Cost effectiveness of sofosbuvir and ledipasvir (Harvoni®) in combination with other medicinal products for the treatment of hepatitis C infection

The NCPE has issued a recommendation regarding the cost effectiveness of sofosbuvir and ledipasvir (Harvoni®) in combination with other medicinal products for the treatment of hepatitis C infection. The NCPE recommends reimbursement of sofosbuvir and ledipasvir (Harvoni®) for patients with genotype 1 and genotype 4 hepatitis C infection.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's Gilead Sciences Ltd. economic dossier on the cost effectiveness of sofosbuvir and ledipasvir (Harvoni®) for the treatment of hepatitis C infection. 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 applicant 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.

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In January 2015 Gilead Sciences Ltd. submitted a clinical and economic dossier on the cost effectiveness of sofosbuvir and ledipasvir (Harvoni®) in combination with other medicinal products for the treatment of hepatitis C virus (HCV) infection. Final comments were received in October 2015. Harvoni® combines two direct acting antiviral agents with distinct mechanisms of action for the treatment of HCV infection in a co-formulated once daily tablet. Sofosbuvir is a uridine nucleotide that inhibits NS5B RNA-dependent RNA polymerase required for viral replication. Ledipasvir is an inhibitor of the HCV NS5A protein.

Harvoni® was granted a licence from the EMA for genotypes 1, 3 and 4. Harvoni® can be used for treatment durations ranging from eight to 24 weeks with or without ribavirin. The duration of treatment is dependent on genotype 1 subtype, cirrhosis staging and the presence of negative predictors of response. The Child-Turcotte Pugh (CTP) classification is used to classify severity of cirrhosis where scores of ≥7 (CTP B/C) are classified as severe cirrhosis. Decompensated liver disease occurs when cirrhotic patients have a documented episode of encephalopathy, variceal bleed or ascites. Response to therapy is measured as undetectable virus 12 weeks after completion of therapy, termed the sustained viral response (SVR).

The submitted dossier included evidence on the cost-effectiveness of Harvoni® with or without ribavirin for the treatment of genotypes 1, 3 and 4 in patients with chronic hepatitis C infection. Of note the current 2015 European Association for the Study of the Liver (EASL) guidelines have recommended Harvoni® for the treatment of genotype 1 and 4 alone, and not for genotype 3. In 2011, it was estimated that genotype 1 accounts for approximately 55% of chronic hepatitis C in Ireland compared to <1% for genotype 4. Based on the current guidelines the comparators are:

- Interferon containing (gentoype 1 and 4):
    - sofosbuvir with pegylated interferon and ribavirin, and
    - simeprevir with pegylated interferon and ribavirin,
- Interferon-free:
    - simeprevir with sofosbuvir and
    - sofosbuvir and daclatasvir
    - paritaprevir/(boosted with ritonavir) with ombitasvir (Viekirax®) and dasabuvir (Exviera®) (genotype 1) and
    - paritaprevir/(boosted with ritonavir) with ombitasvir (Viekirax®) (genotype 4)

As the sofosbuvir regimens in combination with simeprevir or daclatasvir are less commonly used in Ireland for these genotypes the assessment focusses on the cost effectiveness relative to paritaprevir/(boosted with ritonavir) with ombitasvir (Viekirax®) and dasabuvir (Exviera®).

1. Clinical effectiveness

The clinical evidence submitted to support the cost effectiveness of Harvoni® included data from three phase III trials (ION-1, 2 & 3), and two Phase 2b trials (ELECTRON-2 and SYNERGY). SVR12 rates were >90% in patients without cirrhosis, irrespective of prior exposure to treatment in the ION studies. The presence of cirrhosis is associated with lower SVR12 rates, but the addition of ribavirin optimises outcomes. In the on-going SYNERGY, trial 95% (20/21) of treated patients has achieved SVR12. There is no trial data in patients with genotype 4 without cirrhosis, and with more advanced liver disease i.e. CTP B and C, or decompensated liver disease, although real world data is emerging in these patient cohorts.

Due to the lack of comparator trials a comparative assessment of efficacy was not undertaken.

2. Safety

Harvoni® is associated with good tolerability, and no specific safety signals of concern are apparent from the clinical trial programme. The most frequently reported adverse events attributable to Harvoni® were fatigue and headache.

3. Cost-effectiveness of LDV/SOF

The cost (list price) of a 28 capsule pack of Harvoni® is €15,333. The costs of an 8 week and 12 week course of Harvoni® are €30,667 and €46,000 respectively.

- A cost-utility analysis was submitted by Gilead Ltd. comparing a number of scenarios where Harvoni® is used with or without ribavirin. The population presented in the economic model includes patients with genotype 1 or 4 hepatitis C infection, both treatment naïve and treatment experienced. The submission considered two further sub-populations, those without cirrhosis (F0-3), and those with cirrhosis (F4).

