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## Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)

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This guideline replaces Note for Guidance on the Clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (CPMP/BPWG/388/95 rev. 1)

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# Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)

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## **Executive summary**

This Guideline describes the information to be documented when an application is made for a marketing authorisation for a human normal immunoglobulin for intravenous use (IVIg). The guidance covers biological data, clinical trials and patient follow-up. Quality aspects are outside the scope of this guideline.

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 IVIg.

### **2. Scope**

This guideline describes the information to be documented when an application for a marketing authorisation for IVIg 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).

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).

This Guideline covers normal human immunoglobulin for intravenous administration defined by the European Pharmacopoeia monograph 0918. The Guideline does not relate to fragmented or chemically modified products.

Quality aspects are also outside the scope of this guideline.

### **3. Legal basis**

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.

### **4. Background**

The first use of polyvalent intravenous immunoglobulin preparations was as replacement therapy in humoral immunodeficiency situations. As human normal immunoglobulin for intravenous administration (IVIg) is prepared from plasma collected from a high number of healthy blood donors, the spectrum of antibody specificity expressed by the IgG is large. Among the antibody specificity spectrum, IVIg recognises a large number of bacterial, viral and other infectious agent antigens, and also a large number of self antigens. Besides the therapeutic effect in replacement, IVIg has thus also been used for its immunomodulatory activity.

Indications of IVIg are described in two main sections referred to as “replacement therapy” and “immunomodulatory effect”. While the immunodeficient conditions covered by the replacement effect of IVIg are quite well-defined, the immunomodulatory effect of IVIg has been demonstrated in a limited number of diseases only. Lists of such auto-immune-related diseases have been established by various national and international bodies and are constantly updated.

Timeline history of guideline: The original guideline (EC III 581/94, CPMP/388/95) came into operation on 14 August 1996. The first revision (CPMP/BPWG/388/95 rev. 1) came into operation in December 2000.

## 5. Efficacy

Biological data and clinical evidence of efficacy and safety in primary/secondary humoral immunodeficiencies and ITP are the key elements required for the licensing of IVIg in the following claimed indications:

IVIg can be used in all age ranges, unless otherwise specified below.

### Replacement therapy in:

- Primary immunodeficiency syndromes with impaired antibody production.
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma (MM) patients who have failed to respond to pneumococcal immunisation.
- Children and adolescents with congenital AIDS and recurrent bacterial infections.
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).

### Immunomodulatory effect in:

- Primary immune thrombocytopenia\* (ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain Barré Syndrome (GBS)
- Kawasaki disease

The listed indications are considered as “established” for IVIg and this guideline outlines the general principles for design of clinical trials.

For other auto-immune disorders (in particular multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis exacerbations) confirmatory data are required, see 7.3.5.

In other indications, relevant clinical data are required, see 7.3.6.

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\* The term idiopathic thrombocytopenic purpura has been exchanged for primary immune thrombocytopenia according to the recommendations of an International Working Group (IWG) in “Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children”<sup>1</sup>. The acronym will remain the same.

## **6. Safety**

### **6.1. Adverse events**

All adverse events in clinical studies must be recorded and analysed with regard to causality, seriousness, outcome and expectedness (see 7.4.1.). A detailed protocol of the studies specifying the intervals and methods for collection of the data, and duration of follow up is requested.

Safety data from trials in indications not claimed in the application can be used as supportive data.

### **6.2. Safety with respect to transmissible agents**

#### **6.2.1. Viral Safety**

Manufacturers of plasma-derived products, including IVIg, 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.

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.

For products with an entirely novel manufacturing process other principles may apply. These applications should be discussed with the Regulatory Authorities prior to submission.

#### **6.2.2. Other transmissible agents**

Similar principles to those outlined in 6.2.1 apply for safety with regard to other transmissible agents including TSE and other emerging pathogens. Manufacturers should follow the respective guidance documents and position statements. Information can be found in the section "Guidelines on Plasma-derived Medicinal Products" on the Agency website:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000330.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002956b](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000330.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002956b).

### **6.3. Other safety issues**

The effect of passive transmission of haemagglutinins (anti-A/anti-B), and anti-D should be evaluated in patients receiving high doses of IVIg.

