Cost-effectiveness model for sofosbuvir in chronic hepatitis C

Adaptation to the Belgian situation

Katrien De Groote, Peter Michielsen, Jean Delwaide

Gilead Sciences Belgium BVBA, Park Lane Culliganlaan 2D
1831 Diegem, Belgium Phone: 32 24 01 35 50 Fax: 32 24 01 35 51

Introduction

- Hepatitis C is the result of a ribonucleic acid (RNA) virus (hepatitis C virus; HCV), which mutates at a greater rate to that of DNA viruses. Six major HCV genotypes (GT) and a large number of subtypes have been described in the literature, i.e. genotype 1, 2, 3, 4, 5 and 6.
- The treatment of hepatitis C infection aims at eradicating the virus and consequently preventing cirrhosis and its complications, reducing extra-hepatic manifestations, and preventing infection of other people. Depending on the HCV genotype, different treatment regimens are available.
- Sofosbuvir (SOF) is a nucleotide analogue that inhibits NS5B directed HCV RNA replication in vitro and has demonstrated high rates of sustained virological response (SVR) when given with ribavirin (RBV) to subjects with chronic GT- 1,4/5/6 and GT- 2 or 3 HCV infections.

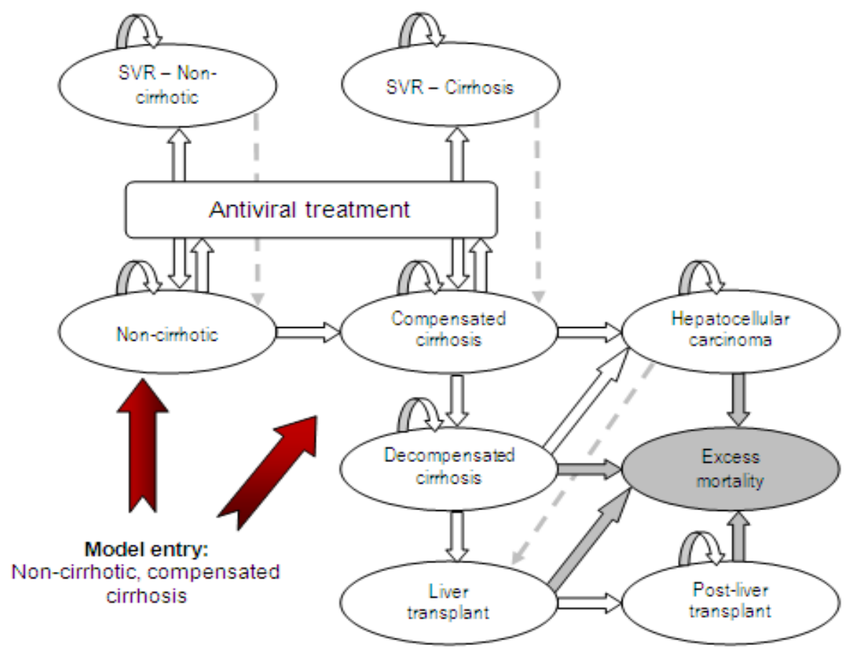
Objective

- This study models the cost-effectiveness of SOF in treatment-naïve (TN) GT4/5/6, TN GT1/2/3 unsuitable for interferon, TN GT 1/2/3 interferon eligible, GT2/3 treatment-experienced (TE) unsuitable for interferon and GT 2/3 TE interferon eligible patients in Belgium, taking into account the guidelines of the Knowledge Centre (KCE) (KCE report 78C, 2008).
- The analysis is a cost-utility analysis (CUA) for sofosbuvir versus standard of care (BE) from the perspective of the RIZIV/INAMI.

Methods

- A cohort of 10,000 patients, with 22% of TN and 30% of TE patients initiating treatment at the cirrhotic stage[2,3] (F3-F4) and which started treatment at 45 years old was followed for a lifetime using a Markov model[1]. The model structure is shown in **Figure 1.**
- There were 2 points of patient entry for treatment into the model (non-cirrhotic and compensated cirrhosis) (the non-cirrhotic includes mild and moderate patients).
- Patients move to the SVR health state after completing treatment if they have undetectable HCV RNA, 12 or 24 weeks (wks) after the end of treatment. They are considered to be virologically cured. Patients without a SVR face an annual probability of progressing to more advanced stages of the disease.

