watch and wait discussion we have set out.

Formatted: Bullets and Numbering

Additional Information for the NICE Costing Unit

We would be very grateful if the information given below could be passed on to the NICE Costing Unit to assist with the further development of section 6 "preliminary views on the resource impact for the NHS".

a) Budget Impact of Pegylated interferon alfa 2a

Our original submission provided an estimate of the likely NHS budget impact of implementing pegylated interferon alfa-2a for the treatment of mild CHC compared to current standard practice. Assuming current practice within the NHS is to watch and wait amongst mild CHC patients, the drug acquisition costs of implementing pegylated interferon will be additive and consequently will require additional budget allocations.

b) Summary of Roche budget impact of Pegylated interferon alfa 2a for the treatment of mild CHC

We estimated a constant 19% diagnosis rate of hepatitis C patients and of all patients diagnosed, 25% were assumed to have mild hepatitis C. Of the total budget impact we presented, a phased implementation of any guidance, growing from 20% diffusion in year 1 to 100% diffusion by year 5.

These results are summarised in the table below:

Assuming a Constant 19% Diagnosis Rate and 25% of patients diagnosed having mild HepC

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of Hepatitis C patients	3,802	3,802	3,802	3,802	3,802
Number of Genotype 1 patients	2,586	2,586	2,586	2,586	2,586
Peginterferon alfa-2a with ribavirin	£23,037,857	£23,037,857	£23,037,857	£23,037,857	£23,037,857
PCR Testing	£168,069	£168,069	£168,069	£168,069	£168,069
Less cost of liver biopsy	£1,935,461	£1,935,461	£1,935,461	£1,935,461	£1,935,461
Annual Budget Impact	£21,270,466	£21,270,466	£21,270,466	£21,270,466	£21,270,466
Annual Budget Impact, assuming a staggered NICE Implementation	**£4,254,093**	**£8,508,186**	**£12,762,280**	**£17,016,373**	**£21,270,466**

The above results illustrate that if only 19% of patients are actually diagnosed and 25% of these have mild CHC, assuming all of these patients are then treated, a total of approximately £21.3m will be required to implement the guidance. Close joint working will be required between NHS commissioners and providers; and between departments within NHS Trusts in order to ensure that appropriate funds and services are made available in a timely manner to enable proper implementation of the guidance.

c) Payment by Results (PBR) tariff

Currently the treatment of hepatitis is excluded from the range of PbR tariffs. However, once fully implemented it will be critical that an appropriate PbR tariff is set to enable successful implementation of this guidance. The tariff must sufficiently reimburse NHS Trusts for using pegylated interferon in order to avoid any “perverse incentives” to utilise alternative less expensive forms of treatment for mild CHC.

d) NHS Capacity Considerations

Again when fully implemented, the guidance will potentially have a large impact upon the number of eligible patients requiring treatment. Consequently, the necessary service delivery resources must also be planned for and made available. For example, relative to cancer and cardiovascular disease, hepatitis is often not viewed as a high public health priority amongst NHS Trusts and consequently special attention may be required to ensure that this guidance is properly implemented in a timely manner.

We hope that this feedback is helpful.

Please do not hesitate to contact me if you require any further clarification or explanation of our feedback.

Yours sincerely.