NICE National Institute for Health and Care Excellence

Sofosbuvir-velpatasvir for treating chronic hepatitis C

2nd Appraisal Committee Meeting
Single Technology Appraisal
26 October 2016

ACD preliminary recommendations

1.1   Sofosbuvir-velpatasvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1, only if the company provides the drug with the discount agreed in the simple discount agreement.

1.2   It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.

1.3   This guidance is not intended to affect the position of patients whose treatment with sofosbuvir-velpatasvir was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

ACD preliminary recommendations

HCV GT	Liver disease stage	Treatment	Untreated HCV	Treated HCV
1	With or without compensated cirrhosis	SOF-VEL	✔	✔
2	Without cirrhosis	SOF-VEL	only if interferon not tolerated/suitable	✔
	Compensated cirrhosis	SOF-VEL	✔	✔
3	Without cirrhosis	SOF-VEL	✔	✔
	Compensated cirrhosis	SOF-VEL ± ribavirin	✔	✔
4	With or without compensated cirrhosis	SOF-VEL	✔	✔
5	With or without compensated cirrhosis	SOF-VEL	✔	✔
6	With or without compensated cirrhosis	SOF-VEL	✔	✔
1–6	Decompensated cirrhosis	SOF-VEL + ribavirin	✔	✔

Abbreviations: GT, genotype; HCV, hepatitis C virus
Treated – the person's hepatitis C has not adequately responded to interferon-based treatment

ACD: key conclusions (1)

4.1	Clinical management	Unmet need for interferon- and ribavirin-free regimens, particularly for GT3 HCV
4.2	Comparators	Appropriate to exclude comparators: • boceprevir + peginterferon alpha & ribavirin • telaprevir + peginterferon alpha & ribavirin • daclatasvir + peginterferon alpha & ribavirin (GT4) • simeprevir + peginterferon alpha (GT4)
4.5	Efficacy of SOF/VEL	SOF-VEL is effective (SVR 89–100%)
4.7	Model structure	Appropriate health states
4.8	Reinfection & transmission	• ERG estimate of reinfection rate (2.4%) too high • Company's base case model (excluding reinfection and transmission) acceptable for its decision-making

GT, genotype; HCV, hepatitis C virus

ACD: key conclusions (2)

4.9, 4.10	SVR rates in model	• Company's method of estimating SVR for comparators introduced uncertainty in results • SVR for PR appropriate o Although **possible** to identify people more likely to respond to treatment, this is **not routine practice** in UK • Model acceptable for decision-making
4.11	TPs for developing cirrhosis	• Study used to inform TPs (Kanwal et la. 2014) was generalisable to the UK • Adjusted data from Kanwal should be used (company base case used unadjusted data)
4.12	TPs for progression in people with cirrhosis	• TPs lie between estimates from Cardoso et al. 2010 and Fattovich et al. 1997

GT, genotype; PR, peginterferon alpha + ribavirin; SVR, sustained virological response; TP, transition probability

ACD: key conclusions (3)

4.16, 4.17	Most plausible ICERs	ICERs incl. preferred assumptions available for 2 subgroups: • untreated GT2 HCV without cirrhosis (between £35,091 and £39,783 per QALY) • untreated GT3 HCV without cirrhosis (between £15,923 and £18,362 per QALY gained) Impact of including preferred assumptions for other GTs: • ICERs likely to remain below £20,000 per QALY gained • regardless of HCV genotype, treatment history and cirrhosis stage
4.19	No analyses of SOF-VEL + RBV in GT3 with cirrhosis	Adding RBV would have minimal impact on ICERs because: • acquisition cost of ribavirin much lower than SOF-VEL • ICERs lower with cirrhosis than without cirrhosis SOF-VEL + ribavirin recommended in this population

GT, genotype; ICER, incremental cost-effectiveness ratio; RBV, ribavirin

ACD consultation responses

- **Consultees**
  - British HIV Association
  - British Society of Gastroenterology (endorsed by Royal College of Physicians)
  - British Viral Hepatitis Group (BVHG) / British Association for the Study of the Liver (BASL)
  - Gilead (sofosbuvir-velpatasvir)
  - Hepatitis C Trust
- **Commentators**
  - AbbVie (ombitasvir-paritaprevir-ritonavir)
- **Experts**
  - No comments
- **Members of the public/healthcare professionals**
  - No comments

Issues arising from consultation

1. Paragraph 1.2 of ACD is unclear

   1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.