Figure 1. Markov model schematic for chronic hepatitis C (CHC)



- The cycle length was three months for the first two years of the analysis and and yearly after. A 100 years time horizon was chosen in order to reflect the life expectancy observed in Belgium.
- **Table 1** presents the active and comparator treatments used in the model for the different subtypes of hepatitis C patients. For GT1 patients, three comparators were considered: Telaprevir (TVR) or Boceprevir (BOC) and PR (PegINF + ribaverin) or no treatment.

Table 1. Treatment strategies per indication

Indication	IFN-eligible / IFN-ineligible	Active treatment	Comparator(s)
GT1 TN	IFN-eligible	SOF + PR (12 weeks)	TVR + PR (24 or 48 wks)
			BOC + PR (24 or 48 wks)
GT 1 TN	IFN-ineligible	SOF + PR (24 weeks)	No treatment
GT2 TN	IFN-ineligible	SOF + RBV (12 weeks)	No treatment
GT2 TN	IFN-eligible	SOF + RBV (12 weeks)	PR (24 weeks)
GT2 TE	IFN-ineligible	SOF + RBV (12 weeks)	No treatment
GT2 TE	IFN-eligible	SOF + RBV (12 weeks)	PR (48 weeks)
GT3 TN	IFN-ineligible	SOF + RBV (24 weeks)	No treatment
GT3 TN	IFN-eligible	SOF + RBV (12 weeks)	PR (24 weeks)
GT3 TE	IFN-ineligible	SOF + RBV (24 weeks)	No treatment
GT3 TE	IFN-eligible	SOF + RBV (12 weeks)	PR (48 weeks)
GT4/5/6 TN	-	SOF + PR (12weeks)	PR (48 weeks)

- Transition probabilities, health state utilities and clinical data for the active and comparator treatments were obtained from the phase III trials or from literature[4-16.]
- Belgian unit cost data are used; local resource use data were collected via the Delphi Panel technique.
- According to the KCE guidelines (KCE report 78C, 2008), costs and outcomes were discounted at a 3% and 1,5% annual rate, respectively.

Results

- Although the model allows reporting of several types of economic outcomes, results are being reported as incremental costs per quality-adjusted life years (QALYs), in line with the RIZIV requirements for Class 1 reimbursement applications
- Results are presented in **Table 2** per paragraph of Chapter IV of the Royal Decree of 21.12.2001. Weighted ICER's are calculated based on the following assumptions for the BE CHC patient population: 59% GT 1, 19% GT 3 and 16% GT 4/5/6 patients[2]; 50/50 use of TVR/BOC[3]; 50/50 use of PegINF alfa-2a/PegINF alfa-2b[3]; 30/70 distribution for TE vs TN patients[3] and 10/90 distribution for IFN-ineligible vs IFN-eligible patients[3].
- The sub-paragraphs §1, §2 and §3 within Chapter IV represent the subpopulations of CHC patients for which reimbursement has been granted:
  - §1: **CHC patients GT 1, 3, 4, 5 of 6** who are IFN-eligible
  - §2: **CHC patients GT 1, 3, 4, 5 of 6** who are IFN-ineligible (due to intolerance and/or contra-indications)
  - §3: **CHC patients GT 2**

