1. EXECUTIVE SUMMARY

1.1 Background

- The hepatitis C virus (HCV) is a cause of significant morbidity and mortality throughout the world. Left untreated it may cause progressive liver disease leading to cirrhosis and the potential consequences of liver failure, hepatocellular carcinoma (HCC) and death
- It is estimated that 0.5% of the UK population have the hepatitis C virus, resulting in an estimated 263,969 people currently infected in England and Wales
- 20% of infected individuals will clear the infection, resulting in the remaining 80% developing chronic hepatitis C (CHC) (Hepatitis C Action Plan for England, July 2004). Of this potential hepatitis C patient pool, only around 19% (40,123) of all hepatitis C cases are presently diagnosed. Of these patients, it is estimated that 25% (10,030) of diagnosed patients have mild hepatitis C (Booth et al, 2001) whereas the actual number of hepatitis C patients who have mild disease is more in the region of 67% (Alberti, 2005)
- 92% of cases of mild hepatitis C are related to current or previous injecting drug use (IDU) and the remaining 8% are related to other risk factors (Hepatitis C Strategy, 2002)
- The low diagnosis rate can be partially explained by the fact that mild disease is characterised by an absence of symptoms. Furthermore, although the Hepatitis C Action Plan for England (2004) suggests that in the next five to ten years, illness and deaths due to hepatitis C will increase, hepatitis C disease and its diagnosis remains low on the NHS public health agenda.

1.2 Diagnosis and Current Treatment Guidelines

- The natural course of mild CHC is poorly defined, and there is conflicting data surrounding rates of progression and the development of end-stage complications in patients (Alberti et al, 1999)
- Alberti et al, (2005) states that the decision as to whether to treat patients or not with CHC should be based on a range of parameters including: patient's age and motivation, disease duration and stage, virological profile and an evaluation of the benefit/risk ratio in individual cases
- It is also important to consider that during treatment with non-pegylated interferons, patients commonly experience symptoms such as tremors, chills, body aches, headaches, mental concentration problems, asthenia, anxiety, and insomnia. These may affect the patient's willingness to continue and comply with therapy, and therefore affect the likelihood of achieving therapeutic success
- There are currently no specific clinical guidelines for the treatment of individuals with mild CHC in England and Wales but mild CHC patients are usually managed using a 'watch and wait policy' (with 6 monthly reviews) with regular liver biopsies performed over the lifetime of the patient. Treatment options available for current clinical practice in England and Wales include non-pegylated interferon plus ribavirin and pegylated interferons also in combination with ribavirin.

1.3 Demonstrating the Clinical Effectiveness of Pegasys® (peginterferon alfa-2a) in Mild Chronic Hepatitis C

- Peginterferon alfa-2a (Pegasys®) is indicated for the treatment of CHC in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV
- The main pivotal trials looking at the efficacy, safety and tolerability of peginterferon alfa-2a included moderate to severe as well as mild CHC patients
- For the purpose of supporting this particular technology appraisal, Roche has therefore undertaken a specific sub-group analysis of the peginterferon alfa-2a pivotal trials (Zeuzem et al., 2004; Fried et al., 2003; Torriani et al., 2004; and Hadziyannis et al.,2004)
- In the trials where peginterferon alfa-2a was compared to no treatment, the mild subgroup achieved 50% sustained viral response (SVR) at 48 weeks while 0% SVR was achieved in the no-treatment arm. The percentage of SVR achieved in genotype 1 and non 1 were as following:

    - Genotype 1: 38.5% (48 weeks)
    - Genotype non-1: 69.0% (24 weeks) and 78.1% (48 weeks)

- Based on an indirect comparison, we assessed the difference in SVR rates achieved between peginterferon alfa-2a versus interferon alfa / ribavirin combinations. Although the peginterferon alfa-2a population (Zeuzem et al., 2004) included a higher proportion of genotype non-1 patients (78% versus 49%) which are known to be more difficult to treat, the proportion of SVRs was still superior (50% versus 33%). In the genotype 1 and non- 1 the SVR rates achieved were as following:

    - Genotype 1: 38.5% (peginterferon alfa-2a) and 18% (interferon alfa and ribavirin)
    - Genotype non-1: 78.1% (peginterferon alfa-2a) and 49% (interferon alfa and ribavirin)

- We therefore conclude that all mild patients treated with peginterferon alfa 2a, whether genotype 1 or genotype non- 1 will benefit from an increased SVR.
- Genotype 1 patients should be treated for 48 weeks whilst genotype non 1 patients should be treated for 24 weeks.

