



## **Cost Effectiveness of simeprevir (Olysio)<sup>®</sup> in combination with sofosbuvir (Sovaldi)<sup>®</sup> for chronic HCV infection**

The NCPE has issued a recommendation regarding the use of drug for this indication. The NCPE recommends reimbursement of simeprevir in combination with sofosbuvir for genotype 1 in some subgroups.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's, Janssen Cilag Ltd., economic dossier on the cost effectiveness of simeprevir (Olysio)<sup>®</sup> (Janssen-Cilag Ltd.) in combination with sofosbuvir (Sovaldi)<sup>®</sup> (Gilead). 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 examine 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 a responsibility for commissioning or providing healthcare, public health or social care services.

## Summary

Janssen Cilag Ltd. submitted a dossier for simeprevir (Olysio<sup>®</sup>) in combination with sofosbuvir (Sovaldi<sup>®</sup>) on 30<sup>th</sup> October 2014. Simeprevir (Olysio<sup>®</sup>) in combination with sofosbuvir (Sovaldi<sup>®</sup>) is indicated for the treatment of chronic HCV infection, genotype 1 (GT1). Patients are characterised at baseline according to disease severity and previous treatment experience i.e. treatment naïve (TN) or treatment experienced (TE). HCV genotype 1, the most prevalent genotype in Ireland is further classified according to subtype i.e. GT 1a or GT1b. In patients with GT1a with the Q80k polymorphism the efficacy of simeprevir containing regimens may be reduced. Testing for the presence of the Q80k polymorphism should be considered before initiating simeprevir in combination with sofosbuvir.

Simeprevir is a macrocyclic inhibitor of the HCV NS3/4A protease while sofosbuvir is a first in class uridine nucleotide that inhibits NS5B RNA-dependent RNA polymerase required for viral replication. Simeprevir is given as a once daily dose of 150mg, and sofosbuvir as a once daily 400mg dose for oral use with food. The combination of simeprevir and sofosbuvir confers synergistic anti-HCV replicon activity as they have different modes of action and are less likely to develop resistance.

### 1. Comparative Effectiveness

- The comparators included in the pharmacoeconomic evaluation were two interferon-containing regimens i.e. simeprevir with pegylated interferon and ribavirin (SIM/PR), and boceprevir with pegylated interferon and ribavirin (BOC/PR), and two interferon-free regimens i.e. sofosbuvir plus ribavirin (SOF/RBV), and daclatasvir plus sofosbuvir and ribavirin (SCV/SOF/RBV). The SOF/RBV comparator was limited to a treatment naïve (TN) cohort of patients with HCV infection as there is no data to support its use in a treatment-experienced (TE) cohort.
- One study provides evidence of efficacy for the combination of simeprevir and sofosbuvir for the treatment of patients with GT1 HCV infection. The COSMOS

study (phase 2 open label, N=168) was published in the Lancet in July 2014. Patients were randomly assigned in a 2:1:2:1 ratio to receive 150 mg simeprevir and 400 mg sofosbuvir daily for 24 weeks with (group 1) or without (group 2) ribavirin, or for 12 weeks with (group 3) or without (group 4) ribavirin, in two cohorts: previous non-responders (i.e. treatment experienced TE) with Metavir scores F0–F2 (cohort 1), and previous non-responders and treatment-naive patients with Metavir scores F3–F4 (cohort 2). The study was an open-label study and did not compare either combination to a current standard of care.

