Dear [redacted]

This is agreeable with the expectation that any name from us will be left out leaving the factual response.

I take also the opportunity to clarify that when we say that "CHMP interpretation is not towards allowing 12 weeks of treatment" we mean that CHMP could not make any recommendation on 12 weeks of treatment.

Best Regards

[redacted]

From: [redacted]
Sent: 11 June 2015 13:18
To: [redacted]
Cc: [redacted]
Subject: RE: Query regarding marketing authourisation of ombitasvir-paretaprevir-ritonavir and dasabuvir for chronic hepatitis C

Dear [redacted]

Thanks for your response.

We would also like to share your responses with the Appraisal Committee at NICE before the second meeting that will be developing the final guidance to the NHS. These will form part of a formal document and be shared on our website to support our decision-making.

Please can you confirm that our request to share this information is mutually agreeable with the EMA?

We would highly appreciate an urgent response.

Kind regards,
Dr [redacted]
Technical Analyst (Appraisals)
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza | Manchester M1 4BT | United Kingdom
Tel: [redacted]
Web: http://nice.org.uk

From: [redacted]
Sent: 29 April 2015 12:30
To: [redacted]; [redacted]
Cc: [redacted]
Subject: RE: Query regarding marketing authourisation of ombitasvir-paretaprevir-ritonavir and dasabuvir for chronic hepatitis C

Dear [redacted]

Thank you very much for your email and for your query.

The CHMP interpretation of the data from the TURQUOISE II study is not towards allowing 12 weeks of treatment in cirrhotic patients in any subgroup. In the published EPARs of both Viekirax (available here: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003839/WC500183999.pdf) and Exviera (available here:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003837/WC500182235.pdf), it is clearly stated in section "Discussion on clinical efficacy", e.g. in the Viekirax EPAR on page 116, that

"During the assessment procedure, the applicant ***proposed different algorithms to identify a subset of GT1a cirrhotic patients for whom 24 weeks of therapy would be indicated, presuming that those not fulfilling criteria might be treated for 12 weeks****. These include prior null responder status or, alternatively, having one or more biomarkers of more advanced disease (platelets, alfa-fetoprotein, albumin) with certain cut-offs (see above).* ***Such approaches however, are fraught with uncertainty****. Given the similar tolerability of 12 and 24 weeks of therapy (the proportion of patients stopping therapy due to adverse events in the Turquoise study was 4/208 versus 4/172 for the two durations), and the abovementioned uncertainty of the effectiveness of retreatment options,* ***a 24 week course of therapy is considered appropriate for all GT1a patients with compensated cirrhosis****.*
Nevertheless, the CHMP agreed to include the information originating from the post hoc analysis on the risk of relapse in subgroups of GT1a cirrhotics in section 5.1. of the Exviera SmPC.*"*

The same is explained in section 2.5.2.2.3. "Patients with genotype 1a or 1b virus and compensated cirrhosis" of the EPARs, e.g. on page 108-109, where the Turquoise II study results are discussed:

"In an attempt to further understand the determinants of relapse after 12 weeks, in order to identify those cirrhotic GT1a patients most suitable for 12 or 24 weeks of therapy, the applicant further analysed this dataset by logistic regression. Some traditional prognostic factors, such as age and baseline HCV RNA, were unrelated to relapse. Former injection drug use identified 10 of the 11 relapsers, but the biological plausibility of this marker is uncertain. IL28b genotype was also associated with relapse, but only when comparing TT genotype with non-TT genotype. Male sex was marginally associated with relapse.
Higher AFP, lower platelets, and lower albumin, all factors identifying patients with more advanced cirrhosis, were each significantly associated with relapse. These variables collectively identified all of the prior null responders who relapsed and 3 of the 4 treatment-naïve subjects who relapsed.

Table 20. Relapse by Baseline Values of AFP, Platelets, and Albumin (12 weeks treatment groups) *Group*	*All*	*Prior Null Responders*	*Subjects Without Prior Null Response*
*Subjects with 1 or more unfavorable values**	*10/48 (20.8%)*	*7/25 (28%)*	*3/23 (13%)*
*Subjects with all 3 values favorable**	*1/87 (1.1%)*	*0/22 (0%)*	*1/65 (1.5%)*
P value	*< 0.0001*	*0.01*	*0.05*

While it is recognized that Gt1a cirrhotics with a higher risk of relapse on 12 weeks of therapy could be identified post hoc using various biologically plausible baseline characteristics, and particularly that data indicate that cirrhosis associated with low platelets or biochemical abnormalities is a risk factor for relapse with a shorter treatment durations, the actual cut-offs presented above are considered clinically arbitrary."

I hope the above clarifies.

Kind regards

[redacted]

From: [redacted]
Sent: 22 April 2015 17:44

To: [redacted]
Cc: [redacted]
Subject: Query regarding marketing authourisation of ombitasvir-paretaprevir-ritonavir and dasabuvir for chronic hepatitis C

Dear [redacted] and [redacted],

I was given your name by [redacted] here at NICE who mentioned you recently helped with a query on the marketing authorisation for ledipasvir-sofosbuvir from chronic hepatitis C. I was hoping that you may be able to assist with a query we have regarding the marketing authorisations for ombitasvir/paritaprevir/ritonavir (Viekirax) and dasabuvir (Exviera) for chronic hepatitis C; or if not, direct it to the appropriate person in the organisation to provide a response.

Ombitasvir/paritaprevir/ritonavir with or without dasabuvir is currently being appraised through the Single Technology Appraisal process at NICE. An Appraisal Committee is meeting in early May to develop provisional recommendations and NICE would like to clarify a question it has about the licensed use of ombitasvir/paritaprevir/ritonavir with dasabuvir plus ribavirin specifically in people with **genotype 1a** chronic hepatitis C **with cirrhosis**.

The summary of product characteristics (SmPC) for both drugs (Table 1 in section 4.2) indicates that the recommended treatment duration for people with genotype 1a chronic hepatitis C with cirrhosis is **24** weeks; it then also states "(see section 5.1"). Abbvie (the manufacturer of both products), on the other hand, feels that that the SmPCs allow for a **12** week treatment in some people with genotype 1a chronic hepatitis C with cirrhosis, specifically for those who have all 3 favourable baseline laboratory values (AFP < 20 ng/mL, platelets ≥ 90 x 10^9/L and albumin ≥ 35 g/L) based on the table 13 of the SmPCs and the following sentence "In subjects with all three favourable baseline laboratory values (AFP < 20 ng/mL, platelets ≥ 90 x 10^9/L, and albumin ≥ 35 g/L), relapse rates were similar in subjects treated for 12 or 24 weeks".

- Would it be possible to clarify whether a 12 week treatment duration in people with genotype 1a chronic hepatitis C with cirrhosis is considered within the marketing authorisation recommendations?
- Is it reasonable to assume that the above mentioned sentence in the SmPCs allows for a 12 weeks treatment for **some** people with genotype 1a chronic hepatitis C with cirrhosis within the marketing authorisation?

We would be very grateful to receive a response by end of **Thursday 30 April** if possible. Please feel free to contact me if you need any clarity on the above or have any questions.

Kind regards,
[redacted]
Technical Analyst (Appraisals)
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza | Manchester M1 4BT | United Kingdom
Tel: [redacted]
Web: http://nice.org.uk

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