## 7. Product for which an application for a marketing authorisation is to be submitted: "New products"

Biological and pharmacokinetic data are the key elements to evaluate activity and safety of IVIg preparations.

### 7.1. *Biological data*

Adequate documentation with regard to batch to batch consistency is provided in Module 3 of the dossier and should follow the Ph. Eur. Monograph 0918 requirements.

However, specific data are needed to support the pharmacodynamic and therapeutic activities as well as the safety profile of the IVIg preparation. The data should include the following parameters and be summarised in Module 5 of the dossier along with the cross-reference to Module 3 (wherever applicable).

#### *i) Biological characteristics*

##### General

- Molecular size distribution: quantification of monomers, dimers, fragments, polymers and aggregates.
- Impurities (proteins -IgA, IgM, IgE, - other).

##### For pharmacodynamic and therapeutic activity

- Distribution of IgG subclasses
- Content of clinically relevant antibodies to:
  - bacteria, such as: *C. diphtheriae*; *H. influenzae* type B; *S. pneumoniae*, *S. pyogenes*
  - viruses, such as: hepatitis A and B viruses; cytomegalovirus; varicella-zoster virus; rubella virus; measles virus; parvovirus B19; poliomyelitis virus type I.

##### Other

- Anti-complementary activity
- Anti-A and anti-B haemagglutinins
- Haemolysins (usually anti-A and anti-B)
- Anti-D antibodies
- Prekallikrein activator.

#### *ii) Biological activity*

- *In vivo* and/or *in vitro* quantification of neutralising antibodies (depending on the claimed neutralising activities)
- Fab and Fc functions (functional integrity): antigen-driven complement fixation, opsonisation, phagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC).

Immunomodulatory and anti-inflammatory activities for auto-immune diseases, depending on the claimed indications and the relevance of *in vitro* and/or *in vivo* models such as:

- Ability to inhibit auto-antibody activity *in vitro*

- Experimental autoimmune models.

## **7.2. Pharmacokinetics**

Pharmacokinetic (PK) data are essential to support the pharmacological activity and efficacy of the product, and may differentiate one product from another. Therefore, they must be provided in each application dossier (see PK study chart).

### PK parameters

1. IgG trough levels should be studied in 40 patients with primary immunodeficiency syndromes (PID), whereby 20 of these should be children or adolescents with an age distribution representative of this patient population. The IgG trough levels of the investigational product should be assessed prior to each infusion over a period of 6 months, starting after 5-6 administrations of the product. The IgG trough levels obtained and treatment intervals should be compared to either the trough levels and treatment intervals of the former product (in previously treated patients) or to literature data (in patients naïve to IVIg treatment), whereby predefined comparability limits should be justified by the applicant.
2. Other PK parameters including plasma concentration-time curve, half-life, area under the curve, volume of distribution, C<sub>max</sub>, T<sub>max</sub>, and elimination rate constant(s) should be measured in 20 adult PID patients assessed by repeated blood sampling after approximately 5-6 administrations of the product until immediately before the next infusion. The other PK parameters obtained should be discussed by the applicant in the light of the literature data.

### PK population

Pharmacokinetic data set can be derived from patients with primary immunodeficiency syndromes (PID) who are either already stabilised on IVIG treatment (group A) or naïve to IVIG treatment (group B) or the set can contain both patient groups.

#### Group A) Patients already stabilised on IVIg treatment

In patients already stabilised with another IVIg preparation, trough levels and treatment intervals should be documented for at least two previous infusions, prior to the introduction of the new IVIg preparation. After a period of approximately 5-6 administrations of the new IVIg product, trough levels and treatment intervals should be measured.

#### Group B) Patients naïve to IVIg treatment

In patients naïve to IVIg the pharmacokinetic profile should be assessed when steady state (T<sub>ss</sub>) is reached.





The secondary endpoints should be prospectively defined and their statistical analyses provided in the study protocol.

The efficacy results from this study would apply to all types of primary immunodeficiency syndromes due to deficiency of functional IgG.

