1. Executive Summary

1.1. *Background*

The hepatitis C virus (HCV) represents a cause of significant morbidity and mortality. Left untreated it may cause progressive liver disease (Chronic Hepatitis C; CHC) leading to cirrhosis and its potential consequences - liver failure, hepatocellular carcinoma (HCC) and death.

It is thought that at least 170 million people worldwide are infected with HCV. The prevalence and distribution of genotypes varies around the world.

In England and Wales, it has been estimated that there is a prevalence of antibody to HCV of 0.5%. Previous NICE guidance from 2004 on the use of interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of CHC suggests that 200,000 to 400,000 people may be infected in England and Wales.

1.2. *Diagnosis and Current Treatment Guidelines*

A number of diagnostic tests are employed for screening patients for the presence of HCV infection; for assessing viral load and for determining response to antiviral therapy.

Measuring biochemical indicators of HCV such as alanine transaminase (ALT) is not sufficient to establish the severity of HCV. An enzyme immunoassay (EIA), which is used to detect the presence of anti-HCV, is recommended as the initial test for patients with clinical liver disease and for screening at-risk patients. The EIA is not enough to establish HCV status therefore to confirm the diagnosis, testing for serum HCV RNA by sensitive polymerase chain reaction (PCR) amplification is recommended. Prior to initiating treatment in patients infected with CHC, it is important to determine patients' baseline viral load with a quantitative assay as well as their HCV genotype. HCV genotype determines the length of therapy and, together with viral load, is predictive of treatment response.

Liver biopsies are performed to assess the severity of liver damage and to determine prognosis. The stage (degree of fibrosis) and grade (degree of inflammation and necrosis) that is seen can indicate the risk of the patient going on to develop more severe liver disease such as cirrhosis.

Effective drug treatment is available for HCV and usually involves taking a combination of pegylated interferon alpha (injected beneath the skin usually once a week) and ribavirin (taken orally each day) for between 6 and 12 months. The National Institute for Health and Clinical Excellence (NICE) approved the use of this drug combination in England and Wales

in 2004, and then again in 2006 specifically for people with the milder form of HCV. The licenses for the two available brands of pegylated interferon alpha have recently been extended to allow people who were not successfully treated with pegylated interferon alpha and ribavirin to undergo a second course, as well as those people who are also infected with HIV to receive treatment. The licence changes will also allow shorter courses of treatment to be given to certain people with particular genotypes of hepatitis C. Given these recent changes in the drug licenses it is important for NICE to update its guidance to health service providers in the UK.

1.3. *Demonstrating the clinical effectiveness of Pegasys in a different patient groups*

The clinical part of this submission is based on clinical data submitted to or requested by EMEA during registration of the new Pegasys indications. In addition to this, a focused literature search was performed to explore new publications relevant to different patient groups in this HTA. Where possible only prospective, randomised, active control group studies are considered together with some retrospective investigational reports.

1.3.1. Retreatment of patients that previously failed to respond to combination therapy of interferon (conventional or pegylated) and ribavirin

The treatment of choice for treatment-naive patients with hepatitis C is a combination of pegylated interferon and ribavirin .Despite the high numbers of sustained virological responses observed with this treatment, many patients still fail by either not responding at all or relapsing during follow-up periods. This is particularly true for patients with Genotype-1 virus, who are the most difficult to treat. This results in an ever growing number of patients who need a clinical alternative once they failed previous treatment with pegylated interferon plus ribavirin for their hepatitis C. This provided the rationale for the undertaking clinical studies that led to the recent extensions of Pegasys' marketing authorisation.

Recent market research in the UK has indicated that of all patients who failed initial therapy still in contact with their physician, only about 9-10% are currently being re-treated (Market research, Roche data on file). In addition, physicians are most likely to only re-treat certain subgroups of patients such as those with a high degree of fibrosis, who they feel cannot wait for alternative therapies, or those that display a number of favorable baseline characteristics such as being motivated, young, a relapser to previous therapy, having non-genotype 1 virus, a low viral load and low body weight. Many patients with less favorable characteristics remain untreated.

