Lead team presentation
Elbasvir-grazoprevir for treating chronic hepatitis C – Single Technology Appraisal

1st Appraisal Committee meeting: 27 July 2016

Background and Clinical Effectiveness

Committee D

Lead team: John Henderson, Tracey Cole

ERG: Kleijnen Systematic Reviews

NICE technical team: Aminata Thiam, Nwamaka Umeweni

Company: Merck Sharp & Dome

Public observer slides

Key issues for consideration

- Are the following comparators relevant for this appraisal?
  - Boceprevir and telaprevir – both excluded from the company analyses
  - Peginterferon alpha plus ribavirin – included in the company analyses
- The robustness of the elbasvir-grazoprevir trials given the following;
  - Trials were mostly randomised and 4 out of the 8 trials had a comparator arm (3 placebo controlled trials and 1 active controlled with sofosbuvir)
  - Limited data for the genotype 4 population – previously considered by the appraisal committee for similar hepatitis C NICE appraisals
  - The ERG agreed with the company's assessment that the risk of bias in the trials was generally low
- What conclusions can be drawn from the results of the network meta-analysis and naïve comparison given the ERG's concerns?

Hepatitis C

- Blood borne (people who inject drugs major source ≈90%)
- Acute infection usually asymptomatic
  - 75-85% develop chronic hepatitis C (CHC)
  - 10-20% CHC progress to cirrhosis
  - 1-4% per year hepatocellular carcinoma (HCC)
- 214,000 people with CHC in UK (PHE, 2014)
- Six major genotypes (GT1-6)
  - GT1 and GT3 most common (approx. 90%)
- Aim of treatment is to cure the infection
  - Historically, treatment included peginterferon plus ribavirin regimens
  - In recent times, direct-acting antivirals (DAAs) with better efficacy and improved safety profile are being used

Published NICE guidance
(non-DAAs)

- **TA75:** recommend ribavirin and peginterferon alfa-2a or peginterferon alfa-2b
  - genotype 1 – 6 HCV
- **TA106:** recommends interferon monotherapy
  - genotype 1 – 6 HCV; for those unable to tolerate ribavirin
- **TA200:** recommends shortened courses of peginterferon alfa and ribavirin
  - for people with specific genotypes and who have a rapid virological response at week 4 during treatment
- **TA252:** recommends telaprevir with ribavirin and peginterferon alfa
  - genotype 1 HCV
- **TA253:** recommends boceprevir with ribavirin and peginterferon alfa
  - genotype 1 HCV

Published NICE guidance
(DAAs)

- **TA330:** recommends sofosbuvir in combination with ribavirin, with or without peginterferon alfa
  - specific people with genotypes 1– 6 HCV
- **TA331:** recommends simeprevir in combination with peginterferon alfa and ribavirin
  - genotype 1 or 4 HCV
- **TA363:** recommends ledipasvir-sofosbuvir
  - specific people with genotype 1 or 4 HCV
- **TA364:** recommends daclatasvir in combination with sofosbuvir with or without ribavirin; or with peginterferon alfa and ribavirin
  - specific people with genotype 1, 3 or 4 HCV
- **TA365:** recommends ombitasvir-paritaprevir-ritonavir, with or without dasabuvir or ribavirin
  - genotype 1a, 1b or 4 HCV

Patient perspectives

- Submission from Hepatitis C Trust
- People with Hepatitis C can experience:
  - Differing symptoms, from mild to debilitating (chronic fatigue, mood swings, sexual dysfunction)
  - Liver damage even with mild symptoms
  - Stigma from association with drug misuse, potentially leading to employment discrimination
  - Anger when infected through NHS and not compensated
  - Uncertainty as to when an interferon-free therapy will be available
- Elbasvir-grazoprevir:
  - Interferon-free alternative
  - Suitable for people with renal dysfunction
  - Effective in people who use drugs

Clinician perspectives

- Submissions from UK Clinical Pharmacy Association, BASL/BVHG, BSG, University of Liverpool Institute of Infection and Global Health, British HIV Association
- Elbasvir-grazoprevir:
  - Offers a useful addition to choice of agents to overcome insurmountable drug-drug interactions in some patients
  - Lack of requirement for ribavirin in compensated cirrhosis
  - High efficacy in genotype 4
  - Enables treatment of patients with end-stage renal disease, which used to represent an unmet need
  - Elbasvir-grazoprevir would be, initially used in secondary care in hepatology, viral hepatitis and co-infection clinics
  - Good SVR rate in people previously treated with NS3/4 PI

