Gilead Consultation Response – 29th August 2014

Single Technology Appraisal – Appraisal Consultation Document –Sofosbuvir for treating chronic hepatitis C

Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). We recognise the complexity of this appraisal and have welcomed both the engagement of NICE and the Appraisal Committee throughout the process in accepting and considering relevant data. We have also appreciated the opportunity to respond to comments during the Appraisal Committee meetings and feel that this has helped address areas of uncertainty and enabled the Committee to release these provisional recommendations for consultation.

We have provided comments below in response to the specific consultation questions. In addition points of clarification and factual inaccuracies relating to specific sections of the ACD are provided in the following table.

- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

We welcome the provisional recommendations that sofosbuvir should be made available for the majority of adult patients with chronic hepatitis C and are pleased that the Committee has recognised the significant unmet need for genotype (GT) 1 treatment experienced patients. We are disappointed that the Committee was unable to give a positive provisional recommendation for people with GT4 and ask the Committee to re-consider their current recommendation for this patient group as GT4 HCV is an area of significant unmet need.

Whilst HCV genotype 4 (GT4) only accounts for 5% of all HCV genotypes in the UK, the prevalence of GT4 in the UK is increasing due to migration, HIV/HCV co-infection and intravenous drug use. GT4 HCV is also typically less responsive to interferon/ribavirin based therapy and the currently NICE-approved oral direct acting agents (DAAs - telaprevir and boceprevir) are not indicated for this patient subgroup.

We appreciate the Committee's concern that the evidence base for GT4 is limited but would highlight that sofosbuvir (in combination with peginterferon alfa and ribavirin for 12 weeks) is the only direct acting HCV antiviral agent to have been studied in this population in Phase 3 trials to date. In the Phase 3 study NEUTRINO treatment with sofosbuvir resulted in high rates of SVR12 in GT4 patients (sub-group analysis: 27/28 patients; 96%).

- In addition, this ICER whilst considered conservative (since the SVR for cirrhotic patients [50%] is based on only 2 patients), demonstrates that sofosbuvir is cost-effective in patients with GT4-6 HCV with an ICER falling within the £20,000 to £30,000 range. This ICER would also likely become lower in the event benefits such as relief of cognitive ability and public health benefits were taken into account, a factor recognised in the ACD (Section 4.39).

- **Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence**

Yes, whilst recognising the complexity of this appraisal we believe these are reasonable interpretations. We have provided comments on areas which would benefit from additional clarification and factual inaccuracies in the attached table.

- **Has all of the relevant evidence been taken into account?**

Whilst we can confirm that all relevant clinical trial evidence has been taken into account we are disappointed that despite the available evidence the Committee felt unable to provide a positive recommendation for the use of sofosbuvir in GT4 HCV patients despite the evidence that sofosbuvir is both clinically and cost-effective in this group. Further details are provided above.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

No and we support the statements in the ACD (Sections 4.11 and 4.38) that any recommendations on the use of sofosbuvir do not exclude patients with present or previous drug use (Section 4.38) or HCV/HIV co-infected patients (Sections 4.11).

- **Given the requirement for relevant health bodies (clinical commissioning groups, NHS England and local authorities) to provide funding to ensure that the health technology is available within 3 months, from the date the recommendation is published by NICE (see section 5.1), is an extension to this normal period appropriate because any of the following circumstances apply:**
    - **The health technology cannot be appropriately administered until training is in place?**
    - **The health technology cannot be appropriately administered until certain health service infrastructure requirements including goods, materials or other facilities are in place?**
    - **The health technology cannot be appropriately administered until other appropriate health services resources, including staff, are in place?**

There are no reasons for an extension to be given for relevant health bodies to provide funding to ensure sofosbuvir is available within three months of the final guidance being published by NICE. No training is required to administer sofosbuvir and there is no requirement for any additional infrastructure or resources to be put in place.

Given the clear and significant unmet need for patients who would benefit from access to this new technology we feel it is imperative that this guidance is published without delay.

We look forward to the final recommendations and respectfully request that the Committee considers expanding the provisional recommendations to include the use of sofosbuvir in GT4 HCV patients.

