



Cost effectiveness of daclatasvir (Daklinza®) in combination with other medicinal products for the treatment of hepatitis C infection

The NCPE has issued a recommendation regarding the cost effectiveness of daclatasvir (Daklinza®) in combination with other medicinal products for the treatment of hepatitis C infection. The NCPE recommends reimbursement of Daklinza® for certain subgroups.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the company's (BMS Ltd.) economic dossier on the cost effectiveness of daclatasvir (Daklinza®) 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 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

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In December 2014 Bristol-Myers Squibb Pharmaceuticals Ltd. submitted a clinical and economic dossier on the cost effectiveness of daclatasvir (Daklinza®) in combination with other medicinal products for the treatment of hepatitis C virus (HCV) infection. Daclatasvir (DCV) is an inhibitor of the non-structural protein 5A (NS5A), a multifunctional protein essential for HCV replication. DCV is licensed for the treatment of HCV genotypes (GT) 1, 3 and 4, in treatment naïve (TN) and treatment experienced (TE) patients and in cirrhotic and non-cirrhotic patients. The dose of DCV is 60mg orally once daily and must be administered as part of a combination regimen, for treatment durations of 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 assessment evaluates the cost-effectiveness of daclatasvir in combination with sofosbuvir (DCV/SOF) for the treatment of chronic hepatitis C patients with GT1, 3 and 4 and the combination of daclatasvir with pegylated interferon and ribavirin (DCV/PR) for GT4 patients. However, the interferon-free DCV/SOF regimen is considered of most relevance. Recently published guidelines from the European Association for the Study of the Liver (EASL) prompted the review group to focus on these recommendations when evaluating the cost-effectiveness versus selected comparators, both interferon-based and non-interferon-based. The comparators for each genotype are as follows:

	Genotype 1	Genotype 3	Genotype 4
Interferon-based	SOF/PR SIM/PR TEL/PR BOC/PR	PR	SIM/PR SOF/PR
Interferon-free	SOF/RBV SOF/LDV SOF/SIM P/rOD/RBV	SOF/RBV	SOF/RBV

SOF=Sofosbuvir; PR=pegylated interferon & ribavirin; SIM=simeprevir; TEL= telaprevir; BOC=boceprevir; RBV=ribavirin; LDV=Ledipasvir; P/rOD= Paritaprevir/ritonavir/ ombitasvir/dasabuvir

1. Clinical effectiveness and safety of daclatasvir

A total of two studies support the clinical efficacy of the interferon-free regimen of daclatasvir in combination with sofosbuvir (DCV/SOF) (two studies), while the interferon-containing regimen of daclatasvir in combination with pegylated interferon and ribavirin (DCV/PR) has also been investigated in two studies.

Interferon-free studies – DCV/SOF:

Study AI444-40 was a Phase 2a randomised open-label study comparing ten treatment arms of DCV/SOF with or without ribavirin at two treatment durations of 12 or 24 weeks in 211 patients with GT 1, 2 and 3. The study included both TN and TE patients; however, cirrhotic patients were excluded. The number of patients per arm ranged from 14 to 41. The study was dominated by patients with GT1, and patients with GT 3 were limited to eleven patients in total in the arms of relevance to the review. For patients with GT1, SVR rates ranging from 95% to 100% were achieved across relevant arms, and all of the eleven patients with GT3 obtained an SVR. There were no apparent differences between TN and TE patients, and the addition of RBV was associated with a lower SVR rate. There were no viral breakthroughs for patients with GT1, while there was one viral breakthrough in a GT3 patient treated with DCV/SOF for 12 weeks without ribavirin. Two patients relapsed following end of treatment, one GT1 patient treated with DCV/SOF without RBV, and one for GT3 patient also treated without RBV.

ALLY-3 was a phase 3, open-label, two cohort study involving a 12 week regimen of DCV/SOF in 150 GT3 patients (100 TN and 50 TE) with a 24 week follow-up. In TN non-cirrhotic patients, SVR12 was achieved by 97% as compared with 94% in TE non-cirrhotic patients. The SVR rates were 58% and 69% for cirrhotic patients in the TN and TE cohorts respectively. There were no viral breakthroughs on treatment. Sixteen patients relapsed post treatment of whom eleven had cirrhosis at baseline. The results of this study prompted the revised recommendation (EASL 2015) for treatment of cirrhotic GT3 patients with DCV/SOF to be of 24 weeks duration and to include RBV to optimise the chances of SVR following treatment.

Interferon-based studies DCV/PR

Study AI444-44 was a Phase 2b, randomised, double-blind study conducted comparing DCV in combination with PR to PR alone in patients with GT4 who were TN. An overall SVR rate of 82% (67/82) was obtained with the DCV/PR combination as compared with 43% (18/42) for PR alone. In patients without cirrhosis, the SVR rate was 81% (56/69) and in those with cirrhosis 78% (7/9) for the DCV/PR regimen. On-treatment failure occurred in eight patients treated with DCV/PR (10%) compared to fifteen patients (36%) treated with PR alone. Two patients (3%) relapsed who were treated with DCV/PR compared to eight patients (30%) treated with PR alone.

