Sofosbuvir for chronic hepatitis C

ERG report on the manufacturer's additional analyses requested by NICE for the fourth Appraisal Committee Meeting

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Introduction

Following the third appraisal meeting for sofosbuvir, NICE requested the manufacturer to provide a new set of analyses for hepatitis C (HCV) genotype 4 (GT4) patients and to provide data on HCV prevalence in relation to patients' ethnicity, haemophilia and HIV/HCV co-infection status. The manufacturer's report was made available to the ERG (25/09/2014). As requested by NICE, the ERG's appraisal of the manufacturer's report is presented below.

1. Alternative SVR rates – treatment naive genotype 4/5/6 patients

The manufacturer has provided details of seven trials of peginterferon and ribavirin (PEG+RBV) identified in their original systematic literature review reporting efficacy data for patients with GT4,5,6 (Table 1 in the manufacturer's report). Within these trials there is a large range of SVR values from 33% (Zeuzem et al.[1]) to 77% (Fried et al.[2]) and the manufacturer has run the model using these SVRs for the revised base case and with a scenario using the Fattovich et al.[3] transition probabilities from compensated cirrhosis without SVR to hepatocellular carcinoma.

The results of these analyses are shown in Tables 2 and 3 in the manufacturer's report. The ERG has checked the model results in these tables and verified the results using the manufacturer's economic model. ICER results range from £19,148 – £244,387 per QALY according to the SVR values chosen.

The ERG notes the following issues with the GT 4/5/6 analysis:

- The number of patients in the reported studies is small (fewer than 20 patients in all study arms).
- The manufacturer has excluded studies based on Middle Eastern patients due to documented differences in terms of response to treatment.
- The manufacturer argues that only two of the studies, by Manns et al.[4] and Lindsay et al.,[5] could have been used in their economic evaluation as they provide combined data on HCV genotypes 4/5/6.

- The manufacturer's analyses have assumed the same SVR for cirrhotic and non-cirrhotic patients and the manufacturer has not reported the number of cirrhotic patients in each of the studies.

The ERG does not agree with the manufacturer's assertion that only studies of combined HCV genotypes 4/5/6 should have been analysed, since this approach excludes some trials on HCV genotype 4 which have superior sample sizes.

To clarify the available evidence for HCV genotype 4, the ERG searched for potentially relevant trials that reported SVR24 after 48 weeks of PEG+RBV therapy. This identified 17 studies that had sample sizes of 10 or more GT4 patients (summarised in Appendix 1). Due to the limited timescale only a rapid review was possible. However, a clinical expert advisor to the ERG felt that we had likely located all relevant evidence (apart from some unpublished data which are discussed below).

Most (10) of the studies with ≥10 GT4 patients were in Middle Eastern, especially Egyptian, populations (Appendix 1). The overall weighted mean SVR24 for the 10 Middle Eastern studies (sample size 28 to 791 patients) is 61.4%. The studies are, however, variable in their quality of reporting with some uncertainties about whether dosing regimens were fully relevant to UK practice. Four of these studies which were well reported and appear more likely to have dosing regimens relevant to the UK (Kamal et al.,[6] Rossignol et al.,[7] Hasan et al.,[8] Varghese et al.[9]) would yield a weighted mean SVR24 of 65.6% (sample size 30 to 109 patients).

Seven European/multinational studies of GT4 patients which might have more relevance to UK clinical practice were identified by the ERG (Appendix 1). These included three RCTs which were also identified by the manufacturer (Fried et al., [2] Rumi et al.,[10] Ferenci et al.[11]), as well as four non-RCT studies (Bourleière et al.,[12] Marcellin et al.,[13] de Galocsy et al.,[14] Savvidou et al.[15]). The weighted mean SVR24 from the three RCTs is 55.7% (sample sizes ranged 12 to 18). The ERG notes that SVR24 is lower in the non-RCTs but for consistency with the appraisal of HCV GT 1-3 the RCT data are considered more robust.

