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4 **Guideline on the clinical investigation of hepatitis B**
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Guideline on the clinical investigation of hepatitis B immunoglobulins

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30 **Glossary**

31	AE	Adverse Event
32	CJD	Creutzfeldt Jakob Disease
33	HBsAg	Hepatitis B surface Antigen
34	HBcAg	Hepatitis B core antigen
35	HBeAg	Hepatitis B e antigen
36	HBIG	Hepatitis B immunoglobulin
37	ICH	International Conference on Harmonisation
38	IU	International Units
39	IgA	Immunoglobulin A
40	IgE	Immunoglobulin E
41	IgM	Immunoglobulin M
42	IgG	Immunoglobulin G
43	IM	Intramuscular
44	IV	Intravenous
45	PK	Pharmacokinetics
46	Ph.Eur.	European Pharmacopoeia
47	RMP	Risk Management Plan
48	SAE	Serious Adverse Event
49	SC	Subcutaneous
50	SmPC	Summary of Product Characteristics
51	TSE	Transmissible spongiform encephalopathy

Executive summary

This guideline describes the information to be documented when an application is made for a marketing authorisation for a hepatitis B immunoglobulin. The guidance covers biological data, pharmacokinetics, clinical trials and patient follow-up. Guidance is also provided for authorised products where a significant change in the manufacturing process has been made.

1. Introduction (background)

The purpose of this guideline is to provide applicants and regulators with harmonised guidance for applications for marketing authorisation for specific immunoglobulins directed against hepatitis B virus.

Hepatitis B is an infectious, inflammatory illness of the liver caused by the hepatitis B virus. The virus is transmitted by exposure to infectious blood or body fluids. Risk factors for developing HBV infection include working in a healthcare setting, transfusions, dialysis, acupuncture, tattooing, overseas travel and residence in an institution. The hepatitis B virus does not cross the placenta but the foetus may be infected during amniocentesis or during labour. About a third of the world population has been infected at some time with hepatitis B virus: 350 million people are chronically infected.

The hepatitis B status of a person may be assessed by testing for the presence of hepatitis B surface antigen (HBsAg) and 'e' antigen (HBeAg) and by testing for the presence of HBs, HBc and HBe antibodies as well as for HBV DNA. People who are tested positive for HBsAg in their blood are potentially infectious.

The amount of hepatitis B virus DNA in clinical specimens (called the viral load) may be used to assess a person's infection status and to monitor treatment.

Hepatitis B vaccines promote effective protection in most uninfected, healthy individuals. Parenteral hepatitis B immunoglobulin may be used to provide immediate protection against the hepatitis B virus until the body's response to vaccination is adequate. Hepatitis B immunoglobulin may also be offered for long-term use when required in individuals who do not show an immune response to vaccination and to prevent re-infection after a liver transplant procedure for liver failure caused by hepatitis B infection.

Human hepatitis B immunoglobulin medicinal products are sterile liquid or freeze-dried preparations of immunoglobulins (mainly IgG) containing specific antibodies against hepatitis B viral antigens. The products are obtained from the pooled plasma of donors with high titres of antibodies against hepatitis B virus.

Products may be intended for intravenous (IV), intramuscular (IM) or subcutaneous (SC) administration.

Indications, dosage and methods of administration of hepatitis B immunoglobulin may differ in Member States of the European Union as a result of divergent clinical practice and national immunisation recommendations: applicants are advised to take these issues into account when designing clinical trials.

The following indications are currently accepted:

(i) Immunoprophylaxis of hepatitis B:

- in case of accidental exposure in non-immunised subjects (including persons whose vaccination is incomplete or status unknown);

- until vaccination has become effective in patients receiving haemodialysis;
 - in the new-born child of a mother with hepatitis B;
 - in subjects who have not shown an immune response (no measurable hepatitis B antibodies) after vaccination and for whom continuous prevention is necessary owing to the ongoing risk of infection with hepatitis B.
- (ii) Prevention of hepatitis B virus re-infection after liver transplantation for hepatitis B induced liver failure.

