Pegasys (peginterferon alfa 2a)
For the Treatment of Chronic
Hepatitis B

Roche NICE Submission

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1. EXECUTIVE SUMMARY

Background

• The hepatitis B virus (HBV) is one of the world's most common infectious pathogens and around 2 billion people worldwide have been exposed to the virus. Current indications suggest that around 350 million people have chronic infection and are therefore at risk of death from liver disease. There is limited epidemiological data available for the UK, however, the Department of Health estimates that 0.3% (180,000) of the UK population is chronically infected with hepatitis B.

• HBV is the tenth leading cause of death worldwide and is responsible for over 1 million deaths every year due to cirrhosis of the liver and liver cancer. Around 80% of all primary liver cancers are attributable to HBV and there is a strong correlation between the prevalence of HBV carriers and the incidence of hepatocellular carcinoma (HCC).

• The virus is present in the blood, saliva, sweat, tears, breast milk and semen of infected individuals. It is a resilient virus, resistant to breakdown and able to survive outside the body and is, therefore, effectively transmitted through contact with infected bodily fluids.

• However, infection with HBV is preventable and safe and effective vaccines have been available since 1982. The immunisation process involves a course of three to four inoculations over a three to four month period which generally confers 95% immunity in those who complete the course and have not already been infected. In 1991, the World Health Organisation (WHO) recommended that vaccination against HBV should be included in all national vaccination programmes. However, vaccination has still not been universally adopted in the United Kingdom and treatment is the only option for those who become or are already chronically infected.

• The costs associated with the care and treatment of chronic hepatitis B (CHB) patients are significant because of the high morbidity and mortality associated with the disease. The association of disease progression with increased cost of disease management suggests that measures to prevent or delay its progression are economically beneficial. As CHB progresses, managing the sequelae of compensated cirrhosis, decompensated cirrhosis and HCC is associated with rapidly escalating healthcare costs. As the development of liver disease in patients with HBV occurs over many years, medical costs accumulate over a long period of time. In addition to this financial burden, hepatitis B exacts a severe burden on patients in terms of quality of life and life expectancy.

• Whilst a genetic classification system of genomic groups has been defined for HBV, and to date, eight genotypes have been identified (A to H), the full clinical

implication of genotype is not yet clearly defined or understood. Unlike hepatitis C, the role of viral genotype in disease pathogenesis and its effect on disease progression is still to be elucidated.

• Different viral sequences can emerge during HBV infection as a result of spontaneous changes and these are more usually termed variants, with the term mutation for drug induced changes in the viral genome. Over the course of chronic infection, increasing numbers of viral variants and quasispecies can accumulate in HBV infected patients. Not all of these variants have a clinical impact but some HBV mutants do affect response to therapy and disease progression. The most important are those which lead to alteration in the expression of the viral protein, HBeAg and associated *HBeAg positive* or *negative* disease, the latter being harder to treat effectively.
• The therapeutic goal of CHB treatment is to achieve immune system control of HBV and thereby induce remission of liver disease before cirrhosis and primary liver cancer develop. In order to achieve this, physicians look for treatments which produce a sustained response following a defined treatment duration.

• In *HBeAg positive* disease, the markers for a successful response to treatment are:

o HBeAg seroconversion, which is indicative of remission and is the recommended treatment endpoint, along with normalisation of ALT levels and reduced viral load

o HBsAg seroconversion, which is considered the ultimate goal of therapy, since it is as close to a cure as it is possible to get and patients who achieve this have a much lower risk of developing liver cancer or cirrhosis.

• In *HBeAg negative* disease, HBeAg seroconversion cannot be used as an endpoint because the virus does not produce the ‘e’ antigen thereby allowing it to escape the immune system control provided by antibodies to HBeAg and so the markers for a successful response are:
o Reduced viral load and normalisation of ALT levels, sustained after the end of treatment

o HBsAg seroconversion.

• Treatment guidelines produced in 2003 by the European Association for the Study of the Liver (EASL) currently recommend conventional interferon alfa (IFN) for first-line therapy in all patients with compensated liver disease and for different durations of treatment according to whether patients have HBeAg positive or HbeAg negative disease (four to six months and 12 to 24 months respectively). The guidelines recommend the use of lamivudine or adefovir in cases where IFN is contraindicated, ineffective or poorly tolerated. It is recommended that lamivudine or adefovir is given for at least one year in patients with HBeAg positive disease and indefinitely in patients with HBeAg negative disease.