One of the ERG's clinical experts commented on the relevance of the Middle Eastern studies to current NHS practice:

- There is a significant difference between patients of Egyptian origin in Europe and those in Egypt. The average age and number of co-morbidities (including severe fibrotic liver disease) is higher in most European studies and this translates into a reduced response rate.

- We are limited by the lack of data in EU populations with GT4 but the UK population will be much more like the populations in the Bourlière/Marcellan trials[12;13] than the Kamal trial[6] (trial details are given in Appendix 1).

ERG analyses

The ERG considers that the Fattovich et al. study[3] provides a better estimate than Cardoso et al.[16] for the transition between compensated cirrhosis (CC) to hepatocellular carcinoma (HCC) (the manufacturer has not reported that they have searched the literature for alternative studies). The ERG is aware of other studies that have looked at the transition between CC and HCC, such as Bruno et al.[17] with a transition probability of 0.021, and these have transition probabilities more similar to those of Fattovich et al.[3] than to Cardoso et al.[16]

The ERG's opinion is that there remains considerable uncertainty around the ICERs presented by the manufacturer. It is unclear which study presented by the manufacturer would provide the best basis for an estimate of cost effectiveness, due to the small numbers of patients in most studies. For illustrative purposes, the ERG has conducted an analysis using the SVR24 from the weighted average of all the studies reported in Table 1 of the manufacturer's report (see our Table 1 below).

Using those study arms highlighted in bold by the manufacturer (in their Table 1), we estimate a weighted average SVR24 of 54%. Using this estimate for cirrhotic and non-cirrhotic patients in the manufacturer's model with the revised base case would give an ICER of £37,280 per QALY, and this would increase to £40,761 per QALY if Fattovich et al. [3] is used for the transition probability (TP) between CC and HCC.

Table 1 ICERs / QALY revised base case

Analysis	Revised base case	Revised base case + ERG pooled SVR	Revised base case + TP Fattovich et al.[3] + ERG pooled SVR
ICER (£/QALY)	£27,505	£37,820	£40,761

The ERG also estimated alternative ICERs using the SVR24 values found in our rapid review (Table 2). Using the SVRs from the four well-reported middle-Eastern studies would give a weighted mean SVR24 of 65.6% and an ICER of £69,181 per QALY. Selecting the four European RCTs that included GT4 patients only and had more than 10 patients in the PEG+RBV group would give a weighted mean SVR24 of 55.7% and an ICER of £40,664 per QALY. Extending this group to include the studies by Manns et al.[4] and Lindsay et al.[5] (i.e. the two RCTs on GT4/5/6) would give a weighted mean SVR24 of 54.8% and an ICER of £39,109 per QALY. The results for each of these analyses with the transition probability for CC to HCC from Fattovich et al. [3] are shown in Table 3.

Table 2 ICERs / QALY based on ERG pooled SVR24 (revised base case)

Analysis	Middle-Eastern studies with relevant dosing SVR24 65.6%	European RCTs (≥10 patients), GT4 only SVR24 55.7%	European RCTs (≥10 patients), including Manns et al.[4] and Lindsay et al.[5] SVR24 54.8%
ICER (£/QALY)	£69,181	£40,664	£39,109

Table 3 ICERs / QALY based on ERG pooled SVR24 using transition probabilities for CC to HCC from Fattovich et al.[3]

Analysis	Middle-Eastern studies with relevant dosing SVR24 65.6%	European RCTs (≥10 patients), GT4 only SVR24 55.7%	European RCTs (≥10 patients), including Manns et al.[4] and Lindsay et al.[5] SVR24 54.8%
ICER (£/QALY)	£68,029	£43,962	£42,501

The ERG's clinical expert provided unpublished academic in confidence data from HCV UK (an MRF-funded biobank/database that aims to collect data on at least 10,000 UK patients with HCV from 12

centres and which at present has [redacted] patients with a known HCV genotype). SVR was achieved in [redacted] of GT4 patients who received the most recent PEG+RBV course and completed both treatment and follow up. As the ERG cannot verify these confidential data we present them as illustrative only.