2. Scope

This guideline describes the information to be documented when an application for a marketing authorisation for hepatitis B immunoglobulin is made, including biological data, pharmacokinetics, clinical trials and patient follow-up.

These data are required for:

1. products for which an application for a marketing authorisation is to be submitted, referred to as 'new products' in the text and
2. authorised products where a significant change in the manufacturing process has been made (e.g. additional viral inactivation/removal steps or new purification procedures).

This guideline covers plasma-derived hepatitis B immunoglobulins defined by the relevant European Pharmacopoeia monographs. The guideline does not relate to fragmented or chemically modified products.

Quality aspects are outside the scope of this guideline.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended, and the following guidance:

- Core SmPC for human plasma-derived hepatitis B immunoglobulin, for intramuscular use (CPMP/BPWG/4222/02) and for intravenous use (CPMP/BPWG/4027/02).
- Guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010).
- Guideline on good pharmacovigilance practices, Module V – Risk management systems (EMA/838713/2011).
- Structure and Content of Clinical Study Reports (ICH E3, CPMP/ICH/137/95).
- Guideline on "Comparability of Biotechnological Products (ICH Q5E, CPMP/ICH/5721/03).
- The clinical trials described in this Guideline should be performed according to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

4. Products for which an application for a marketing authorisation is to be submitted: 'new products'

Quality and pharmacokinetic data are the key elements to evaluate activity and safety of hepatitis B immunoglobulin products.

4.1. Quality data

Adequate documentation with regard to batch-to-batch consistency is provided in Module 3 of the dossier and should follow the corresponding Ph.Eur. Monographs for hepatitis B immunoglobulins. Additional data may be needed to support the pharmacodynamic and therapeutic activities as well as the safety profile of the hepatitis B immunoglobulin preparation e.g. Fab and Fc function (functional integrity): antigen-driven complement fixation, opsonisation, phagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC).

Characterisation of these functions may be of special relevance in some cases, e.g. administration of HBIG in prevention of hepatitis B recurrence following liver transplantation.

4.2. Clinical

Clinical trials should be conducted before marketing authorisation. As appropriate pharmacokinetic data (see pharmacokinetics section below) are considered as a surrogate indicator of efficacy for hepatitis B immunoglobulin product for certain indications, they must be provided in each application dossier. For the indication 'prevention of hepatitis B virus re-infection after liver transplantation induced liver failure', clinical efficacy for the HBIG product should also be confirmed through a study investigating patients who have undergone liver transplant for liver failure caused by hepatitis B.

4.2.1 Pharmacokinetics

The pharmacokinetic profile should be examined in at least 20 healthy adult volunteers negative for HBsAg, anti-HBs, anti-HBc after IV, SC and/or IM administration (depending on the desired method of administration). A descriptive comparison to published literature is requested.

Serum levels of anti-HBs should be determined before and after infusion. It is essential that the methodology that is employed for determining the antibody titres should be carried out in a single laboratory throughout the clinical development programme and should be fully validated. If this is not possible, cross-validation data between laboratories should be provided.

Serum clearance, volume of distribution, maximum concentration, time to reach maximum concentration, area under the curve and mean serum half-life should also be measured.

Safety data should be collected throughout the PK study.

Given the extensive literature for immunoglobulins, PK in adults can be extrapolated to PK in children, therefore a separate paediatric PK study is not deemed necessary.

4.2.2 Efficacy

Immunoprophylaxis of hepatitis B

Taking into account that clinical efficacy in immunoprophylaxis indications cannot be examined using classical principles of clinical trials (many people have already been immunized through vaccination which limits the recruitment of a sufficient number of patients) and that pharmacokinetic data in adults are considered as a surrogate indicator of efficacy for immunoglobulin products, the marketing authorisation of a new HBIG product in all established immunoprophylaxis indications can be granted based on:

- the demonstration of compliance with the quality standards of the relevant Ph.Eur. monograph and

- 169 • the pharmacokinetic and safety data from 20 hepatitis B antibody-negative adult subjects
170 demonstrating results consistent with published data (see section 4.2.1).