Table 2. Weighted ICER's for the different subtypes of CHC patients in BE

ICERs

§1										
IFN eligible	**Strategie**	**ICER**		**TN/TE**		**IFN Eligible**	**Genotype**	**ICER per §**		**Final ICER**
GT1	TN - TEL/PEG2a/RBV	**17.092**	12.250		12.250		59%	**13.870**	**85%**	**15.575**
	TN - BOC/PEG2b/RBV	**7.408**								
GT3	TN - PEG2a/RBV	**16.651**	16.568	70%	14.364		19%			
	TN - PEG2b/RBV	**16.485**								
	TE - PEG2a/RBV	**9.358**	9.219	30%						
	TE - PEG2b/RBV	**9.081**								
GT4/5/6	TN - PEG2a/RBV	**19.487**	19.260		19.260		16%			
	TN - PEG2b/RBV	**19.032**								
§2										
IFN in-eligible										
GT1	TN - no Tx	**32.192**			32.192		59%	**28.815**	**8%**	
GT3	TN - no Tx	**16.876**		70%	18.329		19%			
	TE - no Tx	**21.719**		30%						
GT4/5/6	TN - no Tx									
§3										
GT 2 patients										
IFN eligible	TN - PEG2a/RBV	**30.636**	30.486	70%	24.409	90%		**22.397**	**6%**	
	TN - PEG2b/RBV	**30.336**								
	TE - PEG2a/RBV	**10.383**	10.230	30%						
	TE - PEG2b/RBV	**10.077**								
IFN in-eligible	TN - no Tx	**4.536**		70%	4.285	10%				
	TE - no Tx	**3.699**		30%						

Conclusion

PAN-genotypic cost-effectiveness has been demonstrated for sofosbivir in comparison to the current standard of care in HCV in Belgium. **Overall, the weighted PAN-genotypic ICER** is **€ 15.575**.

References

1. Bennett WG, Inoue Y, Beck JR et al. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997; 127: 855-65 adapted by Shepherd *et al.*, 2007 and Hartwell et al., 2011.
2. De Maeght S, Henrion J, Bourgeois N et al. A pilot observational survey of hepatitis C in Belgium. *Acta Gastroenterol Belg* 2008;71(1):4-8.
3. Local expert opinion, 2013.
4. Gilead Phase III trials : NEUTRINO, FISSION, POSITRON, FUSION and VALENCE studies.
5. Janssen pharmaceutical companies of Johnson & Johnson. Telaprevir for the treatment of genotype 1 chronic hepatitis C: NICE Single Technology Appraisal (STA), 21-10-2011.
6. Lawitz E, Zeuzem, S, Nyberg, L et al. Boceprevir (BOC) Combined with Peginterferon alfa-2b/Ribavirin (P/RBV) in Treatment-Naïve Chronic HCV Genotype 1 Patients with Compensated Cirrhosis: Sustained Virologic Response (SVR) and Safety Subanalyses from the Anemia Management Study. AASLD 2012.
7. McHutchison JG, Lawitz EJ, Shiffman ML et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; 361: 580-93.
8. Krawitt EL, Ashikaga T, Gordon SR et al. Peginterferon alfa-2b and ribavirin for treatment-refractory chronic hepatitis C. *J Hepatol* 2005; 43: 243-9.
9. Manns MP, McHutchison JG, Gordon SC et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358: 958-65.
10. Wright M, Grieve R, Roberts J et al. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol.Assess* 2006; 10: 1-113, iii.
11. Shepherd J, Jones J, Hartwell D et al. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol.Assess* 2007; 11: 1-205, iii.
12. Grishchenko M, Grieve RD, Sweeting MJ et al. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. *Int J Technol Assess Health Care* 2009; 25: 171-80.
13. Poordad F, McCone J, Jr., Bacon BR et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364: 1195-206.
14. FDA. Telaprevir 375-mg Film-Coated Tablet for the Treatment of Genotype 1 Chronic Hepatitis C: FDA Advisory Committee Briefing Document, 2011.
15. Cacoub P, Bourliere M, Lubbe J et al. Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals. *J Hepatol* 2012; 56: 455-63.
16. Jacobson IM, Lawitz E, Lalezari, J and Crespo, J. GS-7977 400 mg QD Safety and Tolerability in the Over 500 Patients Treated for at Least 12 Weeks. European Association for the Study of the Liver, 18-4-2012.

ISPOR 17th Annual European Congress, Amsterdam, The Netherlands ; November 8-12, 2014