In summary, the ERG's analyses illustrate that it is difficult to determine the most appropriate primary data to use for estimating SVR in GT4 patients, owing to small sample sizes, differences in the ethnic composition of the trials, and a lack of data specifically for cirrhotic and non-cirrhotic patients. Illustrative ICERs for several relevant scenarios are presented above for NICE to consider.

2. Prevalence of HCV genotypes

The ERG was unable to verify the source of the prevalence data reported by the manufacturer in their Table 2 as no references corresponding to their citation 15 were found and the source URL of the cited report is missing from the manufacturer's reference list. The ERG checked a range of publications on HCV surveillance from Public Health England and could not find the data given in the manufacturer's Table 2.

The ERG's clinical expert provided unpublished data on the prevalence of HCV genotypes in the UK from the HCV UK database. The HCV UK prevalence data (based on [redacted] patients genotyped) are consistent with the prevalence data provided by the manufacturer, apart from a small difference in the relative prevalence of GT1 and GT3 (Table 4).

Table 4 UK prevalence data for HCV genotypes 1-6

	GT1	**GT2**	**GT3**	**GT4**	**GT5**	**GT6**
Manufacturer's report, 2008-2012	45.4%	6%	44.5%	3.6%	0.2%	0.1%
UK HCV, current data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3. Prevalence of HCV genotypes by ethnic groups

The ERG was unable to verify the ethnicity data presented on pages 7-8 of the manufacturer's report. The data are cited as being from reference 15 in the manufacturer's report but as noted above the ERG could not trace this, or any related reports, containing these data.

4. Prevalence of HCV genotypes in relation to haemophilia

The ERG concurs with the manufacturer's statement on page 8 of their report concerning the distribution of HCV genotypes among haemophilia patients. This is consistent with the cited reference.

5. Prevalence of HCV genotypes in relation to HIV/HCV co-infection

The data provided by the manufacturer are confidential and therefore cannot be verified by the ERG.

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Note that the ERG's clinical expert has declared potential conflicts of interest.

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Appendix 1: Overview of SVR24 obtained from studies of HCV GT4 patients with ≥10 patients receiving PR 48 weeks (PEG IFN 2a unless stated) – ordered by sample size

Study	Ethnicity	Treat-ment history	Cirrhosis status	Study design	No. of HCV GT4 pts	SVR24	Comments
Egyptian & other Middle Eastern studies							
El Raziky et al. (2013)[18]	Egyptian	TN	6% had fibrosis score F4	Retrospective single cohort from an RCT of PEG2a vs PEG2b	PEG2a 791	59.6%*	RBV dose 15 mg/kg/day – unclear how many patients had UK relevant dose; Unspecified data cleaning process employed - possible risk of bias; *Unexplained statistical correction used to calculate SVR due to relatively low numbers at 72 week follow up
Kamal et al (2011)[6]	Egyptian	TN	Not stated but median fibrosis score 1, range 0-4	RCT of PEG2a vs PEG2b	PEG2a 109	ITT: 77/109 = 70.6% Per protocol: 77/107 = 72.0%	
Kamal et al (2005)[19]	Egyptian	TN	Non-cirrhotic	1 relevant arm of an RCT	96	66/96 = 69%	PEG2b
El Makhzangy et al (2009)[20]	Egyptian	TN	15% had fibrosis score F4	Prospective single cohort	95	58/95 = 61.1%	RBV dose ≥11 mg/kg/day – unclear how many patients had UK relevant dose
Hasan et al. (2004)[8]	Kuwait (specific ethnicity not reported)	TN	29% had cirrhosis or severe fibrosis	Prospective single cohort	66	Overall: 68% Mild/no fibrosis: 84% Cirrhosis or severe fibrosis : 29%	PEG2b
El Khayat et al (2012)[21]	Egyptian	TN	18% had METAVIR F4	RCT (PR 24 vs 48 weeks)	44	32/44 = 73%	Population = low viral load + RVR
Rossignol et al (2009)[7]	Egyptian	TN	Not stated but 3% had fibrosis/cirrhosis (Ishak 4-6)	1 relevant arm of an RCT	40	20/40 = 50%	
El-Zayadi et al. (2005)[22]	Egyptian	TN	Not reported (abstract only checked)	1 relevant arm of a controlled trial	40	22/40 = 55%	PEG2b 100µg/week (UK dose is 1.5 mg/kg/day)