Elbasvir-grazoprevir (1)

- Elbasvir-grazoprevir (Zepatier, Merck Sharp & Dome) is a single fixed-dose combination (50 mg EBR and 100 mg GZR), which disrupts the biogenesis of components necessary for HCV replication by inhibiting key HCV proteins
- It received positive CHMP opinion ‘for the treatment of chronic hepatitis C in adults’ with genotypes 1a, 1b and 4 infections
- It is taken orally once daily for 12 weeks. The duration of treatment may be increased to [redacted] at the discretion of physicians

Elbasvir-grazoprevir (2)

Patient population	Treatment	Duration
Patients with genotype 1a chronic hepatitis c		
All	Elbasvir-grazoprevir	12 weeks
[redacted]	[redacted]	[redacted]
Patients with genotype 1b chronic hepatitis c		
All	Elbasvir-grazoprevir	12 weeks
Patients with genotype 4 chronic hepatitis c		
All	Elbasvir-grazoprevir	12 weeks
[redacted]		

Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale for any deviations
Population	People with chronic hepatitis C: • who have not had treatment for chronic hepatitis C (treatment-naive) • who have had treatment for chronic hepatitis C (treatment-experienced)		
Intervention	Elbasvir-grazoprevir	Elbasvir-grazoprevir	In line with the product label
Comparators	• BSC • BOC + PR • DCV + PR • DCV + SOF • LDV + SOF • OPR +/- D (3D and 2D) +/- R • PR • SMV + PR • SOF + PR or R • TVR + PR	• BSC • DCV + PR • DCV + SOF • LDV + SOF • OPR +/- D (3D and 2D) +/- R • PR • SMV + PR • SOF + PR or R	BOC and TVR are no longer representative of current clinical practice following the introduction and approval of the newer DAA technologies

BOC – boceprevir, D – dasabuvir, DCV – daclatasvir, LDV – ledipasvir, OPR – ombitasvir/paritaprevir/ritonavir, PR – peginterferon + ribavirin, R – ribavirin, SMV – simeprevir, SOF – sofosbuvir, TVR - telaprevir

Decision problem contd.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale for any deviations
Outcomes	• sustained virological response • development of resistance to elbasvir-grazoprevir • mortality • adverse effects of treatment • health-related quality of life	• sustained virological response • mortality • adverse effects of treatment • health-related quality of life	Resistance was not considered in post hoc analyses and therefore do not support the economic analyses.

Overview of clinical trials (1)

- Eight trials including 7 RCTs:
  - 4 with comparator arms (3 placebo + 1 head-to head EBR/GZR compared with SOF+PR)
  - 4 without a comparator arm
- Company focused submission on 2 genotypes (HCV 1, 4) and 2 sub-genotypes (1a, 1b), in line with anticipated marketing authorisation
- Studies included subgroups: cirrhosis, non-cirrhosis, treatment-naïve, treatment-experienced populations (12 subgroups in total)

Overview of clinical trials (2)

	C-EDGE TN	C-EDGE CO-STAR	C-SURFER	C-EDGE H2H
Design	Double-blind and open-label RCT (phase III)	Double-blind RCT (phase III)	Double-blind and open-label RCT (phase III)	Open label RCT (phase III)
Pop.	TN: GT 1a, 1b, 4 & 6 +/- cirrhotic	TN: GT 1, 4 & 6 +/- cirrhotic	TN & TE : GT 1a, 1b +/- cirrhotic	TN & TE: GT 1a, 1b & 4 +/- cirrhotic
Int.	EBR/GZR	EBR/GZR	EBR/GZR	EBR/GZR
Comp.	Placebo	Placebo	Placebo	SOF + PR (12 weeks)
Tx duration (weeks)	12	12	12	12
Primary outcome	SVR12	SVR12	SVR12	SVR12

Key: EBR/GZR, Elbasvir-grazoprevir; IFN, interferon; RCT, randomised controlled trial; SVR, sustained viral response; TE, treatment-experienced; TN, treatment-naïve

Overview of clinical trials (3)

	C-EDGE TE	C-SCAPE	C-WORTHY	C-EDGE CO-INFECTION
Design	Open-label RCT (phase III)	Open-label RCT (phase II)	Double-blind and open-label RCT (phase II)	Open-label non-randomized (phase III)
Pop.	TE: GT 1a, 1b, 4 & 6 +/- cirrhotic	TN: GT 1, 4, 5 & 6 non-cirrhotic	TN & TE : GT 1a, 1b & 3 +/- cirrhotic	TN: GT1a, 1b & 4 +/- cirrhotic
Int.	EBR/GZR	EBR/GZR	EBR/GZR	EBR/GZR
Comp.	N/A	N/A	N/A	N/A
Tx duration (weeks)	12	12	12	12
Primary outcome	SVR12	SVR12	SVR12	SVR12