Study AI444-010 was a Phase 2b, randomised, double-blind study conducted comparing DCV in combination with PR to placebo with PR in patients with GT1 and GT4 who were TN. The proportion of GT1 patients with SVR24 was 69.6% vs 37.5% with the placebo/PR arm. All patients with GT4 (12/12) treated with DCV/PR achieved SVR24.

SVR rates are high among patients treated with the interferon-free regimen of DCV/SOF in patients with GT1 and 3, as demonstrated from the results of the Phase 2 open label AI-444-040 study and the Phase 3 open label ALLY-3 study. The studies are limited by small patient numbers for some cohorts, particularly cirrhotic patients who are not well represented in the programme. DCV/SOF for GT4 has not been investigated in clinical trials although it is licensed for use and included in the recent EASL guidelines. The combination of DCV/PR is not included in the guidelines.

Preliminary results from on-going manufacturer-sponsored trials, ALLY-1 and ALLY-2, indicate high rates of SVR in patients in the post-liver transplant setting and in patients co-infected with HIV however this has not been addressed by the applicant in this submission.

The interferon-free regimen of DCV/SOF is associated with an improved toxicity profile as compared with interferon-based regimens. The most common treatment emergent adverse events reported with the combination of DCV/SOF are fatigue, headache and nausea. The addition of ribavirin results in anaemia related to its use and additional ribavirin-related AEs including pruritus, cough, dyspnoea and rash. The AE profile for the combination of DCV/PR is driven by the PR component that include haematological, neuropsychiatric effects, influenza-like illness, thyroid disorders and the potential for precipitating autoimmune disease.

2. Cost-effectiveness of daclatasvir (Daklinza®)

The ex-wholesaler price of a 28 day pack of daclatasvir 60mg tablets is €10,000. The cost of a 12 week course of DCV/SOF is €77,361, based on a price of €30,000 for a 12 week course of DCV 60mg, and €47,361 for a 12 week course of SOF.

- A cost-utility analysis was submitted by BMS Pharmaceuticals Ltd. comparing a number of scenarios where daclatasvir is used in combination with sofosbuvir (DCV/SOF) or pegylated-interferon and ribavirin (DCV/PR). The population represented in the economic model includes patients with GT1, GT3 or GT4 HCV infection, both TN and TE. The initial submission considered two further sub-

populations, those with F3 or higher without cirrhosis and those with cirrhosis. The review team requested a further subgroup of mild (F0 – F2) patients to be analysed.

- Relevant comparators were based on the recently updated EASL clinical guidelines. The paritaprevir/ritonavir/ombitasvir/dasabuvir (P/rOD) triple regimen had not been licensed at the time of the submission and is therefore not included as a comparator. SOF/LDV was not included as a comparator in the original submission, but was supplied by the manufacturer on request by the review team.
- 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

- In TN GT1 cirrhotic patients DCV/SOF is cost-effective vs SIM/PR at a threshold of €45,000/QALY, but not when compared to SOF/PR, SOF/LDV or SIM/SOF. In TE GT1 cirrhotic patients when DCV/SOF is compared to the interferon-free regimens of SOF/LDV and SIM/SOF it is not cost-effective. DCV/SOF may be cost-effective in certain groups of non-cirrhotic GT1 patients.
- In TN GT3 cirrhotic patients, DCV/SOF is not cost-effective when compared to SOF/RBV, but appears to be cost-effective in a TE cirrhotic cohort. DCV/SOF may be cost-effective in certain groups of non-cirrhotic patients when compared to SOF/RBV.
- In TN cirrhotic patients with GT4, SOF/DCV is cost-effective vs SOF/PR, PR and no treatment, but is not cost-effective vs SIM/PR. In TE cirrhotic patients, DCV/SOF is cost-effective vs SIM/PR, PR and no treatment.

The manufacturer did not provide analyses on the cost-effectiveness of DCV regimens in the pre- or post-liver transplant setting nor in patients co-infected with HIV.

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 DCV for the next five years. DCV/SOF represents the interferon-free regimen of choice (EASL 2015) for patients with GT3 with cirrhosis at present. A 24 week course of DCV/SOF costs €154,722 (*list price*). Hence the potential budget impact for DCV/SOF may be considerable.

Conclusion

Bristol-Myers Squibb Pharmaceuticals Ltd. submitted a dossier for daclatasvir (Daklinza®) in combination with other medicinal products (i.e. sofosbuvir (DCV/SOF) and pegylated interferon and ribavirin (DCV/PR) in GT 1, 3 and 4 hepatitis C infection in accordance with the licensed indications. The manufacturer presented several different scenarios across the three genotypes stratified by cirrhosis status and previous treatment experience, with GT1 and 3 considered to be the most relevant. DCV/SOF is considered cost-effective when compared to relevant comparators in some scenarios. Recent guidelines recommend DCV/SOF as the treatment of choice for GT3, however the 24 week regimen (based on full list prices), may not be cost effective in a cirrhotic GT3 cohort.