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3 May, 2006

Dear Alana,

**INTERFERON ALFA AND RIBAVIRIN FOR THE TREATMENT OF MILD CHRONIC HEPATITIS C: SCHERING-PLOUGH RESPONSE TO APPRAISAL CONSULTATION DOCUMENT**

Schering-Plough welcomes this opportunity to respond to the draft guidance. Overall we are pleased with the preliminary guidance, and are satisfied with the manner in which the Appraisal Committee has preserved the original guidance.

***S-P response to consideration of review***

NICE proposes to consider a review of the current guidance on chronic hepatitis C in November 2008, as stated in the ACD, section 9. S-P are responding to this proposal for review in a separate letter, which we will forward to NICE shortly.

We have a number of comments relating to specific points in the ACD and set these out below under the general headings requested by NICE.

## Has all the relevant evidence been taken into account?

***Use of peginterferon alfa-2b in genotype-1 low viral load patients***

We would like to draw attention to the fact that the ACD does not refer to the use of peginterferon alfa-2b (ViraferonPeg) as being considered for use in genotype 1 patients, with low viral load, in mild and moderate to severe hepatitis C, which is within our licensed indication.

As noted in the S-P submission to NICE (May 2005), section 2.3.3.1, '*genotype 1 patients should be treated for the full 48-week period assuming they are viral negative at 12 weeks and 24 weeks. However, for a subgroup of these patients, genotype 1, low viral load (LVL), treatment may be shortened to 24 weeks only if genotype 1 LVL patients are viral negative as early as week 4'*. Applying this stopping rule would reduce the average cost per course of therapy to £6,553, for genotype 1 patients with LVL, for 24 weeks of treatment.

Additionally, as clearly stated in the summary of product characteristics (SPC), genotype 1 patients with low viral load may only require 24 weeks of treatment:

As per section 4.2 of the SPC:

*'Genotype 1: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).*

*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, overall 24 weeks treatment duration may be associated with a higher risk of relapse than 48 weeks treatment duration.'*

In contrast to the above, in section 3.2 of the ACD, it is stated that *'for genotypes 1, 4, 5 and 6, the regimen is peginterferon alfa-2a 180 micrograms once per week (low viral load) or for 48 weeks (high viral load) plus ribavirin 1000mg per day (< 75kg body weight) or 1200 mg day (>75mg) for the same length of time as peginterferon alfa'*.

However, as stated in the summary of product characteristics for peginterferon alfa-2a (Pegasys), section 4.2, *'the duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients infected with HCV genotype 1 regardless of viral load should receive 48 weeks of therapy'*. There is, therefore, no distinction made between low and high viral load in the license for peginterferon alfa-2a and all genotype 1 patients receive 48 weeks of treatment.

We would ask the Appraisal Committee to carefully consider this evidence when developing their final recommendations.

**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and is the preliminary view on resource implications for the NHS appropriate?**

We are satisfied with the interpretation of evidence in relation to the use of peginterferon alfa-2b (ViraferonPeg) and ribavirin (Rebetol) in patients of 18 years or older with mild chronic hepatitis C and feel that the presentation of most of the evidence in this regard is reasonable as it appears in the ACD.

**IS THE PROVISIONAL RECOMMENDATION OF THE APPRAISAL COMMITTEE SOUND AND DOES IT CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS?**

We would like to draw attention to the following errors that have been detected in the ACD that are in contrast to the results of the HTA report.

- The dose of peginterferon alfa-2b (ViraferonPeg), used in combination with ribavirin (Rebetol), in genotype 2/3 patients.
- The dose of peginterferon alfa-2b (ViraferonPeg) used in combination with ribavirin (Rebetol), in genotype 1, 4, 5 and 6 patients.
- The cost of treatment of peginterferon alfa-2b (ViraferonPeg) and ribavirin (Rebetol) for genotype 1 patients and genotype 2/3 patients.
- The cost of treatment of peginterferon alfa-2b (ViraferonPeg) monotherapy for genotype 2/3 patients and all other genotypes.

The cost of treating genotype 2/3 patients and genotype 1 patients with combination therapy peginterferon alfa-2b (ViraferonPeg) and ribavirin (Rebetol) is les than that stated in the ACD.

Additionally, the cost of monotherapy for treating genotype 1 patients with peginterferon alfa-2b (ViraferonPeg) is less than the cost of treating the same patients with peginterferon alfa-2a (Pegasys).

***Dosing of Treatment***

Section 3.3 of the ACD refers to peginterferon alfa-2b (ViraferonPeg) and ribavirin (Rebetol) and states that *'for genotypes 2 and 3 the licensed regimen is peginterferon alfa-2b 180 micrograms once per week plus ribavirin 800 mg per day (< 65 kg body weight) or 1000 mg per day (65–85 kg) or 1200 mg per day (> 85 kg) for 24 weeks'*.

This is not the licensed regimen for peginterferon alfa-2b (ViraferonPeg) used in combination with ribavirin (Rebetol) for genotype 2/3 patients. As stated in the SPC, section 4.2, the licensed dose of peginterferon alfa-2b is 1.5 micrograms/kg/week in combination with ribavirin capsules, for 24 weeks, for these patients.

In the same section, it is stated that '*for genotypes 1, 4, 5 and 6, the licensed regimen is peginterferon alfa-2b 180 micrograms once per week for at least 24 weeks (low viral load) or for 48 weeks (high viral load) plus ribavirin 800 mg per day (< 65 kg body weight) or 1000 mg per day (65–85 kg) or 1200 mg per day (> 85 kg) for the same length of time as peginterferon alpha'*.

Again, this is not the licensed regimen for peginterferon alfa-2b (ViraferonPeg) used in combination with ribavirin (Rebetol). As stated in the SPC, section 4.2, the licensed dose of peginterferon alfa-2b is 1.5 micrograms/kg/week in combination with ribavirin capsules. The duration of treatment may vary from 24 to 48 weeks for genotype 1 and genotype 4 patients.

***Cost of Treatment***

According to the ACD, the cost of treating genotype 1 patients with peginteferon alfa-2b (ViraferonPeg) and ribavirin (Rebetol) is £13,468, for 48 weeks of treatment and the cost of treating genotype 2/3 is £6,734, for 24 weeks of treatment.

In the HTA report, page 111, section 5.4.5.5, it is clearly stated that the cost of treating genotype 1 patients with combination therapy peginterferon alfa-2b (ViraferonPeg) and ribavirin (Rebetol) is £13,106, for 48 weeks treatment, while the cost of treating genotype 2/3 patients is £6,553 for 24 weeks.

When referring to the cost of treatment with peginterferon monotherapy, section 3.3 states that *'for genotypes 2 and 3 the cost of peginterferon monotherapy is £3,169 (for 6 months), and for other genotypes £6,339 (for 12 months) for other genotypes'*. It should be clearly stated that the latter cost refers to the cost of monotherapy treatment of all genotypes with peginterferon alfa-2a (Pegasys) and ribavirin (Copegus).

In the HTA report, page 111, section 5.4.5.5, it has been calculated that the cost of peginterferon alfa-2b (ViraferonPeg) monotherapy for treatment of genotype 1 patients is £5,261, for 48 weeks of treatment and £2,631, for 24 weeks of treatment.

We would urge the committee to clarify the issues that have been raised above with regards to both the cost and dosing of peginterferon alfa-2b (ViraferonPeg) and ribavirin (Rebetol).

Yours sincerely,

James Morris

HTA Manager