Schering-Plough Ltd
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW

Tel: 01707 363636
Fax: 01707 363690

2 February, 2006

Alana Miller
NICE
MidCity Place
71 High Holborn
London
WC1V 6NA

Dear Alana

RE: SOUTHAMPTON HEALTH TECHNOLOGY ASSESSMENT CENTRE SYSTEMATIC REVIEW AND ECONOMIC EVALUATION OF INTERFERON ALFA (PEGYLATED AND NON-PEGYLATED) AND RIBVARIN FOR THE TREATMENT OF MILD CHRONIC HEPATITIS C.

We would like to congratulate the SHTAC team on conducting a thorough assessment of interferon alfa and ribavirin in mild HCV. In general the report appears to be very robust and comprehensive and the HTA team has succeeded in modelling the disease area accurately.

We welcome the opportunity to comment on this report and its technical content and we would like to draw attention to a number of minor errors as well as some more general issues. These are outlined in the remainder of this letter.

1. **Threshold Fibrosis Scores** (page 43): Mild Hepatitis C has rightfully been defined according to fibrosis scores. Table 3 gives the threshold fibrosis scores, below which patients were considered to have mild hepatitis C. Unfortunately, this table appears to be incorrect as it suggests that four commonly used scales (Knodell, Metavir, Scheuer and Batts/Ludwig), produce fibrosis scores up to a maximum of five points, whereas Table 1 (page 28) and other publications in this area[1] state that these scales have a maximum fibrosis score of 4. We recommend that this inconsistency is amended in order to clarify the definition of mild hepatitis C used within the systematic review.

2. **Cost-Effectiveness Acceptability Curves:** The concluding statements in the summary document of the report (page 17) state that 'the results of this systematic review and economic evaluation show that patients with histologically mild HCV can be successfully treated with both pegylated and non-pegylated interferon alfa. Early treatment and watchful waiting strategies are associated with acceptable cost per QALY estimates'. We would like to draw attention to the cost effectiveness acceptability curves (pages 131-2). The CEACs appear to indicate that beyond a willingness to pay threshold of £7,500/QALY, the optimal treatment option is early treatment with pegylated interferon. We would recommend including a comment on the results of this analysis in the summary section of the HTA report.

3. **Watchful Waiting:** There is a large degree of uncertainty associated with both the watchful waiting approach and the assumptions regarding watchful waiting employed in the HTA team's economic evaluation. Whilst we accept that watchful waiting may be considered an appropriate strategy for patients with no fibrosis (F0), we would like to draw attention to the following:
    - **SVR** (page 140)**:** The SHTAC team assumes that SVRs for early treatment and watchful waiting are the same. We would like to comment on the fact that these SVR values are derived from the UK Mild HCV Trial (Wright et al, 2005)[2], where only patients receiving treatment for mild to moderate HCV were measured for response. There is no data from this study to support an SVR for a watchful waiting strategy. As disease progresses, and viral load increases, during 'watchful waiting', the potential for SVR decreases. Therefore, the validity of applying the same SVR rates to both strategy arms and assuming that SVR is not affected by progression is questionable. We recommend that the sensitivity of cost-effectiveness results to this assumption is explored in further sensitivity analyses and that the uncertainty driven by this assumption is clearly acknowledged in the summary section.
    - **Cost of watchful waiting-repeat biopsies:** There are a number of important considerations with respect to the impact of repeat biopsies as part of a watchful waiting strategy. Firstly the healthcare costs of the watchful waiting strategy associated with repeat biopsies are significant. Secondly, this strategy assumes that patients are willing to incur the loss of utility associated with these repeat procedures. Wong et al. have commented that routine liver biopsy before treatment with interferon increases the cost of managing patients with chronic hepatitis C without improving the health outcomes[3]. We recommend that the HTA team explicitly acknowledges these issues and where possible incorporates appropriate costs/effects in their evaluation of cost-effectiveness for watchful waiting.
    - **Clinical risk of biopsies:** The clinical risks are not negligible, as many patients suffer from internal bleeding after the procedure and the procedure is associated with low but real risks of morbidity and mortality[3]. We recommend that the HTA team evaluates the impact of this risk on the cost-effectiveness of a watchful waiting strategy.
    - **Likelihood of compliance:** A large proportion of mild hepatitis C patients are injecting drug users and are less likely to comply with regular monitoring, especially where this involves invasive procedures, such as liver biopsies. This may lead to a large number of patients not being diagnosed until they have progressed to cirrhosis, making further treatment significantly more difficult and costly at this later stage. We recommend that the HTA take account of this in their economic evaluation.