Key: EBR/GZR, Elbasvir-grazoprevir; IFN, interferon; RCT, randomised controlled trial; SVR, sustained viral response; TE, treatment-experienced; TN, treatment-naïve

Trial results:
SVR12 rates for EBR/GZR

Study	Subgroup	Sample size (n/N)	SVR12 % (95% CI)
C-EDGE TN	GT1, GT4, and GT6 TN (+/- cirrhosis)	299/316	94.6 (91.5-96.8)
	GT1a TN (+/- cirrhosis)	144/157	91.7 (86.3-95.5)
	GT1b TN (+/- cirrhosis)	129/131	98.5 (94.6-99.8)
	GT4 TN (+/- cirrhosis)	18/18	100 (81.5-100)
C-EDGE TE	GT1 (1a, 1b), GT4 TE (+/- cirrhosis)	97/105	92.4 (85.5-96.7)*
	GT1a TE (+/- cirrhosis)	55/61	90.2 (NR)
	GT1b TE (+/- cirrhosis)	34/34	100.0 (NR)
	GT4 TE (+/- cirrhosis)	7/9	77.8 (NR)

* P value <0.001

Trial results:
SVR12 for EBR/GZR

Study	Subgroup	Sample size (n/N)	SVR12 % (95% CI)
C-SURFER	GT1 TN or TE (+/- cirrhosis)	115/116	99.1 (95.3-100)
C-WORTHY	GT1b TN (without cirrhosis)	12/12	100 (73.5-100)
	GT1a TN (without cirrhosis)	30/31	96.8 (83.3-99.9)
	GT1a or GT1b TN (with cirrhosis)	28/29	96.6 (82.2-99.9)
	GT1a or GT1b TE (+/- cirrhosis)	30/33	90.9 (75.7-98.1)
	GT1a or GT1b HIV co-infected only TN (without cirrhosis)	26/28	92.9 (76.5-99.1)

Trial results:
SVR12 rates for EBR/GZR

Trial	Subgroup	Sample size (n/N)	SVR12 % (95% CI)
C-SCAPE	GT4, GT5, GT6 TN (without cirrhosis)	10/13	76.9 (46.2-95.0)
	GT4 TN (without cirrhosis)	7/7	100 (59.0-100)
C-EDGE CO-STAR	GT1, GT4, GT6 Overall	189/198	95.5 (91.5-97.9)*
	GT1a Overall	146/152	96.1 (NR)
	GT1b Overall	28/29	96.6 (NR)
	GT4 Overall	11/11	100 (NR)

* P value <0.001

Trial results:
SVR12 for EBR/GZR and SOF+PR

Trial	Subgroup	Sample size (n/N)	SVR12 % (95% CI)	Unadjusted difference % (95% CI)
C-EDGE H2H	**EBR/GZR** GT1, GT4	128/129	99.2	8.7*
	SOF+PR GT1, GT4	114/126	90.5	
	EBR/GZR GT1a	18/18	100	0.0 (-18.0 - 18.9)
	SOF+PR GT1a	17/17	100	
	EBR/GZR GT1b	104/105	99	8.7 (3.2 – 16.0)
	SOF+PR GT1b	94/104	90.4	
	EBR/GZR GT4	6/6	100	40 (-10.9 – 78.1)
	SOF+PR GT4	3/5	60	

* P value <0.001

Adverse effects of treatment

- Clinical trials
  - EBR/GZR had a favourable safety and tolerability profile when compared with placebo or SOF+PR, irrespective of cirrhosis stage and treatment experience
  - Most commonly reported AEs were headache, fatigue, nausea
- Network meta-analysis (NMA)
  - EBR/GZR had a better safety profile compared to regimens containing pegylated-interferon alpha and/or RBV, irrespective of cirrhosis stage and treatment experience
  - EBR/GZR had a similar safety profile as all-DAA regimens