Pegasys ® (peginterferon alfa-2a) – A New Treatment for Hepatitis B

• By April 2005, Pegasys ® will receive an extension to its existing EU Marketing

Authorisation for chronic hepatitis C. Pegasys ® will be additionally indicated for the treatment of both HBeAg-positive and HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and / or fibrosis.

• The recommended dosage and duration of treatment for both HBeAg-positive and HBeAg-negative chronic hepatitis B will be 180 micrograms once weekly for 48 weeks by subcutaneous administration. Treatment should only being initiated by physicians experienced in the treatment of patients with hepatitis B or C.

• We now demonstrate how peginterferon alfa-2a will provide patients with a new clinically and cost effective treatment compared to the currently available treatments of conventional interferon (IFN), lamivudine and adefovir.

Demonstrating the Clinical Effectiveness of Pegasys ® (peginterferon alfa-2a)

• The clinical effectiveness of peginterferon alfa-2a in chronic hepatitis B (CHB) is based upon one of the largest clinical development programmes undertaken in this disease area involving over 1,500 patients from approximately 20 countries.

• Results from the Phase II study in HBeAg positive disease confirmed the most effective dose of Peg IFN alfa-2a in achieving optimal HBeAg seroconversion and combined response as 180 µg administered once weekly.

Efficacy in HBeAg positive chronic hepatitis B

• Efficacy has been demonstrated over conventional IFN in HBeAg positive CHB with HBeAg seroconversion rates of 33% with peginterferon alfa-2a vs 25% with IFN alfa-2a

• The percentage of patients achieving a combined response at the end of follow up was higher with peginterferon alfa-2a compared with IFN alfa-2a (24% vs 12%; p=0.036)
• In the pivotal phase III trial, peginterferon alfa-2a when compared to lamivudine and assessed 24 weeks after stopping 48 weeks of study medication achieved:
o HBeAg seroconversion of 32% overall vs 19% with lamivudine ($p<0.001$)

o HBV DNA suppression of 32% vs 22% with lamivudine ($p<0.012$)

o HBeAg seroconversion rates ranging from 29% to 41% depending on baseline ALT levels compared to 20-28% with lamivudine after 48 weeks of treatment

o HBsAg seroconversion rates of 3% vs 0% with lamivudine after 48 weeks of treatment. Effectively, 3% of the patients were “cured” after a defined duration of treatment..

Efficacy in HBeAg negative chronic hepatitis B

• In the pivotal phase III trial, peginterferon alfa-2a when compared to lamivudine and

assessed 24 weeks after stopping 48 weeks of study medication achieved:

o ALT normalization of 59% vs 44% with lamivudine (p=0.004)

o HBV DNA suppression of 43% vs 29% with lamivudine (p=0.007)

o HBsAg seroconversion of 3% vs 0% with lamivudine after 48 weeks of treatment.

Tolerability

• The proportion of patients who prematurely discontinued study medication for safety reasons was broadly comparable in the peginterferon alfa-2a group and the IFN alfa-2a group (2% and 4% respectively).

• The overall rates of premature withdrawal from study medication were low in the peginterferon alfa-2a monotherapy arms of both phase III studies (6% and 8% in HBeAg positive and HBeAg negative patients, respectively) and were comparable to those in the lamivudine arms (5% and 2% respectively).

• The overall adverse event profile for peginterferon alfa-2a in CHB was similar to that previously observed with peginterferon alfa-2a in chronic hepatitis C.

Demonstrating the Cost Effectiveness of Pegasys ® (peginterferon alfa-2a)

• The availability of peginterferon alfa-2a from May 2005 onwards as a newly licensed and effective treatment for chronic hepatitis B patients will help to reduce the probability of patients progressing to the degenerative and costly health states already described, whilst improving patient quality of life and life expectancy.

• Two separate state-transition Markov models were developed to simulate the treatment and progression of chronic hepatitis B in a hypothetical cohort of patients infected with either HBeAg positive or HBeAg negative disease. The models were used to calculate the lifetime clinical benefits, life expectancy, quality-adjusted life years and lifetime NHS costs associated with peginterferon alfa-2a and the comparators outlined earlier.

Cost Effectiveness in HBeAg positive chronic hepatitis B

• Based on the Cooksley *et al* trial and using a 24 week treatment duration in both treatment arms as in the trial, the cost / QALY for peginterferon alfa 2a compared to conventional IFN is £2,663.

• 48 weeks of peginterferon alfa-2a treatment generates an additional £4,709 in drug costs compared to 24 weeks of conventional IFN treatment. An additional 0.3 QALYs is generated by peginterferon alfa-2a which produces an ICER of £13,921. Despite assuming no improvement in treatment durability from the additional treatment duration, peginterferon alfa-2a still remains a highly cost effective treatment strategy when comparing 48 weeks of treatment versus 24 weeks of conventional IFN treatment. Assuming a dose of 9 MIU of conventional IFN and no additional

effectiveness benefit, the cost / QALY for peginterferon alfa-2a compared to conventional IFN is £8,473.