    The report also states that the greater the SVR then the greater the potential saving in averted supportive care costs (page 115); so watchful waiting may not be cost-saving in the long run, especially if patients with mild disease show higher responses than those with moderate/severe disease.

4. **Exclusion of mild HCV sub-group data:** The rationale applied for including studies in the clinical effectiveness section of the SHTAC report does not seem appropriate. The 70% cut off appears fairly arbitrary, with no justification as to why this threshold was used or how it was established, nor was it included in the published protocol produced by the HTA group prior to submission.

    Studies were only included in the main discussion of clinical evidence on mild hepatitis C, if more than 70% of the patients participating in the trial had mild hepatitis C. Consequently no studies evaluating pegylated interferon plus ribavirin have been included in the main systematic review, although interferon and pegylated interferon account for most of the studies included providing data for subgroups of patients with mild disease.

However, (page 43) in the HTA report it is also stated that *'a trial with less than 70% of mild patients may be considered for inclusion, if outcomes are reported for the sub-group of patients with mild HCV as well as moderate to severe HCV'.* In fact, a subgroup analysis based on a large RCT may represent a more accurate estimate of the efficacy of pegylated interferon in mild hepatitis C, in comparison to estimates derived from relatively small studies, in which up to 30% of patients had more severe disease.
S-P trials for pegylated interferon alfa were designed to reflect UK clinical practice. However, the trials in the clinical effectiveness review included a large proportion of patients with no fibrosis (F0). In UK clinical practice patients with no fibrosis are not considered appropriate for treatment, since their disease has not progressed.

5. **Definition of mild hepatitis C:** We note that the SHTAC report defines mild hepatitis C on the basis of histology and we concur that this is appropriate. The original scoping document created by NICE referenced potentially classifying HCV positive individuals with normal ALT as suffering from 'mild disease'. Schering-Plough would like to reiterate our position from the June 2005 response to the scoping document. The risk of progression is significantly lower in patients with initially mild disease and either normal or persistently normal ALT (PNALT) compared to those with mild disease and elevated ALT[4,5,6]. As Alberti et al (2004)[7] point out, 'most cases of normal ALT have a mild form of liver disease and very slow, if any, progression, particularly when ALT levels are completely normal at frequent testing, over a prolonged period of time'. Herve et al. (2001)[8] reiterate and support this conclusion. Furthermore, Russo & Brown (2001)[9] confirm that in patients with normal or persistently normal ALT, recommendations for treatment should take into account patient preference and findings of liver biopsy. Thus, HCV positive individuals with normal ALT levels should not automatically be considered for treatment without taking other factors into consideration.

Once again, we are grateful for the opportunity to comment on the SHTAC assessment report, and we look forward to continued dialogue with NICE regarding the issues raised in this letter.
Yours sincerely,

Alan Kane
Director, Communications & Public Affairs

References:

1. Brunt EM, Grading and staging the histopathological lesions of chronic hepatitis: the Knodell histology activity index and beyond. Hepatology, 2000; 31(1): 241-6.

2. Wright M, Forton D, Main J, Goldin R, Torok E, Tedder R, Grant P, Thursz M, Naoumov N, Millson C, Mills PR, Bassendine M and Thomas HC, Treatment of histologically mild hepatitis C virus infection with interferon and ribavirin: a multicentre randomized controlled trial. J Viral Hepat, 2005; 12(1): 58-66.

3. Wong JB, Bennett WG, Koff RS and Pauker SG. Pretreatment Evaluation of Chronic Hepatitis C. JAMA, 1998; 280 (24): 2088-2093.

4. Hui CK, Belaye T, Montegrande K, Wright TL. A comparison in the progression of liver fibrosis in chronic hepatitis C between persistently normal and elevated transaminase.[comment]. J Hepatol 2003; 38(4):511-517.

5. Wali M, Lewis S, Hubscher S et al. Histological progression during short-term follow-up of patients with chronic hepatitis C virus infection. J Viral Hepat 1999 Nov;6(6):445-52.

6. Dienstag JL. The role of liver biopsy in chronic hepatitis C. [Review] [59 refs]. Hepatology 36(5 Suppl 1):S152-60, 2002.

7. Alberti A, Benvegnu L, Boccato S, Ferrari A, Sebastiani G. Natural history of initially mild chronic hepatitis C. [Review] [74 refs]. Dig Liver Dis 2004; 36(10):646-654.

8.Herve S, Savoya G, Riachia G et al. Chronic hepatitis C with normal or abnormal aminotransferase levels: is it the same entity? Eur J Gastroenterol Hepatol 2001 May;13(5):495-500.

9. Russo MW, Brown RS Jr. Should patients with chronic hepatitis C who have normal ALT levels be treated? Curr Gastroenterol Rep 2001;3(1):49-53.