- The mean age was 56 years and the GT1a subtype predominated (~70%). The proportion of patients with Q80k polymorphism among the GT1a patients ranged from 27% to 60% across the eight arms. For TN patients included in the trial, the population was limited to those with advanced fibrosis (F3/F4), patients with early disease (F0-F2) were excluded. A broader TE population was studied including patients from F0-F4. Patients with HIV co-infection and post-liver transplant were not included in the trial. Therefore the representativeness of the study population to the patient profile in Ireland is limited.
- Overall SVR12 was achieved by 92% of the total COSMOS intention-to-treat cohort (154/167). The overall SVR12 for TE patients with mild liver disease treated with SIM/SOF for 12 weeks was 93% (n=13/14). For patients with the GT 1a subtype, 90% (9/10) obtained an SVR12 compared to 100% (4/4) for GT1b. For the GT1a subtype, the presence of the Q80k mutation resulted in a lower efficacy rate of 83% (5/6). Among cirrhotic patients treated with SIM/SOF12 i.e. F4, SVR12 was obtained in 86% (6/7) of patients compared to 100% (7/7) in non-cirrhotic (F3) patients. For the GT1a and GT1b subtypes the rates of SVR were 91% (10/11) and 100% (3/3) respectively. No viral breakthroughs occurred on treatment in the trial. Six patients relapsed after end of treatment (EOT), all were GT1a, four of whom had the Q80k polymorphism. Overall SVR rates were generally over 90% but lower in patients with GT1a, and GT1a with Q80k polymorphism, although with the small patient numbers, there is considerable uncertainty. Cirrhosis or previous treatment experience seems to confer a risk of lower SVR rates, but again this is based on extremely small patient numbers. Real world data from a large observational study. TARGET-HCV, indicates numerically lower SVR rates as compared with the clinical efficacy data from

COSMOS overall, and among the GT1a subgroup and these is some evidence that there may be higher relapse rates.

## **2. Safety**

- Data from the COSMOS study reported an overall incidence of adverse effects (AEs) of 93% and 90% in the 24 week groups with and without ribavirin, respectively, and 85% and 71% in the 12 week groups with and without ribavirin, respectively. Most AEs (77%) were Grade 1 or grade 2 in severity. The most frequently reported AEs (>15% of all subjects overall) were fatigue (30%) and headache (20%). AEs of clinical interest, in particular bilirubin increase, rash, and anaemia, were more common with the ribavirin-containing regimen than with the ribavirin-sparing regimen. For 5 subjects sunburn was reported. In the SIM/SOF12 arms, the AEs encountered were minimal. Real world data provided by the manufacturer indicate that the combination of SIM/SOF is well tolerated and AEs are consistent with the AEs obtained in COSMOS i.e. mild fatigue, headache and nausea. For these AEs conservative management will prevail in clinical practice. While no overt safety signals have been reported for the combination, photosensitivity, rash and raised bilirubin merit surveillance among treated patients. Should ribavirin be used in combination with SOF/SIM, anaemia will be a concern, but the extent to which ribavirin will be added to the SIM/SOF regimen in clinical practice is unknown.

## **3. Cost-Effectiveness analysis**

- A cost utility analysis comparing simeprevir (Olysio<sup>®</sup>) in combination with sofosbuvir (Sovaldi<sup>®</sup>) with interferon-containing and interferon-free regimens was submitted by the company. The perspective of the HSE (payer) was presented. The model is composed of two phases, the first corresponds to the initial ‘treatment’ phase, followed by a post-treatment period, when viral response is assessed i.e. SVR. Patients then move into the ‘post treatment’ Markov phase of the model which captures long-term outcomes over the remaining life of the patient, according to whether they have achieved SVR or not, and their disease severity grade using the Metavir score i.e. where no or mild fibrosis is F0-2,

moderate fibrosis is F3 and compensated cirrhosis is F4. The time horizon was lifetime (70 years).