• Compared to 48 weeks of lamivudine treatment, peginterferon alfa-2a generates an additional £4,003 of drug cost per patient but over a lifetime reduces NHS resource costs on average by approximately £1,396 per patient. The additional costs associated with peginterferon alfa-2a however are estimated to generate an additional 1.3 years of life expectancy and 0.76 quality adjusted life years. Therefore, the cost per QALY for peginterferon alfa-2a compared to 48 weeks of lamivudine treatment is £5,281.

• Assuming a longer treatment duration for lamivudine as required in clinical practice, drug costs increase by approximately £2,000 per lamivudine patient, this additional cost is estimated to generate an additional 0.33 discounted QALYs. The ICER for peginterferon alfa-2a compared to long term lamivudine treatment (assuming a 4 year treatment duration) is £5,948.

• Compared to long-term adefovir treatment (assuming a 4 year treatment duration), peginterferon alfa-2a has lower total drug costs of £4,532 per patient. Whilst longer treatment duration for adefovir improves long term outcomes, adefovir still fails to match the estimated life expectancy and QALYs of peginterferon alfa-2a. Consequently, with greater total QALYs and lower total direct costs, peginterferon **dominates** long-term adefovir treatment from a cost effectiveness perspective.

• The option of "no treatment" reduces drug costs to zero but increases NHS resource costs by £2,500 per patient compared to peginterferon alfa-2a and also reduces expected life expectancy from 30.6 years to 28.2 years for the no treatment strategy. Consequently the cost / QALY for peginterferon alfa-2a compared to no treatment is £2,790.

• Probabilistic sensitivity analysis demonstrated that at a cost / QALY threshold of £30,000, peginterferon alfa-2a was a cost effective treatment option in over 97% of simulations.

Cost Effectiveness in HBeAg negative chronic hepatitis B

• Over 48 weeks of treatment, peginterferon alfa-2a compared with lamivudine generates an additional £5,399 of drug cost per patient but over a lifetime reduces NHS resource costs on average by approximately £1,910 per patient. The additional costs associated with peginterferon alfa-2a however are estimated to generate an additional 1.8 years of life expectancy and 1.1 quality adjusted life years. Therefore, the cost per QALY for peginterferon alfa-2a compared to 48 weeks of lamivudine treatment is £3,209.

• Longer treatment duration with lamivudine extends treatment durability but at higher drug costs. Therefore, the cost per QALY for peginterferon alfa-2a is lower at £1,886 when compared to the longer treatment duration of lamivudine (4 years).

• Although a no treatment strategy reduces drug costs by approximately £6,336 per patient, an additional £3,400 in medical resource costs are generated per patient. The decision to treat with peginterferon alfa-2a generates an additional 3.3 years of life

expectancy and approximately 2.0 additional QALYs. Consequently, the cost per QALY of peginterferon alfa-2a compared to no treatment is £1,467.

• One-way sensitivity analysis was performed on the HBeAg positive and HBeAg negative disease models which demonstrated that the cost / QALYs never exceed £22,000.
• Probabilistic sensitivity analysis demonstrated that at a cost / QALY threshold of £30,000, peginterferon alfa-2a was a cost effective treatment option in over 97% of simulations.

Illustrating Budget Impact to the NHS

• Budget impact has been calculated by estimating the percentage of CHB patients receiving treatment in England and Wales from the proportion of the prevalent CHB population currently treated in the UK.

• The prevalence of CHB is estimated at 0.3% and the percentage of these patients receiving treatment is approximately 1.4%, a proportion that has been increasing at a rate of around 500-600 patients per year over the last three years.

• Cost off-sets for current use of conventional IFN and adefovir treatment have not been included in the analysis since lamivudine is presently the most commonly used UK treatment option. A diffusion rate for peginterferon alfa-2a uptake has been included at 25%, 50% and 75% respectively for years 2006 to 2008.

• The budget impact over three years is shown below:

Year	2006	2007	2008	
Number of CHB patients treated				
	2,210	2,729	3,249	
Cost of peginterferon alfa-2a				
	£3,502,194	£8,650,733	£15,445,615	
Cost offset for current UK antiviral use (lamivudine)	£1,682,626	£1,385,412	£824,537	
Total budget impact	£1,819,568	£7,265,320	£14,621,078	