



Cost effectiveness of sofosbuvir (in combination with either ribavirin or pegylated interferon + ribavirin) (Sovaldi®) for the treatment of hepatitis C infection

The NCPE has issued a recommendation regarding the cost effectiveness of sofosbuvir (Sovaldi®) in combination with ribavirin or pegylated interferon + ribavirin for the treatment of hepatitis C. The NCPE recommends reimbursement of Sovaldi® for certain subgroups.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the company's (Gilead) economic dossier on the cost effectiveness of sofosbuvir (Sovaldi®) for the treatment of hepatitis C. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, that the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence that may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics

October 2014

In June 2014 Gilead submitted a clinical and economic dossier on the cost effectiveness of sofosbuvir (Sovaldi®) for the treatment of hepatitis C virus (HCV) infection. Sofosbuvir (SOF) is an NS5B inhibitor licensed for all HCV genotypes (GT) i.e. 1-6, in treatment naïve (TN) and treatment experienced (TE) patients and in cirrhotic and non-cirrhotic patients. It is available as a once daily 400mg dose for oral use to be taken with food. Sofosbuvir is not administered alone and must always be given as part of a combination regimen, and treatment duration is either 12 or 24 weeks depending on genotype, and previous treatment experience. Response to therapy is measured as undetectable virus 12 weeks after completion of therapy, termed the sustained viral response (SVR).

This HTA evaluates the interferon-containing regimen of sofosbuvir and pegylated interferon and ribavirin (SOF/PR), and the interferon-free regimen of sofosbuvir and ribavirin (RBV) (SOF/RBV) alone.

The current standard of care (SoC) for GT1 HCV infection is one of three regimens containing a direct-acting antiviral agent (DAA) (telaprevir, boceprevir or simeprevir) in combination with pegylated interferon and ribavirin (PR) for 24 or 38 weeks. For GT2-6, the current standard of care is PR alone for 24 or 48 weeks. Duration of treatment is dependent on baseline characteristics of patients, cirrhosis stage and previous treatment experience.

1. Clinical effectiveness of sofosbuvir

A number of phase III and phase II studies provided the evidence base supporting the registration of SOF-based regimens for the treatment of HCV infection. The trial programme investigated two treatment regimens, SOF/PR in GT 1, 3, 4, 5, and 6, while the combination of SOF/RBV was investigated across GTs 1, 2, and 3.

The efficacy data used to support the economic evaluation included SVR rates for the SOF/PR combination obtained from four studies i.e. one phase III open-label study single arm, (NEUTRINO), and three phase II studies, PROTON, ELECTRON, and LONESTAR-2. In the NEUTRINO single arm, open-label study, SOF/PR for 12 weeks (SOF/PR12) achieved rates of 91% in GT1 treatment naïve non-cirrhotic patients compared to 81% in cirrhotic patients. For GT3, the interferon-based regimen SOF/PR12 achieved SVR rates in excess of 80% across all subpopulations in a number of Phase II studies, namely ELECTRON, PROTON and LONESTAR-2.

SOF/RBV is licensed for 24 week treatment duration in GTs 1 and 3. Two phase II studies demonstrated rates of SVR comparable to current standard of care regimens for GT 1 treatment naïve patients when treated with SOF/RBV for 24 weeks (SOF/RBV24). In GT3, SVR rates >90% were reported in the phase III VALENCE study for treatment naïve patients eligible for interferon whether cirrhotic or not. In the treatment experienced cohort of GT3 patients, rates of 85% and 60% were obtained for non-cirrhotic and cirrhotic patients respectively.

The combination of SOF/RBV for 12 weeks is licensed for use in GT2 achieving rates of between 82-93% in three phase III trials across a number of subpopulations, combining both non-cirrhotic and cirrhotic patients. Across all genotypes, both cirrhotic and treatment experienced patients achieve lower SVR rates as compared to non-cirrhotic and treatment naïve patients, and evidence of efficacy was frequently drawn from subpopulations with small patient numbers. There is limited evidence available for outcomes in GT1 TE, HIV/HCV co-infected patients and patients awaiting a liver transplant.

The review group had a number of concerns with regard to the available evidence base for sofosbuvir-containing regimens, including:

- The evidence for the relative effectiveness versus standard of care was poor; one non-inferiority comparative study was available comparing SOF/RBV to dual pegylated interferon and ribavirin which demonstrated non-inferiority.
- The manufacturer carried out an evidence synthesis to formally combine the efficacy data across trials and this did not demonstrate a significant difference over standard of care. The review group noted the difficulties associated with combining the data due to the lack of data available to synthesised in a robust manner.
- The efficacy was primarily derived from open-label and single arm studies.
- The use of data from subgroups with very small patient numbers when stratified according to treatment history, presence or absence of cirrhosis, and interferon eligibility.