Data from the MV17150 (REPEAT) study has shown that clinically relevant rates of SVR can be achieved upon re-treatment with PEG-IFN alpha-2a plus RBV even in a most difficult-to-cure patient population of predominantly genotype 1 and non-responders to previous pegylated interferon plus ribavirin combination therapy. Furthermore, on-treatment responses at week 12 can identify patients most likely to achieve an SVR.

72-week treatment duration had a safety profile generally similar to that known for the approved doses of 180 μg of PEG-IFN alpha-2a and 1000 or 1200 mg of ribavirin given for 48 weeks for treatment-naive patients, and no new safety concerns were identified.

1.3.2. Shorter treatment durations in Genotype 2 and 3 patients with Rapid Viral Response and Low Pretreatment Viral Load

The possibility of shortening treatment duration to 16 weeks in genotype 2 or 3 patients was examined based on a sustained rapid virological response observed in patients with rapid virological response by week 4 in the pivotal study NV17317 (ACCELERATE).

In this study patients infected with viral genotype 2 or 3, received Pegasys 180 µg sc qw and a ribavirin dose of 800 mg and were randomised to treatment for either 16 or 24 weeks. Subsequent retrospective analysis of patients who were HCV RNA negative by week 4 and had a LVL at baseline showed that patients who had a rapid viral response by week 4 (HCV RNA<50 IU/ml in the Amplicor HCV Test v.2.0) and a low baseline viral load (<800,000 IU/ml) respond similarly to 16 and 24 week of PEG-IFN alpha-2a and ribavirin combination therapy (89% and 94%, respectively).

Sixteen weeks of treatment was modestly better than 24 weeks in terms of safety. Severe adverse events occurred at a frequency that was approximately one third lower with 16 weeks of treatment than with 24 weeks of treatment. Fewer patients reported adverse events with an onset date between week 16 and week 24 in the group treated for 16 weeks (29%) than in the group treated for 24 weeks (50%), consistent with their shorter duration of exposure.

1.3.3. Shorter treatment durations in Genotype 1 and 4 patients with Rapid Viral Response and Low Pretreatment Viral Load

The Hadziyannis study demonstrated that rapid clearance of HCV RNA from the serum of patients with genotype 1 and 4 infection significantly increased the probability of an SVR after 24 weeks of treatment with peginterferon alpha-2a (40KD) plus ribavirin. Early

clearance of HCV RNA not only increased the likelihood of an end of treatment response, but greatly reduced the likelihood of virological relapse during follow-up.

A multiple logistic regression model demonstrates that HCV RNA level is the only independent and significant baseline predictor of RVR. Patients with higher baseline HCV RNA levels were less likely to achieve an RVR, although this subpopulation with an RVR (9.2% of those with baseline HCV RNA >800,000 IU/mL) were as likely to achieve an SVR as patients with low baseline viral loads.

In conclusion, the retrospective analysis provided demonstrated a very small risk of relapse of virological response in genotype 1 patients with an RVR for both 24 and 48 weeks of treatment, with a higher chance of relapse in the high viral load subgroup treated for 24 weeks. No genotype 4 patients relapsed.

Therefore, treatment for 24 weeks should be recommended for patients with genotype 1 infection and low viral load (≤ 800,000 IU/mL) at baseline who become HCV RNA negative at treatment week 4 and remain HCV RNA negative at week 24,.

For genotype 4 patients who become HCV RNA negative at week 4 and remain negative at week 24, treatment for 24 weeks should be recommended regardless of viral load pretreatment.

In general shortened treatment duration has also demonstrated substantial safety benefits. The percentage of patients in a shorter treatment arm who discontinued treatment for adverse events or laboratory abnormalities was three times lower than the percentage in 48 week arm. Similar results were seen in the overall genotype 1 and 4 population: 5% of patients in 24 week and 14% of patient in 48 week arm discontinued treatment for safety reasons.

