Economic evaluation of Telaprevir (Incivo®) as add-on therapy to pegylated interferon and ribavirin for the treatment of patients infected with Hepatitis C Genotype 1.

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Telaprevir Summary

1. On November 8th 2011, Janssen-Cilag submitted a cost-effectiveness evaluation of telaprevir (Incivo) for the treatment of genotype 1 chronic hepatitis C in combination with peginterferon and ribavirin in adult patients with compensated liver disease (including cirrhosis), eligible for reimbursement under the High Tech drug scheme.

2. Telaprevir is a linear peptidomimetic HCV NS3/4A serine protease inhibitor which inhibits replication of the hepatitis C virus. It is indicated for the treatment of genotype 1 chronic hepatitis C (in combination with peginterferon-ribavirin) in adult patients with compensated liver disease (including cirrhosis) who are treatment naïve and those who have previously been treated with interferon alfa alone or in combination with ribavirin, including relapsers, partial relapsers and null responders.

3. The efficacy data for the cost-effectiveness evaluation of telaprevir was derived from the phase III clinical trials. The ADVANCE trial was a randomised, double blind, placebo-controlled study in which 1088 previously untreated adults with HCV genotype 1 infection were assigned to one of three groups. In one group telaprevir was combined with peginterferon alfa-2a and ribavirin for 12 weeks (T12PR group) followed by peginterferon – ribavirin alone for 12 weeks if HCV RNA was undetectable at weeks 4 and 12 or for 36 weeks if HCV RNA was detectable at either time point. A second group received telaprevir with peginterferon – ribavirin for 8 weeks and placebo with peginterferon – ribavirin for 4 weeks (T8PR group), followed by 12 or 36 weeks of peginterferon – ribavirin on the basis of the same HCV RNA criteria. The third group received placebo plus peginterferon – ribavirin for 12 weeks, followed by 36 weeks of peginterferon – ribavirin (PR group).

4. In the ADVANCE study significantly more patients in the telaprevir treatment groups had a sustained virologic response i.e. 75% in the T12PR group and 69% in the T8PR group as compared with 44% in the PR group. A total of 58% of patients treated with telaprevir were eligible to receive 24 weeks of total treatment. The

overall rate of discontinuation of treatment in the telaprevir groups was 10% as compared with 7% in the peginterferon – ribavirin group.

5. The REALISE trial investigated the effect of combination therapy including telaprevir plus peginterferon alfa-2a – ribavirin in previously treated patients with chronic HCV genotype 1 infection who had no response, or a partial response or who had a relapse after an initial response. A total of 663 patients were assigned to one of three treatment groups including the T12PR48 group which received telaprevir for 12 weeks and peginterferon – ribavirin for a total of 48 weeks. The second group (lead-in T12PR48) had a 4 week lead-in of peginterferon plus ribavirin followed by 12 weeks of telaprevir plus peginterferon – ribavirin followed by peginterferon-ribavirin for 32 weeks and the control group (PR48) which received peginterferon – ribavirin for 48 weeks.

6. In the REALISE trial the rates of sustained virologic response (SVR) were significantly higher in the two telaprevir groups than in the control group among patients who had a previous relapse i.e. 83% in the T12PR48 group, 88% in the lead-in T12PR48 group and 24% in the control group. The corresponding rates for patients with a previous partial response were 59%, 54% and 15% respectively and in patients with no response to previous therapy the SVR rates were 29%, 33% and 5% respectively.

7. A Markov cohort model based on existing validated models was used to evaluate the cost-effectiveness of telaprevir in combination with peginterferon – ribavirin. The model consisted of 14 discrete health states and had a lifetime horizon. A total of 10,000 patients entered the model distributed across the three baseline health states of mild chronic hepatitis C, moderate chronic hepatitis C and compensated cirrhosis. Patients who do not achieve a sustained virologic response can progress to the decompensated cirrhosis, liver transplantation, post-liver transplant or death health states. The base case patient profiles were based on the clinical trials outlined above. The sustained virologic response rates for the treatment naïve and treatment experienced patients were taken from strategies based on the clinical trials ADVANCE and REALISE. The perspective was that of the Health Service Executive (HSE).

8. Patients entering the model reflected the patient population entering the ADVANCE and REALISE clinical trials. Treatment experienced patients were stratified according to their previous response to therapy. Resources identified included drug acquisition costs, monitoring costs for patients on therapy, hepatitis C health state costs and the management of adverse drug reactions. Transition probabilities and health state utility values were taken from the literature. Health related utilities were undertaken as part of the ADVANCE and REALISE trials and these formed the basis for an alternative base case scenario. Costs and consequences were discounted at an annual rate of 4%.

9. For treatment naïve patients the incremental cost-effectiveness ratio (ICER) for telaprevir when added to peginterferon - ribavirin was € 16,023. The alternative scenario based on utility estimates from the ADVANCE trial resulted in an ICER of € 14,186/QALY. For treatment experienced patients the base case ICER was estimated at € 5,537/QALY which decreased to € 4,358/QALY when utility estimates from the REALISE trial were used.

10. Sensitivity analysis indicated that the greatest effect on the base case ICERs for treatment naïve patients were utility rates assigned to the sustained virologic response health states for mild and moderate hepatitic C disease. Reducing the price of telaprevir by 10% in treatment naïve patients resulted in a reduction in the ICER from € 16,023/QALY to € 12,698/QALY.

11. The main influences on the base case ICER for treatment experienced patients included the cost of telaprevir, discount rate, cost assigned to decompensated cirrhosis and utility rates for sustained virologic response health states. A reduction of 10% in the price of telaprevir resulted in a reduction in the ICER from € 5,537/QALY to € 2,941/QALY. Probabilistic sensitivity analysis demonstrated that the probability of telaprevir being cost-effective when added to the current standard of care in treatment naïve patients was 66% at the € 20,000/QALY threshold. In the treatment experienced population the probability of cost-effectiveness was 96% at the € 20,000/QALY threshold. The submitted budget impact analysis indicated a gross expenditure of approximately € 1.1 million in year one increasing to just over € 5.2 million in year 4

declining to € 4.1 million in year five resulting in an estimated expenditure of approximately € 18.5 million over the five year period.

12. The addition of telaprevir (Incivo) to the current standard of care could increase drug acquisition costs by approximately € 27,900 per patient. Despite this additional cost we believe that telaprevir (Incivo) may be considered a highly cost-effective therapy when added to peginterferon – ribavirin for the treatment of patients infected with genotype 1 hepatitis C virus in the Irish healthcare setting.