23 July 2015
EMA/CHMP/BPWP/356886/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the clinical investigation of hepatitis B immunoglobulins' (EMA/CHMP/BPWP/585257/2009)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	IPFA
2	European Liver Patient Association (ELPA)
3	The European Association for the Study of the Liver (EASL)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Page 9/11 Line 246 4.3.1. Adverse events Post-marketing safety data collection in children should be proposed in the Risk Management Plan. The only possible challenge could be writing a Risk Management Plan to collect post-marketing data in children for new products. However, we see no other option how to organise this otherwise.	Accepted. Sentence has been reworded to be aligned with the SCIg guideline

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
61	2	Track changes: illness has to be replaced by disease. It is common use to speak about infectious diseases (like hepatitis B) and not mentioning hepatitis B as an infectious illness.	Accepted.
Line 62	3	Comment: organ transplantation from anti-HB case positive donor should be added. Proposed change (if any): “include working in a healthcare setting, transfusions, dialysis, organ transplantation from anti-HB core positive donor, acupuncture … “	Accepted.
62-63	2	Comment: add among the risk factors also unprotected sex and born in a country with a high prevalence of hepatitis B	Partly accepted : Only the addition of “unprotected sex” is agreed. Indeed, the guideline is not intended to be a comprehensive account of HBV infection.
Line 68	3	Comment: delete “as well as for” and add “Quantitative” and “may be assessed”. Proposed change (if any): “… antibodies. Quantitative HBV DNA may be assessed”.	Not accepted : Rationale: It is preferred to keep the wording broad. In addition, the HBV DNA assay is referred to in the paragraph following that of line 68.

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Line 77	3	Comment: add “or caused by hepatitis B infection acquired by the donor graft”. Proposed change (if any): “ infection or caused by hepatitis B infection acquired by the donor graft”	Not accepted : The concerned paragraph presents the general use of HBIG and generally covers the prevention of reinfection after LT. However, LT caused by hepatitis B infection acquired by the donor graft is a really specific situation (concerning a restricted population). As this is not in line with the indications proposed in the HBIg core SmPC, and thus with the accepted indications of marketed products, this addition does not appear relevant.
Line 98	3	Comment: add “or caused by hepatitis B infection acquired by the donor graft”. Proposed change (if any): “failure or caused by hepatitis B infection acquired by the donor graft”.	Not accepted: see comment above
Line 151	3	Comment: in the text it is reported that anti-HBs titers should be determined before and after HBIG infusion, our comment is that HBIG formulations are not only e.v. formulation, but also i.m. and s.c. formulation. Proposed change (if any):	Partly accepted: The PK section has been reworded in order to take in consideration IV administration and SC /IM administration as a separate way. This section is now in line with SC and IVIG guideline regarding the PK data requested. Nevertheless, in certain/selected parts of the document, we replaced the term “infusion” by “administration” when it was relevant.
Population (lines 190 to 199)	3	Comment: suggest two more recommendations are added as below Proposed change (if any): • Viral load before antiviral treatment before liver	Not accepted. Indeed, the line 194 states that: “*Recommended baseline data include (<u>but are **not necessarily limited to**</u>):”*. In addition, the titre of circulating hepatitis B virus DNA”

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		transplantation • Viral load at liver transplant (to stratify low and high risk recipients).	mentioned at line 199, already encompasses the two more recommendations suggested by EASL. Also, the guideline is not intended to be a comprehensive account of HBV infection.
Line 205	3	Comment: add new line just after 205 and include the suggestion below: Proposed change (if any): insert: “during the first 6 months after liver transplantation, in HBVDNA negative\HBsAg negative patients, at six months from transplant, the anti-HBs titres can be maintained between 250 – 500 IU/L or even lower”.	Not accepted: The recommended titres are aligned with the core SmPC and the more open wording of the core SmPC is preferred as different centres have their own protocols.
Line 214	3	Comment: add at end of sentence “at least at 1 year after liver transplantation if liver biopsy is not indicated earlier and/or later according to liver function tests abnormalities”. Proposed change (if any): “ …. may include histology reports of the liver graft “at least at 1 year after liver transplantation if liver biopsy is not indicated earlier and/or later according to liver function tests abnormalities”	Not accepted This is a clinical management issue. No international recommendations exist to assess the liver fibrosis in HBV disease. As this management can vary between EU countries, it appears difficult to specify a delay for performing this sampling into the guideline.
215	2	Comment: the histology report should be performed with liver biopsy or fibroscan? Both are allowed?	Not accepted : see comment above