1.3.4. Patients with HCV-HIV coinfection

In APRICOT, the largest, randomised, placebo-controlled trial in HCV-HIV coinfected patients, peginterferon alpha-2a plus ribavirin elicited significantly higher rates of sustained virological response than interferon alpha-2a plus ribavirin in patients infected with both HIV and HCV (40 % vs. 12 %, P<0.001). These data are consistent with published results from studies in patients with mono HCV infection.

The 29% rate of sustained virological response in patients infected with HCV genotype 1 who were treated with peginterferon alpha-2a plus ribavirin was higher than the rates previously reported in patients coinfected with HIV and HCV. In the two groups that received ribavirin, relapse rates, indicated by the difference between responses at the end of

treatment and responses at the end of follow-up, were remarkably low and similar to those in patients infected only with HCV, underscoring the importance of ribavirin in viral clearance. The highest response rate was among patients with HCV genotype 2 or 3 who received peginterferon alpha-2a plus ribavirin.

Patients who did not have an early virological response at week 12 were highly unlikely to have a sustained virological response. The negative predictive value of the absence of an early response was not improved when such a response was defined as occurring by week 24. Thus, in accordance with current guidelines for HCV-infected patients without HIV coinfection, discontinuation of therapy can be considered if patients do not have a virology response by week 12.

The spectrum and frequency of adverse events were similar to those previously reported in HCV infection. Hematologic abnormalities were more frequent among patients treated with peginterferon alpha-2a. The overall frequency of AIDS-defining events and of death, as well as events associated with mitochondrial toxicity, such as pancreatitis and lactic acidosis, was low and similar among the treatment groups. Although combination therapy was associated with a decline in absolute CD4+ cell counts, it had no effect on the CD4+ percentage. Notably, mean HIV RNA levels did not increase during treatment with peginterferon alpha-2a and, in opposite, decreased by approximately 0.7 $\log_{10}$ copies in patients who had detectable HIV-1 RNA at baseline.

1.4. *Cost effectiveness of Pegasys*

1.4.1. Introduction

Peginterferon alfa-2a (trade name Pegasys®) is a once-a-week injection indicated for the treatment of hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis and/or co-infected with clinically stable HIV.

In August 2006 the National Institute for Health and Clinical Excellence (NICE) recommended the use of combination therapy, comprising peginterferon alfa-2a and ribavirin within the licensed indications, for the treatment of mild chronic hepatitis C.

The licensed indications considered in this evidence submission include further subgroups of patients, as described in the clinical section of the document.

1.4.2. Type and structure of the economic model

The economic evaluation is a cost-utility analysis. The model is based on clinical trial data and follows the assumptions of a previously developed health technology assessment report in hepatitis C.

1.4.3. Model input clinical data and transitions

The rate of sustained virologic response (SVR) is a common treatment efficacy assessment in patients with chronic hepatitis C. The primary efficacy parameter in the economic model is the proportion of the cohort achieving SVR.

For patients on re-treatment or relapse administered peginterferon alfa-2a and ribavirin combination, the licensed indication requires an early virologic response (EVR) test at week 12. If the test is positive (patients have detectable virus) the license recommends patients to stop re-treatment. In the comparisons for patients on re-treatment or relapse the model includes a stopping rule for the proportion of the cohort with a positive HCV-RNA test. The stopping rule has an impact only on the cost of treatment, since the proportion of patients with positive test stop treatment following week 12. In the comparisons of naïve patients the stopping rule is not relevant and therefore applied to the model.

Following treatment, the proportion of the cohort achieving an SVR is considered cured and progresses only to the absorbing state based on annual mortality risk. Due to lack of data on the life expectancy of cured HCV patients, the model assumes the annual mortality risk is the same with that of the general population.

The proportion of the cohort without an SVR remains in the chronic hepatitis C state. From the chronic hepatitis C health state the model assumes progression of disease through a series of degenerative health states until patients reach the absorbing state.