- Relevant comparators were based on the recently updated EASL clinical guidelines. The Viekirax® and Exviera® triple regimen had not been licensed at the time of the submission, but a comparison was supplied by the applicant on request by the review team for evaluation for genotype 1, and the Viekirax® dual regimen was provided for genotype 4.
- A Markov state-transition model was used to describe the progression of disease over the lifetime of a patient cohort. The model represents the natural history of chronic hepatitis C patients and allows patients to enter the model based on baseline staging of disease.
- Quality-adjusted life years (QALYs) were used to measure benefits and morbidity. Costs included drug acquisition costs, health state costs, monitoring costs and costs associated with treatment of adverse events and liver progression events i.e. decompensated cirrhosis, hepatocellular carcinoma and liver transplant. The analysis was presented from the healthcare payer's perspective.

Results

Genotype 1 Treatment naive non-cirrhotic

- Patients are assumed to receive eight weeks of Harvoni®. Harvoni® is a cost-effective treatment compared to the interferon-containing regimens (1) simeprevir with pegylated interferon and ribavirin and (2) sofosbuvir with pegylated interferon and ribavirin in non-cirrhotic patients with genotype 1 infection. Compared to the combination of Viekirax® and Exviera®, Harvoni® is also cost-effective. As the QALYs are very similar for both treatments cost effectiveness is mainly driven by the longer treatment durations of the comparator treatments compared to the eight week treatment duration for Harvoni®.

Genotype 1 Treatment Naive cirrhotic

- Treatment duration is assumed to be 12 weeks Harvoni® for 95% of cirrhotic patients and 24 weeks for 5% of cirrhotic patients. Harvoni® is a cost-effective treatment compared to the interferon-containing regimens of (1) simeprevir with pegylated interferon and ribavirin and (2) sofosbuvir with pegylated interferon and ribavirin in cirrhotic patients. The comparison with the Viekirax® and Exviera® combination regimen is driven by drug cost; QALYs are very similar. Harvoni® is likely to be cheaper in a genotype 1a cohort due to the 24 week treatment duration with the Viekirax® and Exviera® regimen; while Viekirax® and Exviera® appears slightly cheaper in a genotype 1b cohort due to

the 5% of patients treated for 24 weeks with Harvoni®. The prevalence of genotype 1a is assumed to be 70%, and 30% for genotype 1b.

Genotype 1 Treatment Experienced

- Harvoni® is cost-effective when compared to interferon-based regimens for non-cirrhotic treatment naïve patients; and when compared to the Viekirax® and Exviera® regimen, the costs and QALYS are very similar. In treatment experienced cirrhotic patients, Harvoni® is cost-effective when compared to interferon-based regimens; and to the Viekirax® and Exviera® regimen is less effective and less costly. Of note, the treatment experienced patients included in the analysis received prior interferon-based therapy.

Genotype 4

The evaluation considered the cost-effectiveness of Harvoni® in patients with genotype 4 who may represent <1% of the total population of patients with HCV infection in Ireland. The cost effectiveness in this cohort was based on the assumption that Harvoni® has similar efficacy in a genotype 1 and genotype 4 cohorts.

- Harvoni® appears to be cost-effective when compared to (1) simeprevir with pegylated interferon and ribavirin and (2) sofosbuvir with pegylated interferon and ribavirin for non-cirrhotic and cirrhotic patients, and may represent a cost-effective treatment compared to Viekirax® in cirrhotic patients.

Due to the considerable additional cost for sofosbuvir regimens containing simeprevir or daclatasvir, Harvoni® is cost effective in all strategies where these are comparators.

Budget Impact Analysis

There is significant uncertainty in the future market regarding available treatments for HCV infection, making it difficult to estimate the potential market share of Harvoni® for the next 5 years.

The applicant assumed that 1,000 patients will be treated for HCV every year. The 5 year gross budget impact is estimated to be €40,049,754, excluding patients with genotype 3 HCV

infection. It is difficult to estimate the net budget impact of Harvoni® given the uncertainty in relation to the number of patients to be treated, and the availability of existing and additional treatment regimens.

Conclusion

Gilead Sciences Ltd. submitted a dossier for Harvoni® with or without ribavirin in genotypes 1, 3 and 4 hepatitis C infection in accordance with licensed indications. The applicant presented several different scenarios across the three genotypes stratified by cirrhosis status and previous treatment experience; genotypes 1 and 4 were considered to be the most relevant given that the current EASL guidelines do not recommend Harvoni® for patients with genotype 3 infection. Harvoni® is considered cost-effective when compared to interferon-based comparators in both non-cirrhotic and cirrhotic patients. When compared to the Viekirax® and Exviera® regimen in genotype 1 and Viekirax® in genotype 4, little difference is observed in effects and difference in cost is driven by treatment duration.

The NCPE recommends reimbursement of Harvoni® in genotype 1 and 4 patients. Harvoni is not recommended for GT3.