171 Moreover, as the literature does not reveal any major differences between adults and children suffering
172 from the same disorder with regard to pharmacokinetic, efficacy and safety for immunoglobulin
173 products, paediatric investigations in immunoprophylaxis are not considered necessary.

174 The claimed dose should be in line with the relevant current guideline on core SmPC for human
175 plasma-derived hepatitis B immunoglobulin. If other dosage regimens are requested, they should be
176 supported by clinical data. Indications other than those listed above (see section 1) cannot be granted
177 without relevant clinical data, including controlled clinical trials.

178 ***Prevention of hepatitis B virus re-infection after liver transplantation for hepatitis B induced***
179 ***liver failure***

180 The risk of recurrence of hepatitis B is associated with the nature of the liver disease leading to
181 transplant and with the titre of circulating hepatitis B virus DNA prior to antiviral therapy. Prophylaxis
182 against graft re-infection is associated with better long-term outcome. Most clinical centres employ a
183 combination of hepatitis B immunoglobulin plus an antiviral agent: the preferred protocol is a matter of
184 ongoing research.

185 Any deviations from the following recommendations should be justified.

186 Clinical safety and efficacy data will be required for a new hepatitis B immunoglobulin. The new
187 immunoglobulin should be studied in accordance with the intended mode and route for administration.

188 Study design

189 Open studies are acceptable. A descriptive comparison to published literature is requested.

190 Population

191 For efficacy evaluations, the number of patients studied should be adequate to provide confirmatory
192 data. 25 patients who have undergone liver transplant for liver failure caused by hepatitis B are
193 recommended.

194 Recommended baseline data include (but are not necessarily limited to):

- 195 • status of the disease: acute versus chronic hepatitis B;
196 • co-infection with other viral infections (e.g. hepatitis C, D and HIV);
197 • exposure to immunosuppressive and antiviral therapies;
198 • time elapsed between liver transplant and start of prophylaxis; and
199 • the titre of circulating hepatitis B virus DNA.

200 Recommended titres

201 For hepatitis B immunoglobulin as monotherapy, it is recommended that anti-HBs titres should be
202 maintained:

- 203 • >100-150 IU/L for patients without active viral replication pre-transplantation (HBeAg and/or HBV
204 DNA negative) and
205 • >500 IU/L for patients with active viral replication (HBeAg and/or HBV DNA positive).

206 For hepatitis B immunoglobulin combined with antiviral therapy, targets for trough titres of hepatitis B
207 immunoglobulin during the study should be justified.

208 Inter-subject variability of anti-HBs and use of antiviral medication should be reported.

209 Endpoints

210 The primary endpoint should be the proportion of patients who develop recurrence of hepatitis B as
211 demonstrated by positive results for HBsAg and/or HBeAg.

212 Secondary endpoints will include the titre of anti-HBs, the titre of circulating hepatitis B virus DNA,
213 time to recurrence of hepatitis B and overall survival.

214 Supportive evidence on efficacy may include histology reports of the liver graft.

215 All endpoints should be assessed prior to infusion of the investigational product and on a regular basis
216 thereafter for at least 12 months. It is advised to collect longer-term data on recurrence and overall
217 survival with either a Risk Management Plan (RMP) or a post-approval efficacy study.

218 Any data on administration at home should be provided.

219 Elderly Patients: specific data in the elderly are not needed as the benefit/risk can be extrapolated
220 from the available data in adult patients.

221 **4.3. Safety**

222 Product safety is evaluated based on all pertinent safety findings. A comprehensive RMP has to be
223 submitted as part of the dossier (see 'Guideline on risk management systems for medicinal products
224 for human use', EMEA/CHMP/96268/2005).

225 **4.3.1. Adverse events**

226 All adverse events in clinical studies must be recorded and analysed with regard to causality,
227 seriousness, outcome and expectedness. Safety data from trials in indications not claimed in the
228 application can be used as supportive data.