1.4.4. Model utility scores

The model applies different utility scores to the cohort according to health state membership. The assumptions of utility values follow a previously developed health technology assessment report.

1.4.5. Model cost data

Drug costs were calculated based on unit prices listed in MIMS. The planned dose used in this analysis was calculated on a weekly basis. Since both drugs can be self-administered by the patient (subcutaneous and oral administration, respectively) no drug administration costs were applied. Patients re-treated for chronic hepatitis C need the same monitoring and surveillance during and after treatment as treatment-naïve patients. The economic model incorporates a costing protocol developed by a previously developed health technology assessment report to estimate the appropriate monitoring and surveillance cost.

Following consultation with experts (personal communication), the protocol was modified to include:

- an additional quantitative HCV viral load test at week 4

- a quantitative HCV viral load instead of qualitative viral load at week 24, 48 and 24 weeks post-treatment (week 72)
- a lower cost for HCV quantitative viral load (£90 per test). Since the protocol was developed, the cost of this diagnostic procedure became significantly lower.

The monitoring protocol was extended to cover the duration of monitoring for extended treatment with peginterferon alfa-2a.

The model also applies a different annual cost to the cohort according to health state membership. The assumptions of health state costs follow a previously developed health technology assessment report.

1.4.6. Sensitivity analysis and probabilistic sensitivity analysis

One-way sensitivity analysis tested different scenarios of patient characteristics (age, weight, gender), and mortality of HIV co-infected patients.

Uncertainty around key model variables was explored with probabilistic sensitivity analysis.

1.4.7. Model results

In all populations / model comparisons, the estimated cost-effectiveness of Pegasys is well below a threshold of £15,000.

In particular, in the subgroup of patients who have genotype-1 hepatitis C virus, and did not respond to previous treatment with pegylated interferon alone or in combination therapy with ribavirin, peginterferon alfa-2a combination is associated with an ICER of £3,334. In the non-genotype 1 group the ICER is lower (£809). In patients who relapse previous treatment peginterferon alfa-2a dominates the alternative strategy (no treatment).

In treatment naïve populations, in genotype 2 and 3 with low viral load and rapid virologic response the ICER of 16 weeks peginterferon alfa-2a combination treatment is £2,718, comparing to 24weeks. In genotype 1 and 4 patients the ICER or 24 weeks of peginterferon alfa-2a is £15,471. In HIV-HCV co-infected patients peginterferon alfa-2a combination treatment dominates interferon alpha combination.

1.5. *Illustrating budget impact to the NHS*

1.5.1. Methods

A model was developed to assess the budget impact of introducing Pegasys to the NHS. The model evaluating the budget impact of peginterferon alfa-2a in combination with ribavirin

for the treatment of patients with chronic hepatitis C was developed using cost data from BNF 57.

1.5.2. BIM results

The resource implication for treating all eligible patients in the different indications can is presented below:

- Budget impact for treating all eligible hepatitis C patients who relapse after a SVR: £2,169,979 in 2010 increasing to £2,199,315 by 2014.
- Budget impact for treating all eligible hepatitis C patients who do not respond (genotype 1): £6,568,442 in 2010 increasing to £6,657,243 by 2014.
- Budget impact for treating all eligible hepatitis C patients who do not respond (non-genotype 1): £1,684,628 in 2010 increasing to £1,707,402 in 2014.
- Budget impact for treating all eligible hepatitis C patients who are co-infected with HIV: £415,764 in 2010 increasing to £428,391 in 2014.

Cost-savings result by shortening the treatment for patients who have a LVL nad a RVR:

- The cost-savings result by shortening the treatment for hepatitis C patients with LVL and a RVR after four weeks with genotype 1 or 4 are: £4,997,385 in 2010 increasing to £5,149,164 in 2014.
- The cost-savings result by shortening the treatment for hepatitis C patients with LVL and a RVR after four weeks with genotype 2 or 3 are: £1,808,542 in 2010 increasing to £1,863,470 in 2014.