2. Sofosbuvir-velpatasvir less effective for genotype 3 HCV in people with resistance-associated mutations

3. Uncertainty in company's estimates of sustained virological response rates for comparators

4. Utility estimates not sourced from trials

Issues arising from consultation: ACD paragraph 1.2 unclear

- Same wording was used in TA363, TA364 and TA365
  - concerns that clinicians might be overwhelmed by demand
  - NICE intended to prioritise patients according to clinical need
  - wording relates to system capacity and not cost / affordability

- NHS England have capped the number of people offered treatment for hepatitis C (10,000)
  - consultees consider that this cap resulted from misinterpretation of paragraph 1.2
  - people with advanced liver disease are being offered treatment, whereas people with mild disease are not

Issues arising from consultation: mutations associated with resistance (1)

- Sofosbuvir-velpatasvir may be less cost-effective in people with genotype 3 HCV who have the Y93H resistance-associated variant (RAV)

- Y93H RAV associated with lower sustained virological response rates at 12 weeks (SVR12) – see table

- 9% of people in ASTRAL-3 had the Y93H RAV

	SVR12 in ASTRAL-3	
	With Y93H RAV	Without Y93H RAV
people without cirrhosis	90.5% (19/21)	98.8% (171/173)
people with cirrhosis	50.0% (2/4)	93.4% (71/76)

commentator considers these might be overestimates – see next slide

Issues arising from consultation: mutations associated with resistance (2)

- ASTRAL-3 may have overestimated SVR12 in people with the Y93H resistance-associated variant

- Resistance-testing in ASTRAL-3 inconsistent with European guidelines for treating hepatitis C:
  - ASTRAL-3 used a 1% detection threshold (that is, included people with resistance-associated variants in >1% of HCV sequences)
  - European Association for the Study of the Liver (EASL) guideline (2016) recommends a 15% threshold

- Including people with clinically irrelevant resistance levels could overestimate the SVR12 rate

Mutations associated with resistance: comments from experts

- Effect of the Y93H mutation
  - associated with lower SVR
  - especially in GT1a, people with cirrhosis and/or disease which has not responded to pegylated interferon-based regimens
  - only affects efficacy of NS5A inhibitors such as velpatasvir
- Clinical practice
  - Y93H mutation not routinely tested in the NHS
  - no commercially available test, difficult to perform, unreliable results
  - no consensus on threshold for significant level of RAVs
  - detection of mutation (before/during treatment) would not alter practice
- Analysis of people with resistance in ASTRAL-3
  - reasonable to assume 9% UK patients with GT3 HCV have Y93H RAV
  - only 4 people with the mutation did not have SVR12
  - does not alter validity of ASTRAL-3 relevant to current clinical practice

European Association for the Study of the Liver (EASL) guideline (2016)

- Systematic testing for HCV resistance prior to treatment is not recommended. Indeed, this obligation would seriously limit access to care and treatment regimens can be optimized without this information (**B1**).

- Physicians who have easy access to a reliable test assessing HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93) can use these results to guide their decisions, as specified in these recommendations. The test should be based on population sequencing (reporting RASs as "present" or "absent") or deep sequencing with a cut-off of 15% (only RASs that are present in more than 15% of the sequences generated must be considered) (**B1**).

Issues arising from consultation: estimates of SVR rates for comparators

- Concern that SVR estimates based on a single source for each treatment in each sub-group

- Suggestion: scenario analyses using mean estimates from all available sources (incl. observational and non-randomised studies)

- *Notes from NICE technical team:*
  - *Committee shared this concern (ACD paragraph 4.9)*
  - *Hearing that the rates for peginterferon alpha plus ribavirin were appropriate[a], committee concluded that results based on company's estimates of SVR were acceptable for decision-making (ACD paragraph 4.10)*
  - *[a]cost-effectiveness results were sensitive to SVR for peginterferon alpha plus ribavirin in people without cirrhosis; estimates for other comparators had less of an effect*

Issues arising from consultation:
utility estimates not sourced from trials

- Utility estimates in the model were taken from published literature (Wright et al. 2006 and Vera-Llonch et al. 2013) instead of sofosbuvir-velpatasvir clinical trials

- This practice represents inconsistent use of data sources

- Suggestion: exploratory analyses using trial utility values

- *Notes from NICE technical team:*
  - *Committee shared this concern but accepted the company's estimates (ACD paragraph 4.13)*
  - *In line with previous technology appraisals for chronic hepatitis C*
  - *Company stated that SF-36 data from clinical trials not formally mapped to produce SF-6D utility values for economic model*

Key issues for discussion

Do any of the responses to consultation change the committee's preliminary recommendations?

- Wording of ACD paragraph 1.2
- Mutations associated with resistance in GT3 HCV
  - Are these mutations routinely tested for in the NHS?
  - Does clinical practice differ when mutations are detected?
  - How robust is the analysis in this group of ASTRAL-3?
  - Effect of mutation on SVR12 with comparator treatments eg peginterferon alpha plus ribavirin?