Clarification comments and factual inaccuracies

Page	Section	Comment
36	3.62	Factual inaccuracy The following statement is incorrect: '*Using the estimates from Roberts et al. the manufacturer's ICER for sofosbuvir plus peginterferon alpha and ribavirin compared with peginterferon alpha and ribavirin increased to £18,209 per QALY gained'* The estimates used by the ERG were 51% (F0-F2) and 24% (F3-4) rather than 51% (F0-3) and 6%, (F4). Had these figures been used the ICER would actually have been below the Gilead base case. We would recommend that the current text is amended as follows: '*Using the following estimates from Roberts et al.51% (F0-F2) and 24% for people (F3-4) the manufacturer's ICER for sofosbuvir plus peginterferon alpha and ribavirin compared with peginterferon alpha and ribavirin increased to £18,209 per QALY gained'*
58	4.16	Clarification Clarification is required as to which GT following sentence refers. *'The Committee noted that the ICER from the combined cohort appeared artificially low, considering that the majority of the subgroup would not have cirrhosis*' We would also highlight that this statement does not make sense given that the economic model is based on the % split of cirrhotic and non cirrhotic patients taken from the UK HCV research database:
60	4.18	Clarification The following statement is incorrect: *'It also noted that the ERG considered the estimates from Hadziyannis to be more relevant because they were most generalisable to patients with HCV in England. This was because the study included people with the genotypes most relevant to the UK population, that is, genotypes 1 and 3.'* The economic analysis considered only patients with GT1 HCV and to state that Hadziyannis

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		was more relevant because it included both patients with GT1 and GT3 HCV is misleading as only GT1 HCV patients were relevant in the analysis. We recommend that the text is amended to clarify as follows: *It also noted that the ERG considered the estimates from Hadziyannis to be more relevant because they were most generalisable to patients with HCV in England. This was because the study included people with the genotypes most relevant to the UK population, that is, genotypes 1 and 3.' It was clarified by the manufacturer that the ICER presented for this particular analysis was only relevant for the GT1 patient subgroup and thus the given ERG rationale would not apply in this context.*
61	4.19	Clarification The following statement is misleading: '*generic cost of ribavirin had a small effect on the ICER as demonstrated by the ERG analysis and that sensitivity analyses around the generic costs of comparator treatment was appropriate'*. In the scenario analysis model Gilead submitted in response to the initial ACD the primary factor driving increased ICERs/QALY was the use of a generic ribavirin price. In addition use of generic ribavirin should therefore not be considered the standard ribavirin of choice due to its low market share and restrictions for use in combination with peginterferon alfa-2a (generic ribavirin is only licensed for use with peginterferon alfa-2b and not 2a). This point was raised in the ERG's report on the Gilead additional analysis (page 10) the ERG noted '*that the manufacturer's model analyses have been conducted using peginterferon alfa-2a, and it is therefore not appropriate to use a generic ribavirin in these analyses'*.
63	4.21	Clarification It would be helpful to add that while quality of life was measured in the clinical trials patients were not aware of their SVR status when completing the quality of life questionnaires during post treatment follow up. We would recommend the addition of the following text to highlight this and also additional text to explain why the data was not used in the model: *'The Committee noted that the manufacturer stated it would not be appropriate to use any*

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		such data because patients were not aware of their SVR status when completing the QoL questionnaires post treatment. ~~it was unable to incorporate the estimates from the pivotal clinical trials because the data were not available~~, but provided a revised base-case model incorporating an alternative utility increment (0.041; Vera-Llonch et al. 2013) after a sustained virological response'
70 and 71	4.30 and 4.31	Typographical error VALANCE should be VALENCE
72 - 73	4.32	Clarification In response to the Committees view that there is '*some uncertainty*' that the 24 week regimen of sofosbuvir plus ribavirin will not be used in clinical practice in patients for whom interferon therapy is suitable we would like to reiterate: • Gilead is not requesting, nor do we anticipate, that any patient who is interferon eligible would be given the option of the 24 week IFN-free sofosbuvir regimen. For patients with genotypes 1, 4, 5 and 6 HCV, section 4.4 of the Summary of Product Characteristics for sofosbuvir states that interferon-free regimens *'should only be used for patients that are intolerant to or ineligible for interferon, therapy, and are in urgent need of treatment.'* • UK clinical opinion has consistently asserted that where interferon can be tolerated by the patient the 12 week regimen would be preferable for reasons of efficacy, overall treatment duration as well as cost.
72 - 75	4.32 to 4.35	We would ask the Committee to reconsider their recommendation for patients with GT4 HCV and have provided further details in response to the specific consultation questions.
77 - 85	Summary of Appraisal Committee's key conclusions	Typographical errors • Page 84, 3rd paragraph, last sentence: 'like' should be 'lie' • Page 85, incorporation of health-related quality-of-life benefits and utility values should reference section 4.39 in addition to the sections already listed (4.12, 4.34 and 4.36)

Page	Section	Comment
		• Page 86, Equalities considerations and social value judgements: section number 4.28 should be 4.38