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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

**DRAFT**

# GUIDELINE ON THE CLINICAL INVESTIGATION OF HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION (IVIg) (CPMP/BPWG/388/95 rev. 2)

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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

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.

# 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:

Replacement therapy in:

- Primary immunodeficiency syndromes with failure of 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:

- Idiopathic thrombocytopenic purpura (ITP) in children or adults 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.

# 6 SAFETY

## 6.1 Adverse events

All adverse events in clinical studies must be recorded and analysed with regard to causality, seriousness and expectedness. A detailed protocol of the studies specifying the methods for collection, intervals 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. Therefore it is no longer considered appropriate to use clinical trials to investigate viral safety with regard to enveloped viruses.

These procedures may be of limited value against non-enveloped viruses, such as hepatitis A virus and parvovirus B19. The safety of the products with respect to non-enveloped viruses cannot currently be adequately evaluated in clinical studies.

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 6.1.2.1 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 EMEA website: (http://www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm).

## 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 PRODUCTS 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. However, specific data are needed to support the pharmacodynamic and therapeutic activities as well as the safety profile of the IVIg preparation. These data should thus be summarised along with the cross-reference to Module 3, in Module 5 of the dossier.

For the values not defined in the Ph. Eur. monograph 0918, ranges and/or limits are to be defined.

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; 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 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 (6.5 times the expected half-life), starting after 5-6 administrations of the product. The IgG trough levels obtained should be compared to either the trough levels 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, Cmax, Tmax, 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 the day before the next infusion. The other PK parameters obtained should be compared to literature data, whereby predefined comparability limits should be justified by the applicant.

PK population

Pharmacokinetic data should be derived from patients with primary immunodeficiency syndromes (PID) whether they are A) already stabilised on IVIG treatment or B) naïve to IVIG treatment

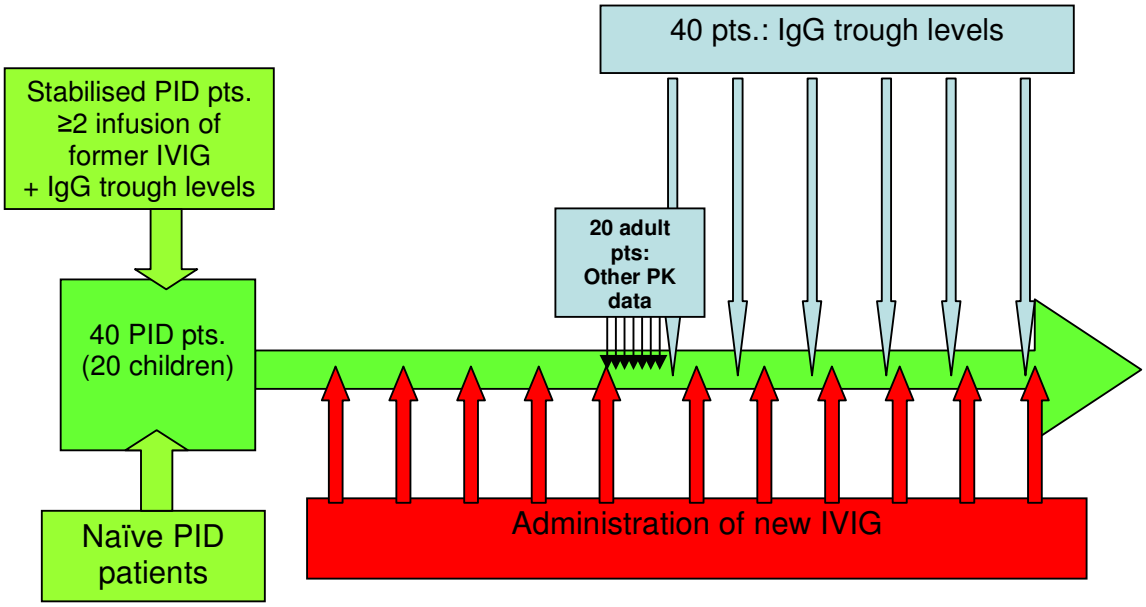
A) Patients already stabilised on IVIg treatment

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 product (3-5 estimated half-lives) with the new IVIg product, trough levels and treatment intervals should be measured.

B) Patients naïve to IVIg treatment

In patients naïve to IVIg the pharmacokinetic profile should be assessed when steady state (Tss) is reached, i.e. no sooner than 5 infusions after beginning of new treatment.

PK study chart




### 7.3 Efficacy

IVIg is used as replacement therapy for the treatment of primary and secondary immunodeficiencies.

#### 7.3.1 Replacement therapy in primary immunodeficiency syndromes

Efficacy should be proven in an open clinical trial of one year duration in primary immunodeficiency syndromes. The patients selection should take into account statistical considerations (see below).