1.4 Impact on Quality of Life Using Pegasys®

- The MOS short form questionnaire (SF-36) and the fatigue severity scale (FSS) have both demonstrated good reliability and validity in measuring the quality of life of chronic Hepatitis C patients
- When used in patients treated with peginterferon alfa-2a plus ribavirin these quality of life measures demonstrated that patients who achieved an SVR consistently performed better than virological non-responders, irrespective of treatment duration (24 weeks or 48 weeks)

- Patients on peginterferon alfa-2a achieving an SVR performed consistently better on both SF36 and FSS when compared with untreated controls and non-responders
- While scores over time have been shown to decrease during treatment duration with both pegylated and non-pegylated regimens, patients on peginterferon alfa-2a demonstrated better HRQL scores versus those receiving non-pegylated interferon
- Bernstein et al., 2002 concluded that declines in FSS and SF-36 summary mental and physical scores were significant predictors of treatment discontinuation
- Chronic hepatitis C patients treated with peginterferon alfa-2a reported better HRQL and less fatigue than non-pegylated interferon and therefore treatment choice is likely to impact on patient adherence
- Improving adherence has been shown to increase the chance of patients achieving a SVR (Ferenci et al., 2001). Therefore, use of peginterferon alfa-2a may minimise the adverse impact of therapy on HRQL and help to reduce the degree of early treatment discontinuation.

1.5 Demonstrating the Cost-Effectiveness of Pegasys® (peginterferon alfa-2a) in Mild Chronic Hepatitis C

- Our economic model aimed to assess whether peginterferon alfa-2a in combination with ribavirin was cost-effective compared to either no treatment or to non-pegylated interferon treatment, as required by the final scope for the appraisal. Modelling was performed from the perspective of the NHS
- We modelled the progression of mild disease from diagnosis until death using a conventional Markov approach and published literature to identify transition probabilities. Two separate models of progression were estimated for patients with normal or elevated baseline ALT
- The cost effectiveness of peginterferon alfa 2a was also evaluated by genotype and baseline viral load due to the significant differences in SVRs observed across these sub-groups
- For mild CHC patients with normal ALT, compared to no treatment and standard interferon, peginterferon alfa-2a generates an additional £6,285 and £1,430 direct costs per patient respectively. However, peginterferon alfa-2a generates an additional 1.0 and 0.4 QALYs per patient compared to no treatment and to non-pegylated interferon respectively
- A pooled/weighted analysis of all results evaluating the cost effectiveness for all mild CHC patients produced a cost / QALY of £6,174 and £2,867 compared to no treatment and to non-pegylated interferon respectively
- We therefore conclude that irrespective of the comparator used (no treatment or combination non pegylated interferon treatment), irrespective of genotype (1 or non-1), and irrespective of baseline viral load (high or low) peginterferon alfa 2a in combination with ribavirin is cost-effective with the results obtained always being under £10,000 cost per QALY
- We also undertook probabilistic sensitivity analysis on these results. This analysis concluded that in all cases, peginterferon alfa 2a was cost effective at a level never

higher than £30,000 in 100% of all scenarios. Furthermore, the 95% upper confidence limit for the baseline cost per QALY never exceeded £12,000 per QALY

- We have also concluded that there would appear to be no economic rationale justifying the continued performing of biopsies at baseline and that all mild hepatitis C patients would benefit from being treated with peginterferon alfa-2a.

1.6 Illustrating Budget Impact to the NHS

- Based on current epidemiology data, diagnosis rate and clinical practice, there are currently an estimated 3,802 mild patients who would be eligible to receive peginterferon alfa-2a
- We have assumed a diffusion rate of 20% per year over a five year period starting from the date of publication of NICE guidance
- Based on these uptake estimations, 760 patients would be treated in the first year, in the second year 1,521 patients will be treated, year three will see 2,281 patients treated, year four 3,042 and in year five 3,802 mild patients would be treated
- We therefore estimate a gross budget impact of £4,641,185 in year 1; £9,282,370 in year 2; £13,923,556 in year 3; £18,564,741 in year 4; and £23,205,926 in year 5
- When taking into account current NHS treatment costs for mild patients and due to the highly clinical and cost-effectiveness provided by peginterferon alfa-2a, there might no longer be a need to perform biopsies. In this case, the resulting net budget impact would be £4,254,093 in year 1; £8,508,186 in year 2; £12,762,280 in year 3; £17,016,373 in year 4; and £21,270,466 in year 5.

1.7 Conclusions

- Our submission has demonstrated that it is both clinically and cost effective to treat mild CHC patients with peginterferon alfa-2a regardless of: genotype; baseline ALT; or viral load. Consequently, the current practice in the UK of undertaking baseline histology diagnosed via a biopsy to inform treatment decisions may now no longer be required
- It appears that the need for liver biopsies may no longer be clinically or economically justified in mild disease since all mild CHC patients have now been demonstrated to benefit from treatment with peginterferon alfa-2a.