Appendix 1 continued

Study	Ethnicity	Treatment history	Cirrhosis status	Study design	No. of HCV GT4 pts	SVR24	Comments
Varghese et al. (2009)[9]	Kuwait (Egyptian, Kuwaiti, Syrian)	TN	Non-cirrhotic	Prospective single cohort	30	19/30 = 63.3%	
Alfaleh et al. (2004)[23]	Saudi Arabian	TN	Appears to be non-cirrhotic (none had histology stage 4 and only 3 had histology grade 4)	1 relevant arm of an RCT	28	12/28 = 42.9%	PEG2b 100µg/week + RBV 800 mg/day (not UK regimen)
European/multinational studies							
Marcellin et al. (2012)[13]	Multi-national: 19 countries in Europe, Canada, and USA	TN	16% of GT4 (51/317) had bridging fibrosis or cirrhosis	3 prospective cohorts (PROPHESYS 1, 2, 3)	ITT: 317 Complete cases 282	ITT: 41.0% Complete cases 46.1%	Country-specific legal and regulatory requirements followed regarding drugs and posology – so dosing may not reflect UK? Mean PR treatment duration was 41.6 weeks
Bourlière et al. (2012)[12]	France (specific ethnicity not reported)	Overall 70% were TN (GT4 % not reported)	Overall 23% had cirrhosis (not reported for GT4)	Prospective single cohort	ITT: TN 120 TE 46 Complete cases: TN 91 TE 38	ITT: TN 37.5% TE 32.6% Complete cases: TN 49.5% TE 39.5%	Data are SVR12 – assumed reflective of SVR24 Majority of population, but not all, had relevant PEG doses to UK, but unclear how many had low-dose ribavirin (<1000mg/day)

Appendix 1 continued

Study	Ethnicity	Treatment history	Cirrhosis status	Study design	No. of HCV GT4 pts	SVR24	Comments
de Galocsy et al (2010)[14]	Belgium - Caucasian & Black	TN+TE	19% had cirrhosis	Retrospective single cohort from 2 Belgian RCTs	78	Overall 40/78 = 51.3% Black 40.9% Caucasian 64.7%	42% of Genotype 4 patients had received amantadine (amantadine arm pooled with PEG+RBV arm as argued that amantadine does not influence therapeutic results with PEG+RBV)
Savvidou et al. (2013)[15]	Greece (specific ethnicity not reported)	84.7% of GT4 were TN	Not stated but 19.6 % of GT4 had advanced fibrosis	Retrospective review of databases from 5 major hepatology units	63	25/63 = 39.7%	PEG2a or PEG2b
Rumi et al. (2010)[10]	Italy, single hospital	TN	28% of GT4 had cirrhosis	1 relevant arm of an RCT	18	44% (95% CI 21% to 69%)	
Fried et al. (2002)[2]	Multi-national, 81 centres worldwide	TN	Over all genotypes 12% had cirrhosis or bridging fibrosis	1 relevant arm of an RCT	13	10/13 = 77%	
Ferenci et al. (2010)[11]	Austria, 13 centres	TN	Not stated but over all genotypes 20.2% had fibrosis stage 3-4	1 relevant arm of an RCT	12	6/12 = 50% (95% CI 21.1% to 78.9%)	

ITT: intention to treat analysis (missing data typically analysed as treatment failures); TE: treatment experienced; TN: treatment naive