Indirect evidence

- Naïve indirect comparison by pooling individual arms of included studies and comparing them directly with each other
  - Company stated that this is the least robust way of comparing treatments across trials
- Network meta-analysis
  - Compared EBR/GZR vs. PR, SMV +PR, SOF + PR, LDV/SOF, OPR + D, DCV + SOF (presented analyses for the 12 subgroups)
  - For the following outcomes: SVR, discontinuation related to AEs (DAE), overall AEs (OAE)
  - Imputed control arms: for each non-comparative trial, an imputed PR control arm was created (estimated from PR arms of comparative trials)
  - Assumptions: GT1 data used as a proxy for GT4

NMA results (random effects) – GT1a

Regimen (treatment duration in weeks)	TN NC		TN C		TE NC		TE C	
	Pooled SVR	RR	Pooled SVR	RR	Pooled SVR	RR	Pooled SVR	RR
EBR/GZR (1-12)	96.72		96.23		92.65		91.14	
PR (1-48)	49.96	1.86	34.00	2.68	38.05	2.28	26.32	4.03
SMV+PR (1-12), PR (13-24) or PR (13-48)	81.76	1.20	60.51	1.50	80.09	1.13	74.36	1.30
SOF+PR (1-12)	97.61	1.05	80.00	1.18	79.93	1.12	71.43	1.33
LDV/SOF (1-8, 1-12)	92.98	1.01	97.15	1.00	98.26	0.96	98.48	0.99
3D+R (1-12, 1-24)	96.10	0.98	92.86	1.04	96.58	0.96	95.38	1.00
DCV+SOF (1-12)	96.67	0.98	-	-	100.00	0.97	-	-

Notes: - Values in red represent those that are statistically significant

- CIs are not presented because of the size of the table

NMA results (random effects) – GT1b

Regimen (treatment duration in weeks)	TN NC		TN C		TE NC		TE C	
	Pooled SVR	RR	Pooled SVR	RR	Pooled SVR	RR	Pooled SVR	RR
EBR/GZR (1-12)	98.27		100.00		99.12		100.00	
PR (1-48)	49.96	1.92	34.00	2.89	38.05	2.58	26.32	3.58
SMV+PR (1-12), PR (13-24) or PR (13-48)	81.76	1.24	60.51	1.58	80.09	1.22	74.36	1.27
SOF+PR (1-12)	96.76	1.00	91.67	1.09	84.68	1.16	50.00	1.60
LDV/SOF (1-8, 1-12)	97.67	1.02	97.15	1.01	98.26	1.00	98.48	1.00
3D+R (1-12, 1-24)	98.84	0.99	100.00	1.01	100.00	0.99	97.83	1.02
DCV+SOF (1-12)	100.00	1.00	-	-	100.00	1.00	-	-

Notes: - Values in red represent those that are statistically significant
- CIs are not presented because of the size of the table

NMA results (random effects) – GT4

Regimen (treatment duration in weeks)	TN NC		TN C		TE NC		TE C	
	Pooled SVR	RR	Pooled SVR	RR	Pooled SVR	RR	Pooled SVR	RR
EBR/GZR (1-12)	96.97		100.00		100.00		66.67	
PR (1-48)	39.47	2.36	25.00	5.26	38.05	2.59	26.32	2.47
SMV+PR (1-12), PR (13-24) or PR (13-48)	84.38	1.09	66.67	1.23	63.64	1.43	46.43	1.45
SOF+PR (1-12)	-	-	83.77	1.11	-	-	64.61	0.96
LDV/SOF (1-8, 1-12)	-	-	97.15	1.00	98.26	1.00	98.48	0.65
2D+R (1-12, 1-24)	100.00	1.00	97.87	1.02	100.00	1.00	96.15	0.68
DCV+SOF (1-12)	-	-	-	-	100.00	1.00	-	-
DCV+PR 1-24 or DCV+PR 1-24, PR 25-48	71.01	1.35	77.78	1.25	71.01	1.34	77.78	0.70

Notes: - Values in red represent those that are statistically significant

- CIs are not presented because of the size of the table

Evidence Review Group's critique

- Search should have included the term "PR", the most used comparator, and not be restricted to English language
- Concerns about the methodology of both naïve ITC and NMA (most of PR data were imputed); the outcomes are considered to be unreliable
  - ERG could not perform a NMA given the available data presented

Key issues for consideration

- Are the following comparators relevant for this appraisal
  - Boceprevir and telaprevir – both excluded from the company analyses
  - Peginterferon alpha plus ribavirin – included in the company analyses
- The robustness of the elbasvir-grazoprevir trials given the following;
  - trials were mostly randomised and 4 out of the 8 trials had a comparator arm (3 placebo controlled trials and 1 active controlled with sofosbuvir)
  - limited data for the genotype 4 population – previously considered by the appraisal committee for similar hepatitis C NICE appraisals
  - the ERG agreed with the company's assessment that the risk of bias in the trials was generally low
- What conclusions can be drawn from the results of the network meta-analysis and naïve comparison given the ERG's concerns?