- A total of twelve health states are included in the model corresponding to three baseline health states i.e. mild, moderate and compensated cirrhosis, progressive liver disease health states including decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant (LT) and post liver transplant (PLT) and three SVR health states according to baseline status i.e. SVR mild, SVR moderate and SVR compensated cirrhosis. The final health states are liver-related death and death from non-liver causes. Patients who achieve an SVR transition to SVR mild, SVR moderate or SVR compensated cirrhosis health states. Patients who achieve SVR from mild or moderate health states are assumed to be free of future liver complications and do not progress further. Compensated cirrhotic F4 patients who achieve an SVR are assumed to still be at risk of developing DCC, HCC and therefore of receiving a liver transplant. It is assumed that there is no spontaneous reactivation of HCV infection once SVR has been achieved. A re-infection rate was not included in the model, a potential outcome that the review group consider a possibility in the context of higher numbers of patients treated, and in patient cohorts with on-going acquisition risks. Patients who do not achieve an SVR progress through the various health states associated with worsening liver disease.
- For the base case analyses, the patient profile of the cohort treated with SIM/SOF had a mean age of 45 years, a weight of 79kg and the proportion of males to females was 68% to 32%. A distribution of disease severity of 44.7% mild, 26.3% moderate and 29% cirrhotic was applied to patients entering the model. The proportion of patients with GT1a (75%) in the Irish cohort was based on data from the National Virus Reference Laboratory (NVRL) database with 19% estimated to have the Q80k mutation.
- Treatment effects applied in the model included SVR rates and rates of adverse effects. SVR outcome data were obtained directly from the clinical trials used to support registration of the technology and comparator regimens and subsequently applied in the model. Summary relative effect measures were not applied in the model. Similarly, absolute rates of adverse effects as obtained in the clinical studies were applied in the model. Adverse effects included in the trial were

haematological (anaemia and neutropenia) and dermatological (rash and pruritus).

- QALYs, were used to measure health benefits and morbidity. The key utility values used in the model were those relating to the baseline health states, utilities relating to disease progression in the absence of SVR, treatment related utility decrements and a post-SVR utility increment. A utility increment of 0.05 was applied to baseline health utilities when SVR was achieved and decrements in QoL were applied for adverse effects attributable to the various treatment regimens. Scenario analyses using utility increments of 0.1 and 0.04 were investigated. Treatment specific utility decrements attributable to adverse events were derived from a number of sources depending on the treatment regimen and the liver status of the patient.
- Direct costs included in the model include drug costs, treatment-related adverse event costs, monitoring costs and health state costs. The cost of SIM/SOF per 12 weeks is €71,962. Drug acquisition costs were calculated for each treatment regimen based on individual components of the regimen and stratified according to previous treatment status where appropriate. It was assumed in the base case scenarios that no patients would have extended durations of therapy to 24 weeks for SIM/SOF, although there is provision for extension included in the licence in patients with negative predictors of response. Therefore the impact of these additional costs was not considered, and was requested by the review group in scenario analyses. Ten health state costs were included in the model. The manufacturer provided scenario analyses to test the impact of higher health state costs.

### *Results*

- In treatment naïve patients, the cost/QALY for all four patient cohorts when SIM/SOF is compared to SIM/PR are above the €45,000/QALY threshold ranging from €58,697/QALY (all F4) to €265,927/QALY (F0-F2). In treatment experienced patients, when SIM/SOF is compared to SIM/PR all scenarios fall below the €45,000/QALY threshold ranging from €7,684/QALY (all F4) to €44,539/QALY (all F0-F2).
- The results of the analyses when SIM/SOF is compared to SOF/DCV in treatment naïve and treatment experienced patients across all patient cohorts,

demonstrates that SIM/SOF is less effective and less costly for all scenarios (south-west quadrant).

- When SIM/SOF12 was compared to the interferon-free regimen of SOF/RBV for 24 weeks in treatment naïve patients, it resulted in cost savings with an associated gain in QALYs across all scenarios i.e. SIM/SOF dominated SOF/RBV. SOF/RBV24 was not compared in treatment experienced patients due to the absence of data.
- When SIM/SOF is compared with BOC/PR in treatment naïve patients across four patient cohorts, the ICERs fall below the €45,000/QALY threshold with the exception of patient with mild disease (€80,391/QALY). For treatment experienced patients, the costs/QALY for all patient cohorts are below the €45,000 cost/QALY threshold with the exception of a mixed cohort of F0-F4 patients.
- If 24 weeks of SIM/SOF are used, the ICERs are above the cost-effectiveness threshold. When ribavirin was added to the 24 week treatment regimen of SIM/SOF there was no change in the cost-effectiveness conclusions. A change in the utility rate from 0.05 to a higher utility gain of 0.1, or a lower utility gain of 0.04 resulted in no changes to the base case ICERs. Scenario analyses where costs for pricing structure, health state costs and the cost of the Q80k test had little impact on the ICERs. When the review group requested variations on the efficacy (a reduction of 10% and 20%) of SIM/SOF, the greatest impact was seen in the TN cohort where the ICERs doubled in most cases. However, the impact in the TE cohort was less and resulted in minor changes in ICERs. The inclusion of a re-infection rate of 4% at year 3 or year 5 had little impact on the ICERs. Reducing the time horizon to 60 and 50 years had little impact on the ICERs.