At least 40 patients should be included; approximately half of these patients should be children and adolescents of various age categories. The patients should be followed over 12 months to avoid a seasonal bias (due to a greater rate of infections in the winter months).

The recommended primary endpoint is the number of serious bacterial infections (less than 1.0 infection/subject/year). The protocol should prospectively provide specific diagnostic criteria for each type of serious infection to be included in the primary efficacy analysis. Serious bacterial infections include:

- bacteraemia or sepsis,
- bacterial meningitis,
- osteomyelitis / septic arthritis,
- bacterial pneumonia,
- visceral abscess.

Secondary endpoints are IgG trough levels (see PK section), all other infections, antibiotic treatment, days lost from school/work, hospitalisations, fever episodes, quality of life.

Statistical considerations

The number of subjects to be included into the study might exceed 40 patients as the study should provide at least 80% power to reject the null-hypothesis of a serious infection rate greater or equal 1 by means of a one-sided test and a Type I error of 0.01.

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

The efficacy results 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 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 adult ITP patients with a baseline platelet count of about 20 x $10^9$/l. The results should be compared to data from the literature, whereby comparability limits should be predefined and justified by the applicant.

Baseline data on splenectomy and co-medication (especially affecting bleeding or platelets) should be provided. Corticosteroids are permitted if the patient is either on long-term stable doses of corticosteroids or the platelet count falls below 20 x $10^9$/l again, 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 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 percent of responders i.e. patients who have platelet counts > 50 x $10^9$/l at least once prior to Day 15 and do not require a booster dose or other medication prior to Day 15
- Number and percent of responders with platelets reaching normal levels
- Mean and median platelet count in responders
- Duration of platelet response: defined by two different sets as:
    - From the day the platelet count reached or exceeded 50 x $10^9$/l to the interpolated measurement when the platelet count first fell to < 50 x $10^9$/l ,
    - From the day the platelet count reached or exceeded 50 x $10^9$/l to the interpolated measurement when the platelet count first fell to <20 x $10^9$/l
- Time to reach platelet count > 50 x $10^9$/l
- Maximum platelet level
- Regression of haemorrhages
- Relationship of any new haemorrhages to platelet count.

Standard doses should be studied (0.8 - 1 g/kg on day one, which may be repeated once, or 0.4 g/kg/day for 2-5 days). If other dosage regimens are requested, they should be supported by clinical data.

Statistical considerations

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

Response rates and mean duration of response lower than those described in the literature may lead to a restriction of the indication.

### 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[1]. 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), including a justification for the scope of the confirmatory dataset,
- 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).

1 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.

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 infusions 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 SPC.

Post-marketing safety data collection in children should be proposed in the risk management plan.

A separate safety evaluation of the excipients, including a summary of the non-clinical and literature data, should be provided.

### 7.4.2 Safety with respect to transmissible agents

Compliance with CHMP recommendations with regard to viral safety and other transmissible agents under 6.1.2 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 Coomb's test in the patient.

## 7.5 Paediatric regulations

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 covering the recommendations described in this guideline for the paediatric population. In addition, the applicant should review other areas where further study of IVIg in the paediatric population is needed and include within the plan a proposal to study at least one of these areas.

# 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.

Biological and pharmacokinetic data are the key elements to evaluate activity and safety of IVIg preparations. If a significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics and safety in PID patients and efficacy and safety in ITP patients should also be provided with the application.

## 8.1 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 include full data on antibody integrity and function in Module 3 and cross-refer to this in Module 5 of the dossier as for new products.

## 8.2 Pharmacokinetics

A limited set of pharmacokinetic data in PID patients for the changed product is required (see point 2 of 7.2). This encompasses:

Plasma concentration-time curve, half-life, area under the curve, volume of distribution, Cmax, Tmax, and elimination rate constant(s) should be measured in 20 adult PID patients assessed by repeated blood sampling after approx. the 5-6 administrations of the product until the day before the next infusion. These PK parameters should be compared to data obtained with the predecessor product, whereby predefined comparability limits should be justified by the applicant. These PK patients should be part of the safety data set (see 8.4.1)

## 8.3 Efficacy

- If the biological, pharmacokinetic and safety data show no change from the parent product:
  - For replacement therapy no further efficacy or safety data would be required.
  - 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. These patients should be part of the safety data set (see 8.4.1)
  - 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, providing that efficacy has been established in ITP for the changed product.
- If the biological, pharmacokinetics or safety data are different from the parent preparation, the product is then considered as a new product and, as such, should comply with the requirements defined in section 7.

Any new indication would have to be supported by efficacy and safety data as for a new product.

## 8.4 Safety

### 8.4.1 Adverse events

PID patients included in the limited PK study (8.2) and ITP patients (8.3) should be evaluated for safety according to the principles outlined in 7.4.

### 8.4.2 Safety with respect to transmissible agents

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