229 Comprehensive baseline data and patient histories are essential to compare the safety signals arising
230 from the studies. The safety signals should be compared with data and frequencies described in the
231 literature. Any deviation from known signals and rates should be discussed. Adverse events (AEs) and
232 serious adverse events (SAEs) from all subjects followed throughout the clinical studies should be
233 recorded and reported regardless of whether the AE is determined to be related to the product or not.
234 The reporting should be in accordance with the ICH Guidelines on 'Structure and content of clinical
235 study report' (CPMP/ICH/137/95 E3). Preferably the reporting should apply the terminology used in the
236 'Medical Dictionary for Regulatory Activities' (MedDRA).

237 Safety evaluation should include monitoring of short term tolerance (blood pressure, heart rate,
238 temperature, and monitoring of other relevant parameters) at repeated intervals following the infusion
239 of the new product. All AEs that begin during or within 72 hours after an infusion should be classified
240 and analysed as infusional AEs.

241 AEs should be evaluated with regard to the infusions rates. Renal function should be monitored,
242 particularly in patients at risk and in those receiving high doses of specific Igs.

243 All collected safety data should include a separate evaluation of any safety data in children and
244 adolescents. This should be compared to the adult dataset and relevant discrepancies listed in the
245 SmPC.

Post-marketing safety data collection in children should be proposed in the Risk Management Plan.

A separate safety evaluation of the excipients should be provided if applicable (e.g. for new excipients, new route of administration, considerably higher quantities administered compared with previous uses).

4.3.2. Safety with respect to viruses and other transmissible agents

Compliance with CHMP recommendations with regard to viral safety and other transmissible agents is necessary for all plasma-derived products and is verified by information supplied in Module 3 of the dossier.

Manufacturers of plasma-derived products, including specific immunoglobulins, are obliged to optimise viral safety by selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective steps for the inactivation/removal of viruses in the manufacturing processes. Similar principles to those outlined for viral safety should apply for all transmissible agents including TSE and other emerging pathogens. Manufacturers should follow the respective guidance documents and position statements. Information can be found in the guidelines on the EMA website (under *Biologicals - Drug Substance - Plasma-derived Medicinal Products*).

The above-mentioned procedures are now considered to be highly effective and demonstrative of the viral safety of the product with respect to enveloped viruses. These procedures may be of limited value against non-enveloped viruses, such as hepatitis A virus and parvovirus B19. There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

The applicant is nevertheless required to provide all available data gathered on patients treated with the product in clinical trials. Investigators should continue with their normal clinical practice of monitoring patients. The applicant should demonstrate that there are systems in place to collect information on patients treated with the product and to respond rapidly to any reports of infection with a full investigation.

Moreover, a pre-treatment serum sample from each subject included in the clinical trials should be stored at -70 °C for possible future testing.

4.3.3. Other safety issues

The effect of passive transmission of haemagglutinins (anti-A/anti-B) should be evaluated in patients receiving high doses of hepatitis B immunoglobulin.

5. Change in the manufacturing process of authorised products

Changes in the manufacturing procedures may lead to significant changes in the product and may thereby alter the structure of the immunoglobulin and/or its activity or the safety of the product.

When a change is introduced to the manufacturing process of a given product, the marketing authorisation holder will have to demonstrate that the “post-change” and the “pre-change” product are comparable in terms of Quality, Safety and Efficacy (see ICH Q5E Guideline on “Comparability of Biotechnological Products (CPMP/ICH/5721/03). This will be a sequential process, beginning with investigations of quality and supported, as necessary, by non-clinical and/or clinical studies.

285 The extent of clinical data to be provided has to be judged on a case-by-case basis depending on the
286 anticipated impact of the changes and could vary from a pharmacokinetic trial comparing “pre-change”
287 versus “post-change” product up to the full clinical data set as outlined for a new product.

288 As a consequence, applications should be accompanied by assessment of the potential impact of a
289 change on efficacy and safety of a given product and the rationale behind the clinical development plan
290 should be outlined and justified.

291 **5.1. Pharmacokinetics**

292 If a PK study is needed, the pharmacokinetic profile should be examined in at least 20 healthy adult
293 volunteers negative for HBsAg, anti-HBs, anti-HBc after IV, SC and/or IM administration (depending on
294 the desired method of administration). The PK results obtained should be compared to data obtained
295 with the “pre-change” product.

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