### **7.3.2. Replacement therapy in other immunodeficiency syndromes**

1. Hypogammaglobulinaemia and recurrent bacterial infections in patients with CLL, in whom prophylactic antibiotics have failed.
2. Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase MM patients who have failed to respond to pneumococcal immunisation.
3. Children and adolescents with congenital AIDS and recurrent bacterial infections.
4. Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT)

The above indications would be granted as long as efficacy has been proven in primary immunodeficiency syndromes (see 7.3.1). Standard doses are 0.2-0.4 g/kg every three to four weeks. If other dosage regimens are requested, they should be supported by clinical data.

### **7.3.3. ITP**

IVIg is used for the treatment of ITP in children, adolescents or adults at high risk of bleeding or prior to surgery to correct the platelet count.

There are no data to support the equivalence of different IVIg preparations, especially with regard to immunomodulatory activities. Thus a clinical efficacy study is required to establish the product efficacy in this indication.

#### Efficacy study

An open, study with the investigational IVIg should be performed in 30 chronic (> 12 months duration) adult ITP patients with a baseline platelet count of  $<30 \times 10^9/l$ . The results should be compared to data from the literature. Standard doses should be studied (0.8 - 1 g/kg on day one, which may be repeated once within 3 days, or 0.4 g/kg/day for 2-5 days). If other dosage regimens are applied for, they should be supported by clinical data.

Baseline data on splenectomy and co-medication (especially affecting bleeding or platelets) should be provided. Patients included in the study may have refractory ITP i.e. the failure to achieve a response or loss of response after splenectomy and the need of treatment(s) to minimize the risk of bleeding considered as clinically significant by the investigator. In clinical practice refractory patients may need on demand IVIG to temporarily increase the platelet count sufficiently to safely perform invasive procedures or in case of major bleeding or trauma; the platelet count to be reached will depend on the nature of the invasive procedure

Corticosteroids are permitted if the patient is either on long-term stable doses of corticosteroids or the platelet count falls below  $30 \times 10^9/l$  again after IVIg treatment, but should not to be given as a pre-treatment to alleviate potential tolerability problems. Patients with increases in corticosteroid doses during the duration of the response period of the study should be regarded as treatment failures. Any concomitant medication during the trial should be documented and possible confounding impact on the outcome of the trial assessed.

#### Efficacy parameters:

Number and % of patients with response (R), complete response (CR), no response (NR) and loss of response as well as time to response and duration of response.

These patient parameters are defined according to the proposals of an International Working Group<sup>1</sup>:

- patients with R: platelet count  $\geq 30 \times 10^9/l$  and at least 2-fold increase of the baseline count, confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding.
- patients with CR: platelet count  $\geq 100 \times 10^9/l$ , confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding.
- patients with NR: platelet count  $< 30 \times 10^9/l$  or less than 2-fold increase of baseline platelet count, confirmed on at least 2 separate occasions approximately 1 day apart, or bleeding.
- patients with loss of CR or R: platelet count below  $100 \times 10^9/l$  or bleeding (from CR) or below  $30 \times 10^9/l$  or less than 2-fold increase of baseline platelet count or bleeding (from R). Platelet counts confirmed on at least 2 separate occasions approximately 1 day apart.
- Time to response: time from starting treatment to time of achievement of CR or R. (Late responses not attributable to the investigated treatment should not be defined as CR or R).
- Duration of response: measured from the achievement of CR or R to loss of CR or R

#### Statistical considerations

- Wherever possible, platelet parameters should be provided as mean (and standard deviation) and median (and minimum and maximum) values for each patient, as well as for summary data.

### **7.3.4. Guillain Barré syndrome, Kawasaki disease**

In the absence of specific clinical trial data in these indications, the efficacy in primary immunodeficiency syndromes and in ITP should be established.

Published literature in Guillain Barré syndrome and Kawasaki should be provided. The applicability of these data, including the dosage regimen, to the IVIg should be justified in the expert report. If other dosage regimens are requested, they should be supported by clinical data.

In Kawasaki disease, patients should receive concomitant treatment with acetylsalicylic acid.

