NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C [ID731]

Dear [redacted],

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have now had an opportunity to take a look at the submission by AbbVie received on 16/12/2014. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **4 February 2015**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Anwar Jilani, Technical Lead (anwar.jilani@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (kate.moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Literature searching

1. **(Priority question)** Please provide details regarding the identification and selection of studies of telaprevir, used as the historical comparisons for 3D/2D regimens (for example search criteria, screening methods, and a flow chart explaining reasons for excluded studies).

2. **(Priority question)** Please clarify how studies were identified and selected to derive the sustained virological response rates (SVR) presented in Table 58 of the submission.

3. **(Priority question)** The submission lists Hezode *et al* 2014 and Pol *et al*. as the primary study references for the PEARL-I trial (in Table 25,) but neither of these has been supplied to the ERG and the full reference for Pol *et al* is not listed in the reference list. Please supply these references.

4. Reference 37 for the M14-103 study 'Integrated Summary of Efficacy (ISE). AbbVie data submission to EMA 2014' has not been included with the other references. Please supply this reference.

5. Please provide a flow chart showing the inclusion and exclusion of clinical effectiveness studies of 3D/2D, and provide reasons for exclusion of studies.

6. Please provide the full reference for the ILLUMINATE telaprevir study.

Quality assessment

7. **(Priority question)** The detailed quality assessment for the study 'PEARL I' is missing (Appendix 10, p126). Please provide this.

8. Please provide details of the study screening, data extraction, quality assessment processes, and measures taken for quality control of the systematic review (for example whether the data extraction was undertaken by more than one reviewer, did reviewers carry out these tasks independently of each other, whether there was any protocol for identifying and resolving disagreements)?

Clinical trials and evidence synthesis

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9. **(Priority question)** Please provide baseline characteristics of participants in the studies included for the estimation of sustained virological response (SVR) with telaprevir and used as historical control rates for comparison with 3D/2D regimens (such as ADVANCE, ILLUMINATE and REALIZE). Please comment on any similarities and/or differences to the populations in the 3D/2D studies.

10. Please provide information about the dosing regimens used in the above mentioned telaprevir studies (question 9).

11. Please provide the clinical study reports for all the 2D and 3D trials included in the submission.

12. Please explain whether a network meta-analysis was considered for comparators where complete networks existed?

13. In section 6.6 of the submission (regarding meta-analysis), only random effect estimates are presented. Please provide the corresponding fixed effects estimates (Figure 17-19).

14. Section 6.5.1.7 of the submission (page 175) states that only arms G and L of the AVIATOR trial used treatment regimens of 3D that are relevant to the proposed marketing authorisation. The regimen used in arm E also seems relevant to the proposed marketing authorisation (for genotype 1b non-cirrhotic patients) – please clarify why the company does not consider arm E relevant.

15. Please provide the SVR rates (% achieving SVR) for GT1a and GT1b in the AVIATOR trial who received regimens E, G and L. Please also provide SVR rates for GT1a and GT1b patients in the M14-103 trial.

16. Please clarify the exact doses of each drug used in the 3D + RBV treatment regimen in the M14-103 trial.

Section B: Clarification on cost-effectiveness data

Literature searching

17. **(Priority question)** The base case analysis uses non-treatment-specific transitional probabilities as described in Shepherd et al. (2007) which were based on the economic evaluation undertaken alongside the UK Mild hepatitis C Trial (Wright et al. 2006).It is not clear whether any general or targeted searches were conducted to identify new evidence to update these transition probabilities. Please state whether any such searches were undertaken. If so please provide details.

Model validation

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18. **(Priority question)** Please provide a full description of the independent, technical and internal model validation exercise carried out by the company, as referred to in section 7.8.1.

Resource use and costs

19. **(Priority question)**The submission states that the treatment costs for all treatment regimens were based on mean treatment duration from selected clinical trials, using data on treatment discontinuation. Did these estimated treatment costs include all potential stopping rules (including response-guided treatment for telaprevir and boceprevir as well as futility-based stopping rules for pegylated interferon plus ribavirin)?

20. Please clarify whether all potential stopping rules (including response-guided treatment for telaprevir and boceprevir) were included in the calculation of treatment costs in the probabilistic sensitivity analysis? If so please explain how.

Modelling of treatment effect and uncertainties

21. **(Priority question)** Please provide details on how the SVR was calculated in the probabilistic sensitivity analysis. Please clarify whether methodological uncertainty arising from the assumption of the proportionate difference in SVRs by fibrosis stage and sub-genotypes (section 7.3.1), is captured in the probabilistic sensitivity analysis.

22. Please provide further detail on the approach to sampling SVRs for parameter uncertainty in the probabilistic sensitivity analysis. The description in section 7.6.3 refers to using beta distributions and suggests that these were sampled between imputed lower and upper bounds (derived for the deterministic sensitivity analysis), while tables in section 7.3.1 report number with SVR and sample size for trials (n/N) and also imputed values for those subgroups where data were not available.

    - Please clarify exactly how variation for the SVRs was estimated and how the values were sampled in the probabilistic sensitivity analysis.
    - Please clarify whether correlation between SVR for each treatment regimen, stratified by fibrosis stage and/ or sub-genotype, was included in the probabilistic sensitivity analysis. If so please explain how.

Utility values

23. Section 7.4.7 of the company's submission states that "for health states beyond compensated cirrhosis, such as DCC [decompensated cirrhosis] and HCC [hepatocellular carcinoma], we extrapolate the decrement observed in Wright et al. (2006) between mild health state and DCC and HCC onto the EQ-5D scores of mild Hep

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C patients collected in our trails [sic] to derive utility values for DCC and HCC". However Table 100 in section 7.3.6 states the sources for utility values beyond compensated cirrhosis as Grieve et al. (2006); Wright et al. (2006); Shepherd et al. (2007); Hartwell et al. (2011). Please clarify the source for the utilities used for health states beyond compensated cirrhosis.

24. The submission presents EQ-5D-3L utilities (calculated using the UK cross-walk to EQ-5D-5L) in Tables 104 and 105 for each trial separately.

    - Did the company consider pooling utility values from comparable populations?
    - Please provide further information on the justification for applying the UK cross-walk to responses from non-UK participants.
    - Separately for each trial, please provide a summary of baseline and end of treatment EQ-5D-3L estimates using the UK crosswalk from the EQ-5D-5L collected exclusively from the UK participants (accepting there are likely to be very small numbers or zero counts for some cells).

25. The company's submission states that EQ-5D-5L utility values, derived from the clinical trials, were not suitable for use in the model as only 5.7% of the total enrolled adult population were UK patients. Please clarify whether the utility decrements applied for adverse events, derived from the clinical trials (Table 110, section 7.4.8) were based on all patients or the sub-group of UK patients.

Section C: Textual clarifications and additional points

26. Please explain the term "historical control" used in the submission. The ERG understands this to mean an analysis of matched patient-level data. However the historical control used in the submission (and to calculate power of the trials) appears to be the overall SVR reported from telaprevir trials, where matching has only been attempted at the aggregate level (in terms of genotype and degree of fibrosis [non-cirrhosis versus cirrhosis]). Please clarify.