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216	2	Comment: “regular basis” should be better specified: every month? Every three months?	Partly accepted: A minimal frequency for the endpoints assessment is now specified in brackets namely “at least every 3 months”. Indeed, in previous HBIG dossiers, the assessments were not performed on a regular basis, which complicates the results analysis. Thus, this addition would ensure the results homogeneity in term of assessment frequency and would allow simplifying the analysis.
Line 238	3	Comment: see comment on line 151. Proposed change (if any):	Accepted : The term infusion can be replaced by administration in this sentence.
239	2	Comment: “at repeated interval” should be better specified	Not accepted: This section has been aligned with the SCIg and IVIg guidelines.
254 - 266	2	Comment: This should also mention **hepatitis E (HEV)**, plasma products should be tested for it. According to a recent review, up to 10% of plasma pools in Germany were found positive for HEV RNA. While Hepatitis E is mostly a subclinical, acute and self-resolving infection, it may cause serious or fatal complications in pregnant women and chronic liver patients; it has also been shown to take a chronic course in immunocompromised patients (e.g. in solid-organ transplanted and HIV+/Aids) and cause serious liver damage, including cirrhosis and liver failure. *(Wedemeyer H et al.: Pathogenesis and Treatment of Hepatitis E Virus Infection. GASTROENTEROLOGY 2012;142:1388–1397. p 1391)* That means that	Not accepted : An HEV test is now included in the SD plasma monograph (January 2015). However, to date, no recommendations have been made for fractionated plasma. Therefore, this general issue cannot be covered by HBIG guideline for the time being. This comment has been brought to the attention of the Biologics Working Party (BWP). Viral safety of plasma-derived medicinal products with respect to hepatitis E was addressed in an EMA workshop in October 2014.

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		patients who might be most in need for immunoglobulin treatments may also be at the highest risk if the plasma is contaminated with HEV. Proposed change (if any): *demand that plasma used for immunoglobulin also gets screened for Hepatitis E.*	
Line 291 onwards	3	Comment: General suggestion: If the study should be performed in liver transplant recipients with previous HBV-related acute or chronic liver disease, we would suggest the following: 1. to exclude patients transplanted for acute liver failure/fulminant hepatitis due to HBV when the underlying status is different from patients transplanted for HBV-cirrhosis. 2. to discuss if HCC patients should be excluded, since the presence of HCC and HBV may influence the rate of recurrence of both HCC and HBV after transplant. Proposed change (if any):	Not accepted (note comment relates to line 191): This comment is noted however, as this is a clinical management issue, we can not accept the specification of such exclusions. Indeed, the Guideline aims to describe the information to be documented in the frame of a MAA and tries to direct companies on the clinical development of the product. Guideline does not consist on a scientific advice. Moreover, certain patients that are suggested to be excluded can be covered by the current SmPC indication.
Line 297	3	Comment: Please add the reference indicated below (PDF of published article attached). Proposed change (if any): add: Burra et al, Liver transplantation for HBV-related cirrhosis in Europe: An ELTR study on evolution and outcomes, Journal of Hepatology 2013 vol. 58 j 287–296.	Not accepted: This publication does not particularly deal with HBIG as it exposes the evolution and the outcomes of induced HBV LT in EU. We do not think that the addition of this article as reference is relevant in the HBIG guideline context.

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Line 326		Typos to be corrected as below. “…. Samuel D.	Accepted.
Line 332		Typos to be corrected as below. “ … in neonates of HBe antigen positive …”	Accepted.