Lead team presentation
Elbasvir-grazoprevir for treating chronic hepatitis C – Single Technology Appraisal

1st Appraisal Committee meeting: 27 July 2016

Cost Effectiveness

Committee D

Lead team: Matt Bradley

ERG: Kleijnen Systematic Reviews

NICE technical team: Aminata Thiam, Nwamaka Umeweni

Company: Merck Sharp & Dome

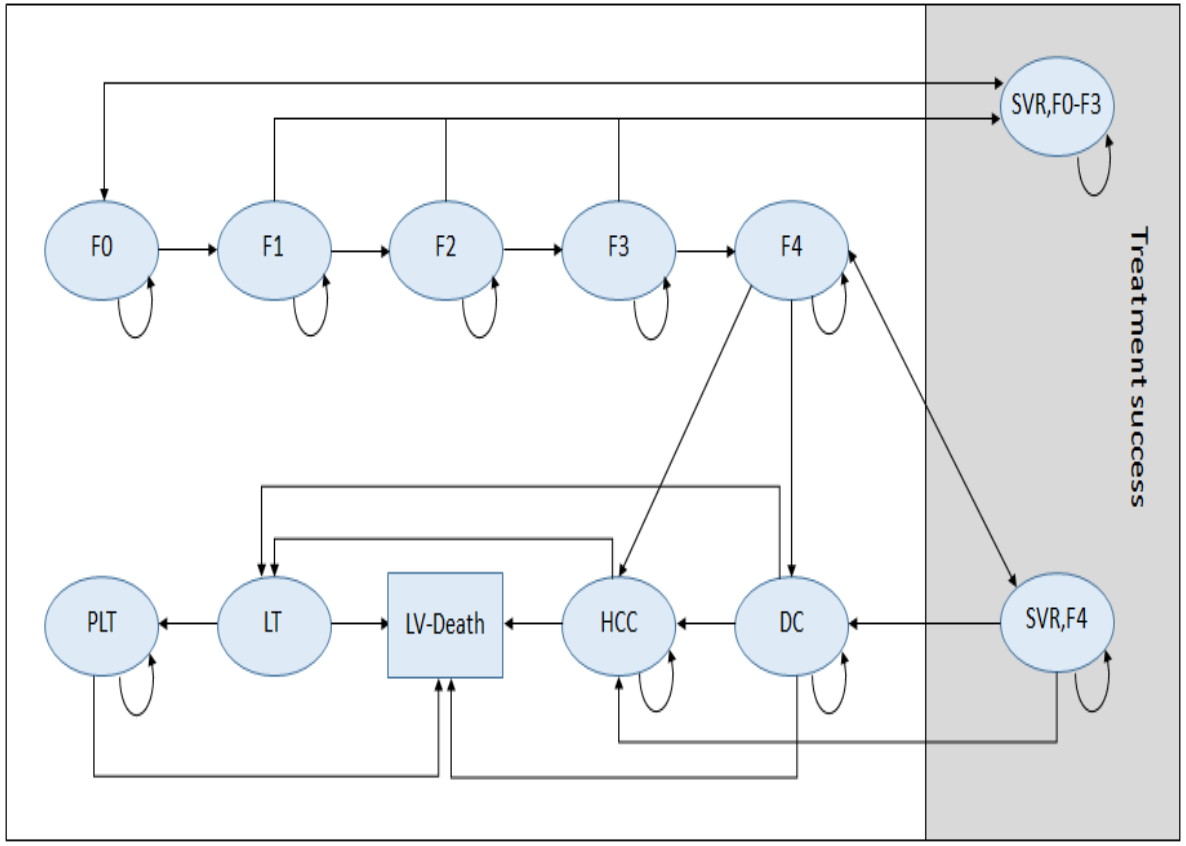
Public observer slides

Preview
Key issues for consideration

- Is the comparison with PR appropriate given the uptake of DAAs?
- Where applied, does the committee accept the use of similar modelling assumptions and subgroups analysis as for previous HC appraisals?
- What is the most plausible ICER based on the committee's preferred assumptions?
- Is elbasvir-grazoprevir an innovative treatment?
- Potential equality issues?