The manufacturer has not demonstrated statistically significant superiority of sofosbuvir compared to existing treatments. As a result of these concerns, the efficacy informing the model is associated with significant uncertainty.

Safety of sofosbuvir

The adverse event profile of sofosbuvir regimens is consistent with the existing profile of the respective pegylated interferon and ribavirin regimens. The SOF/RBV combination is consistent with that of ribavirin and the adverse effect profile of the sofosbuvir with pegylated interferon and ribavirin (SOF/PR) containing regimens are consistent with the existing profile of the pegylated interferon and ribavirin combination. The addition of sofosbuvir does not appear to worsen the existing adverse effect profile and no new signals of safety events have been noted to date.

2. Cost effectiveness of Sovaldi®

The ex-wholesaler cost price for a 28 day pack of sofosbuvir 400mg tablets is €15,787 i.e. €563.82 per tablet. A 12 week regimen costs €47,361, while a 24 week regimen will cost €94,722.

Methods

- A cost-utility analysis was submitted by Gilead comparing a number of scenarios where sofosbuvir is used with pegylated interferon and ribavirin (SOF/PR) and where it is used with ribavirin alone (SOF/RBV). The comparators were specific to the genotype and included PR (GTs 1-6) or boceprevir + PR (GT1) or telaprevir + PR (GT1). ‘No treatment’ was included as a comparator for some scenarios. Simeprevir was not included as a comparator as it was not reimbursed at the time of this dossier submission.
- A Markov state-transition model was used to describe the progression of disease over the lifetime of a patient cohort. The model consists of nine health states with transition between the states, and costs, mortality and morbidity associated with each state.
- Health benefits were measured in quality-adjusted life years (QALYs) and disutilities associated with adverse events and being on treatment were included. Costs included drug acquisition, health state costs, monitoring costs and costs associated with treatment of hepatocellular cancer and liver transplant. The analysis was presented from the healthcare payer’s perspective.

Results

Results are presented for sofosbuvir when given in combination with peg-interferon and ribavirin (SOF/PR) and separately for sofosbuvir in combination with ribavirin (SOF/RBV) (interferon free).

Results were presented for genotypes 1, 2, 3 in separate scenarios and for GTs 4/5/6 in a single scenario, for a combined cohort of non-cirrhotic and cirrhotic patients for patients who have previously received treatment (treatment experienced) and those who have not (treatment naïve). Additional scenarios for each genotype stratified according to absence (non-cirrhotic) or presence (cirrhotic) of cirrhosis were presented, following request from the review group.

Sofosbuvir in combination with pegylated interferon and ribavirin (SOF/PR)

Genotype 1 (~55% of the Irish cohort)

In treatment naïve, non-cirrhotic patients, SOF/PR12 is not cost effective at a threshold of €45,000/QALY when compared to telaprevir/PR12. SOF/PR12 is cost effective when compared to PR for 48 weeks (PR48) and when compared to boceprevir in combination with PR (Boc/PR) for 28 to 48 weeks. The manufacturer assumed that treatment experienced patients in this group would respond in a similar manner to treatment naïve patients, however there is little clinical data to support this assumption.

In treatment naïve cirrhotic patients, SOF/PR12 is cost effective at a threshold of €45,000/QALY when compared to all comparators in the cirrhotic cohort. However if the duration of SOF/PR is increased to 24 weeks (SOF/PR24) in all cirrhotic patients, the ICER is increased greatly above €45,000/QALY.

Genotype 3 (~39% of the Irish cohort)

In treatment naïve, non-cirrhotic patients, SOF/PR12 is not cost effective at a threshold of €45,000/QALY compared to PR24. In treatment experienced non-cirrhotic patients, SOF/PR12 is cost effective at a threshold of €45,000/QALY compared to PR48. If SOF/PR24 is given the cost/QALY increases above the €45,000/QALY threshold.

In cirrhotic patients SOF/PR12 is cost effective at a threshold of €45,000/QALY compared to PR for 24 weeks in both treatment naïve and treatment experienced patients.

Genotype 4, 5 and 6 (~<1% of the Irish cohort)

SOF/PR12 is not cost effective versus PR48 at a threshold of €45,000/QALY.

Co-infected cohort

The manufacturer only presented cost effectiveness evidence for GT 1 treatment naïve patients. The analysis provided was based on efficacy data derived from small patient numbers and is associated with significant uncertainty. The review group do not consider these estimates to be robust.