### **7.3.5. Other auto-immune disorders**

Published literature indicates a positive effect of IVIGs in some auto-immune disorders in particular multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and myasthenia gravis exacerbations<sup>†</sup>. For these indications the efficacy in primary immunodeficiency syndromes and in ITP should be established. The applicant should also provide

- An analysis of the existing literature and,
- Confirmatory data with the applicant's IVIg (see also 'Guideline on Clinical Trials in Small Populations', CHMP/EWP/83561/2005), This should include a justification for the
  - scope of the confirmatory dataset (sample size, dose, time frame, patient population),

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<sup>†</sup> The existing legislation provides various incentives for the development of new indications through orphan medicinal products, paediatric-use marketing authorisations, and an additional year of data exclusivity for a new indication of an existing product.

- choice of the neurological scale and clinically meaningful differences within the chosen scale
- comparator arm, or lack of comparator
- wash-out period of previous medication and/or stable co-medication
- The investigation of other auto-immune indications should be in accordance with the Paediatric Regulation ([EC No 1901/2006](#))

### **7.3.6. Other indications**

Other possible indications cannot be granted without relevant specific clinical data. Biological and pharmacokinetic data alone are not sufficient to support clinical efficacy.

Controlled clinical trials comparing the IVIg preparation with placebo or with an established therapy are thus required to substantiate marketing authorisation in other indications.

The investigation of other indications should be in accordance with the Paediatric Regulation.

## **7.4. Safety**

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

### **7.4.1. Adverse events**

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

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

AEs should be evaluated with regard to the infusion rates. Renal function should be monitored, particularly in patients at risk and in those receiving high doses of IVIg.

All safety data should include a separate evaluation of the safety dataset in children and adolescents. This should be compared to the adult dataset and relevant discrepancies listed in the 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, which should encompass a summary of the non-clinical and literature data.

### **7.4.2. Safety with respect to transmissible agents**

Compliance with CHMP recommendations with regard to viral safety and other transmissible agents under 6.2 above is necessary for all plasma-derived products and is verified by information supplied in Module 3 of the dossier.

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

### **7.4.3. Other safety issues**

The effect of passive transmission of haemagglutinins and haemolysins (anti-A/anti-B), and anti-D should be evaluated in patients receiving high doses of IVIg, by searching for haemolysis and performing a Direct Antiglobulin Test (DAT; direct Coombs' test) in the patient.

### **7.5. Paediatrics regulation**

Where a paediatric investigation plan is required in order to comply with the Paediatric Regulation ([EC No 1901/2006](#)), the applicant should provide a plan that includes the recommendations described in this guideline for the paediatric population.

## **8. 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.

### **8.1. General aspects**

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.

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

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

If a significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics and safety in PID patients is required. In addition, since the biological rationale for efficacy in ITP is not completely elucidated, efficacy and safety in ITP patients should also be provided with the application.

If the biological data and/or pharmacokinetics data are significantly different from the parent preparation, then the product should comply with the requirements for a new product as defined in section 7.

## **8.2. Biological data**

The effects of changes in the manufacturing process (e.g. viral inactivation steps, changes in pH, changes of excipients, changes in dimer content or new purification procedures) on the biological characteristics and activity of the product should be investigated.

Thus, it is important to provide full data on antibody integrity and function as for new products (see section 7.1).

## **8.3. Pharmacokinetics**

Plasma concentration-time curve, half-life, area under the curve, volume of distribution, C<sub>max</sub>, T<sub>max</sub>, and elimination rate constant(s) should be measured in 20 adult PID patients assessed by repeated blood sampling after approximately 5-6 administrations of the product until immediately before the next infusion. These PK parameters should be compared to data obtained with the predecessor product.

## **8.4. Efficacy and safety**

For ITP, since the biological rationale for efficacy is not completely elucidated, a further clinical study is required as outlined above in 7.3.3.

The remaining indications that were granted for the parent product (i.e. prior to the changes in the manufacturing procedures) can be granted by reference to the literature, provided that efficacy has been established in ITP for the changed product.

PID patients included in the limited PK study (8.3) and ITP patients should be evaluated for safety according to the principles outlined in 7.4.

Requirements for viral safety and other transmissible agents are the same as for the parent product (see 7.4.2).

## **Definitions**

CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CLL	Chronic lymphocytic leukaemia
GBS	Guillain Barré Syndrome
ITP	Primary immune thrombocytopenia
MM	Multiple myeloma
MMN	Multifocal motor neuropathy

## **References**

- 1 Rodeghiero F. *et al.* Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009; 113:2386-2393