Company's model structure

13 health state-transition Markov model
Life-time time horizon up to 100yrs, starting age of 40 or 45 years



- Consistent with previous Hep C appraisals
- Patients are initially distributed equally within the mild (F0-F1) or moderate (F2-F3) health states (no cirrhosis states) or they may enter the model in the cirrhosis health state (F4)
- Cycle length is 1 year with half cycle correction
- NHS / PSS perspective
- Discount rate 3.5%

Source: source: company's response to clarification, page 100

Company's model inputs and assumptions

Similarities with previous Hep C NICE appraisals

- Patients with HIV co-infection are treated the same as those with HCV mono-infection and have the same outcome
- Genotype 1a or 1b outcome data (SVR, trt. discontinuation and adverse events) were used as a proxy for GT 4 in the base case
- Non-treatment specific transition probabilities of moving to more severe health states were taken from a variety of different studies
- Fibrosis health state utility values and SVR-related utility increment of 0.05 taken from Wright et al., 2006
  - Some of the previous appraisals used values from Vera-Llonch et al., 2013
  - In TA365, the committee concluded that the SVR-related utility value would lie between the trial estimate and the estimate from Wright et al., 2006
- Utility decrements to adjust for the impact of adverse events
- Costs and resource use data similar to previous appraisals

Company's model inputs and assumptions

Differences from previous Hep C NICE appraisals

- Re-infection after achieving SVR results in restarting treatment from F0 (no fibrosis), that is, assuming that liver damage caused by HCV is fully reversible
- SVR, treatment discontinuation rates and adverse events rates for the base case analysis taken from the NMA
  - Outcome data in previous Hep C models taken directly from individual comparator studies or based on naïve indirect comparisons
- Age-based utility decrements included in the model
- Previous models have included boceprevir, telaprevir and peginterferon alpha plus ribavirin (PR)
- PR is the appropriate reference comparator

Treatments & pooled SVR rates

Regimen	Treatment duration	Subgroups SVR % for EBR/GZR and comparators											
		GT1a				GT1b				GT4			
		TN		TE		TN		TE		TN		TE	
		C	NC	C	NC	C	NC	C	NC	C	NC	C	NC
EBR/GZR	12	96.2	96.7	91.1	92.7	100	98.3	100	99.1	100.0	96.7	66.7	100.0
BSC	0	SVR rates assumed to be 0%											
PR	48	34.0	50.0	26.3	38.1	34.0	50.0	26.3	38.1	25.0	39.5	26.3	38.1
SOF/PR	12/12	80.0	97.6	71.4	79.9	91.7	96.8	50.0	84.7	83.8		64.6	
SMV/PR	12/24	60.5	82.0	74.4	80.1	60.5	81.8	74.4	80.1	66.7	84.4	46.4	63.6
2D/3D	3D12/RBV12		96.1		96.6	100.0	98.9	97.8	100.0				
	3D24/RBV24	92.9		95.4									
	3D12												
	2D12/RBV24										100.0		100.0
	2D24/RBV24									97.9		96.2	
LDV/SOF	8		93.0				97.7						
	12	97.2			98.3	97.2		98.5	98.3	97.2		98.5	98.3
DCV	DCV12/SOF12		96.7	98.5	100.0		100.0		100.0				100.0
	DCV24/PR24									77.8	71.0	77.8	71.0

Notes: Values in red represent those where the comparison with EBR/GZR in the NMA showed stat significant differences

Source: Appendix 10, page 246-268 Appendices to CS

Company's utility values & costs

Health states	Utility value		Costs	
	Mean	SE	Mean	SE
F0 – no fibrosis	0.77	0.02	£237.01	£27.71
F1 – portal fibrosis without septa	0.77	0.02	£237.01	£27.71
F2 – portal fibrosis with few septa	0.66	0.03	£289.81	£33.88
F3 – portal fibrosis with numerous septs without cirrhosis	0.66	0.03	£289.81	£33.88
F4 – compensated cirrhosis	0.55	0.05	£512.75	£59.94
SVR, F0	0.82	0.04	£189.27	£157.73
SVR, F1	0.82	0.04	£189.27	£157.73
SVR, F2	0.71	0.05	£983.40	£104.33
SVR, F3	0.71	0.05	£983.40	£104.33
SVR, F4	0.60	0.06	£1,560.82	£307.23
DC - Decompensated cirrhosis	0.45	0.045	£12,508.53	£2,083.38
HCC - Hepatocellular carcinoma	0.45	0.045	£11,146.43	£2,619.42
LT - Liver transplant	0.45	0.045	£37,484.43	£3,956.63
LT - Liver transplant (1st year)	0.45	0.045	£12,972.11	£3,494.66
PLT - Liver transplant (subsequent years)	0.67	0.067	£1,899.60	£486.93