### *Sensitivity analysis*

#### *One-way deterministic sensitivity analysis*

- One-way deterministic sensitivity analysis tested the impact of the model inputs described in the PSA. The impact of a change in the SVR rate for the SIM/SOF F3/F4 patients had the largest impact on the cost/QALYs across all comparators. In the mixed cohort the SVR rates for SIM/SOF in all patients from F0 to F4 were

the main driver for changes in cost/QALYs. This highlights the potential impact of any change in efficacy when used in the real world setting. In all scenarios for treatment experienced patients SVR rates for SIM/SOF had most impact on cost/QALY.

#### *Probabilistic sensitivity analysis*

- The probabilistic sensitivity analysis tested the impact of varying all parameter inputs on the costs/QALYs generated in the base case scenarios. For treatment naïve patients with more advanced liver disease, (F3/F4) the probability that SIM/SOF12 is the most cost effective of all the treatment regimens at a willingness to pay threshold of €45,000 per QALY is approximately 10%. In a mixed cohort comprising of more patients with mild to moderate liver disease, the probability that SIM/SOF is the most cost effective of all treatments at a willingness to pay threshold of €45,000 per QALY is approximately 5%. This latter scenario may reflect the population of patients most likely to be treated in the Irish setting over the next number of years. For treatment experienced patients in both an advanced F3/F4 cohort and a mixed cohort of mild, moderate and severe disease (F0-F4), the probability that SOF/SIM is most cost effective of all the treatment regimens at a willingness to pay threshold of €45,000/QALY is 100%.

#### **4. Budget impact:**

- The budget impact analysis was restricted to interferon-free regimens alone. The costs of simeprevir and sofosbuvir for 12 weeks is €71,962, sofosbuvir and ribavirin for 24 weeks is €94,519 and a weighted average of 12 or 24 weeks of sofosbuvir and daclatasvir (depending on whether patients are TN or TE) is €109,720. The cost of the sofosbuvir backbone accounts for 63% of the total cost of SIM/SOF regimen. The analysis assumed that interferon-free regimens would account for 40% of the total HCV market, and that of this, SIM/SOF would represent 63% of this share in the first year, and decrease in the following two years. The gross budget impact for SIM/SOF was estimated to be €2,734,544 in year 1 based on treating 38 patients, decreasing to €1,079,429 in year 2 and further to €575,696 in year 3 when SIM/SOF's share would be reduced to 12.5%



of the total market. This would amount to a total gross budget impact of €4,389,680. A scenario analysis was provided where 200 patients were treated per annum, resulting in a gross budget impact of €5,756,957 for SIM/SOF over 3 years. The assumption that interferon-free regimens will be limited to 40% of patients on treatment may be an underestimate, and the overall number of patients who will be treated each year may be in excess of 150 patients.

- A net budget impact was not provided.

## **5. Conclusion**

Janssen Cilag Ltd. submitted a dossier for simeprevir (Olysio<sup>®</sup>) in combination with sofosbuvir (Sovaldi<sup>®</sup>) on 30<sup>th</sup> October 2014. The combination is licensed for the treatment of both genotypes 1 and 4, although this evaluation is limited to assessment of the cost effectiveness of the regimen in genotype 1 alone.

- In treatment naïve GT1 patients, SIM/SOF is not cost-effective when compared to the interferon-containing regimen, SIM/PR.
- In treatment-experienced GT1 patients SIM/SOF is cost effective when compared to SIM/PR.
- SIM/SOF is less effective and less costly for almost all scenarios (south-west quadrant) compared to SOF/DCV in treatment naïve and treatment experienced patients.