Sofosbuvir in combination with ribavirin (SOF/RBV)

a) 24 weeks of therapy SOF/RBV

Genotype 1 (~55% of the Irish cohort)

In patients who are treatment naïve (combined cohort of cirrhotic and non-cirrhotic), SOF/RBV24 is not cost effective compared to no treatment at a threshold of €45,000/QALY. In treatment experienced patients there is no data to support SOF/RBV24 and therefore it was not possible to estimate the cost effectiveness.

Genotype 3 (~39% of the Irish cohort)

In non-cirrhotic treatment naïve and treatment experienced patients SOF/RBV24 is not cost effective compared to no treatment. SOF/RBV24 is cost effective at a threshold of €45,000/QALY compared to no treatment in cirrhotic patients.

b) 12 weeks of SOF/RBV

Genotype 2 (~6% of the Irish cohort)

SOF/RBV12 is not cost effective at a threshold of €45,000/QALY when compared to PR24 in non-cirrhotic patients.

In a cirrhotic cohort SOF/RBV12 is cost effective at a threshold of €45,000/QALY when compared to no treatment or PR48 irrespective of previous treatment experience.

Twenty four weeks of SOF/RBV is only cost effective at a threshold of €45,000/QALY when compared to no treatment in all cirrhotic patients.

Genotype 4, 5, 6 (~<1% of the Irish cohort)

The manufacturer did not provide cost effectiveness of SOF/RBV in this cohort due to lack of clinical data.

Co-infected Cohort

The manufacturer did not provide any data on cost effectiveness for this cohort for SOF/RBV.

The manufacturer provided no information on the cost effectiveness any SOF regimens in pre- or post-transplant patients.

The review group carried out further sensitivity analysis to establish what the impact of increasing sofosbuvir treatment from 12 to 24 weeks, decreasing effectiveness by 10%, applying reinfection rates and adjusting the number of cirrhotic patients in the cohort.

The results for the base case analyses indicate that probability of cost-effectiveness of SOF-containing regimens at a threshold of €45,000/QALY for the various scenarios ranges from 4.3% (GT1 Treatment naive unsuitable for interferon) to 100% for GT2 Treatment naive unsuitable for interferon).

3. Budget impact of Sovaldi®

A total of 250 patients per annum was selected based on expert opinion and was assumed to remain static for the time horizon of the model. Cirrhotic patients were subsequently predicted to account for between 19% (GT1) and 24% (GT3) of each subgroup. Gilead predicted that SOF-based regimens will have approximately two-thirds of the market in all genotypes within 5 years. The review group note that in Ireland, it is estimated that between 6,000 and 8,000 patients with HCV infection are engaged in care and are currently untreated.

The estimates given by Gilead are in the opinion of the review group underestimated. The costs included in the budget impact are for sofosbuvir for 12 weeks only and expert opinion available to the review group advised that 24 weeks is likely to be required in a significant proportion of the sicker cohort of patients.

The review group acknowledge the difficulties in estimating the numbers of patients with HCV infection that may be treated over the next 5 years as it is dependent on a number of factors including the capacity to treat patients through the current model of care, the potential budgetary constraints and the availability of newer regimens that may displace all existing regimens particularly those with interferon and possible expansion of screening due to treatment being available.

4. Conclusion

Sovaldi® is licensed for all genotypes of Hepatitis C. It is licensed in combination with peg-interferon and ribavirin and is the first direct acting anti-viral to be licensed with ribavirin alone (interferon free). Gilead has presented many different scenarios across different genotypes stratified by cirrhosis status and previous treatment status.

The review group consider that the clinical evidence used to support this application is associated with uncertainty, in particular in patients where a greater clinical need may be identified such as cirrhotic, decompensated cirrhosis and pre-and post-transplant patients. The review group also take into account the real world data presented on previous DAAs boceprevir and telaprevir where the effectiveness was less than that reported in the clinical trials. There is insufficient data on sofosbuvir to indicate whether a similar trend will present with real world sofosbuvir data.

The cost effectiveness of sofosbuvir is influenced greatly by the presence of cirrhosis and previous treatment. In non-cirrhotic patients who have not been previously treated, sofosbuvir is not a cost effective treatment option. In non-cirrhotic patients who have previously been treated, sofosbuvir + PR may be cost effective in G3 patients if given for 12 weeks only. In cirrhotic patients sofosbuvir is cost effective if given for 12 weeks however the ICER increases above €45,000/QALY if given for 24 weeks in some scenarios.