Source: table 5.17 & 5.20, page 95 & 98 of the ERG report

Company's costs and resource use

- For active treatment, only non-cirrhotic costs are presented as they are generally similar to cirrhosis costs

	Initial evaluation	Further investigation
Non-cirrhotic	£642.72	£480.51
Cirrhotic	£838.59	£480.51

	Weekly drug cost (list price)	Weekly active treatment (monitoring cost) Non-cirrhosis			
		8	12	24	48
EBR/GZR	£3,041.67		£1,144.65		
PEG	£130.79				PR: £2,626.98
RBV	£16.22				
SOF*	£2,915.25		£1,144.65		
SMV*	£1,866.50			£1,913.87	
3D	£2,916.67		£1,144.65	£1,392.56	
2D	£2,683.33		£1,144.65	£1,392.56	
LDV/SOF	£3,248.33	£1,020.19	£1,144.65		
DCV	£2,043.15		£1,144.65	£1,392.56	

Note: - SOF and SMV are associated with PR for the cost of the weekly active treatment

- Monitoring costs were derived from previous appraisals and consisted of outpatient appointments, inpatient care, test and investigations

Source: table 5.18 & 5.19, page 97-98 of the ERG report

Company's base case results for GT1a, GT1b and GT4

- Pair-wise ICERs that compared each treatment to PR alone were presented
  - Company did not believe that comparing the new DAAs based on efficacy was justified given that NMA showed no significant differences between these treatments
- Base case ICERs for EBR/GZR compared with PR across the 12 subpopulations were all below £10,000 per QALY gained

Company's deterministic sensitivity analysis

- At a willingness to pay threshold of £20,000 for the comparison of EBR/GZR vs PR the ICER was most sensitive to following variables for all 12 subpopulations:
  - Discount rate for utility
  - Utility of the F4 state in most cirrhotic populations
  - Discount rate for costs
  - Starting age in most non-cirrhotic populations
  - Drug cost for EBR/GZR
  - SVR of EBR/GZR
  - RR of the SVR for PR (reference comparator)
- The probabilistic ICERs appeared similar to the deterministic ICERs

Company's scenario analyses

Scenario analysis	Impact on ICER
SA1: use of GT4 specific clinical data instead of applying GT1 data to GT4	GT4 TE NC: ICER =21,192 £/QALY
SA2: use of naïve indirect comparison results instead of NMA results	ICER <10,000 £/QALY
SA3: use age-dependent transition probabilities across fibrosis health states instead of using age-independent transition probabilities	GT1a TN/TE NC & GT1b TN NC: ICER= 20,000-25,000 £/QALY
SA4: using SVR related utility increments based on European patients from the EBR/GZR clinical trials instead of SVR utility increment from Wright 2006	ICERs increase slightly
SA5: implementing probability of transition from "SVR,F4" state to "SVR,F0-F3" state based on the D'Ambrosio	ICERs decrease significantly in cirrhosis population
SA6: different time horizons (5 and 10 years) instead of life time	All populations: ICERs > £30,000 £/QALY

Company's full incremental analysis

- The company provided a full incremental analysis in an appendix (based on list prices)
- EBR/GZR was cost-effective only in the populations:
  - GT1a TN C
  - GT1a TE C
  - GT4 TE C
- In all other populations, EBR/GZR was either dominated by more cost-effective interventions, or the ICER compared to the previous interventions was above £20,000 per QALY gained
- These results should be interpreted with caution given that there were marginal differences in QALYs across all treatments (small differences in costs had a dramatic effect on the results)

ERG critique (1)

- The ERG noted similar issues to previous TA models that have already been highlighted but accepted
- Differences with previously accepted TA models are
  - Concerns about the approach to modelling utility decrements due to adverse events and ageing that differed from most of the previous TAs: including age-based utility decrements could lead to double-counting
- Additional comments:
  - The ERG noted that the company's model does not account for the genotype 1a group, for whom [redacted] of elbasvir-grazoprevir treatment is recommended in line with the anticipated marketing authorisation
  - The ERG commented that separate subgroup analyses could have been presented for people with HIV co-infection and people who are intolerant to or ineligible for interferon treatment (as per scope)

ERG critique (2)

- Additional comments contd.
  - Potential for clinical differences between the TE populations
    - Previous treatment with a DAA versus non-DAA
    - Intolerance to previous treatment versus inadequate response to previous treatment
  - ERG agreed with the company's position that the NMA and naive indirect comparison should be viewed with caution given inherent limitations with the model inputs
  - Treatment discontinuations resulted from adverse events only

ERG exploratory analysis

- The ERG revised the company's base case using the following preferred assumptions:
  - Adjusting the model structure so that patients who become re-infected after achieving an SVR return to their pre-SVR fibrosis health state
  - Using SVR-related utility increments derived from the European subgroup of the EBR/GBR trials
  - Excluding age-based utility decrements from the base case
- The list price ICERs for EBR/GZR compared with PR for the no cirrhosis subpopulations increased by approximately £3,000 per QALY gained, whereas the ICERs for the cirrhosis populations were similar to the company's base case ICERs

ERG's scenario analysis

The ERG conducted 7 scenario analyses:

1. GT4 data replacing GT1 data in this population for SVR, AEs and discontinuations
2. Replace NMA SVR data with naive indirect comparison SVR, AEs and discontinuation rates
3. Applying age dependent transition probabilities across fibrosis health states
4. Company's base case assumption of patients returning to health state F0 after re-infection
5. Company's base case assumption of a uniform disutility for AEs but set to 0.035 (equal to DCV/SOF)
6. Company's base case assumption of SVR related utility increments from Wright et al., 2006
7. Company's base case assumption applying age-based utility decrements

ERG's scenario analysis

Base-case pairwise ICERs for EBR/GZR vs. PR

With the exception of scenario 1 for GT4, TE-C (£22,125 per QALY), only scenario 3 resulted in ICERs for EBR/GZR above £20,000 per QALY

Scenario 3 Population	ICER (£/QALY)
GT1a	
TN NC	37,920
TE NC	34,782
GT1b	
TN NC	35,350
TE NC	27,799
GT4	
TN NC	29,385
TE NC	26,952

Source: table 5.48 – 5.59, page 145 - 156 of the ERG report

ERG's full incremental analysis

- The ERG's full incremental analysis led to similar conclusions as the company's analysis (based on list prices)
- EBR/GZR was cost-effective only in the populations:
  - GT1a TN C
  - GT1a TE C
  - GT4 TE C
  - GT4 TN C (£21,335 per QALY)
- In all other populations, EBR/GZR was either dominated by more cost-effective interventions, or the ICER compared to the previous interventions were above £20,000 per QALY gained
- These analyses should be viewed with caution given the uncertainties previously identified

Equality issues

- The following potential equality issues were raised:
  - A higher prevalence of disease or specific genotypes (genotype 4) in people who inject drugs and among minority ethnic groups
    - From company and professional organisations
  - There is stigma associated with people who have hepatitis C and chronic kidney disease because they are made to receive dialysis treatment in a separate ‘special’ room
    - From company
  - People with HIV co-infection are more likely to disclose their HIV status than their hepatitis C status because of the perceived stigma around hepatitis C due to lack of hepatitis C awareness
    - From company

Innovation

- The company stated that there is significant unmet need in people with chronic hepatitis C complicated by severe renal disease. The label of EBR/GZR does not require dose adjustment with regard to any degree of renal impairment

Key issues for consideration (1)

- Is the comparison with PR appropriate given the uptake of DAAs?
- Where applied, does the committee accept the use of similar modelling assumptions as for previous HC appraisals?
  - Use of Wright et al., 2006 vs trial data for health state utility values and SVR-related utility increment
  - Using genotype 1 data as a proxy for genotype 4 (acceptable in previous TAs)
  - Dynamic model to capture impact of future transmissions
  - HIV co-infection treated the same as mono-infection, therefore no separate subgroup analysis
- The committee's views on other assumptions used in the company's model:
  - Clinical input data, given the ERG's concerns about the robustness of the network meta-analysis
  - Including age-based utility decrements
  - Assumption that liver damage is fully reversible

Key issues for consideration (2)

- Should subgroup analyses have been presented for
  - Intolerance to or ineligible for interferon treatment (included in some but not all previous TAs)
  - Treatment with a DAA versus non-DAA (in the EBR/GZR trials all patients received non-DAA treatments while 2 comparator trials present SVRs for DAA-experienced patients)
  - Mild disease (F0-F1) and moderate disease (F2-F3)
- What is the most plausible ICER based on the committee's preferred assumptions?
- Is elbasvir-grazoprevir an innovative treatment?
- Potential equality issues?