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Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)

Draft

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This guideline replaces Note for Guidance on the Clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular use (*CPMP/BPWG/283/00*)

Comments should be provided using this template. The completed comments form should be sent to **BPWPSecretariat@ema.europa.eu**

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Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)

Table of contents

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 subcutaneous and/or intramuscular use (SCIg/IMIg). The guidance covers biological data, 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 SCIg/IMIg.

The first use of polyvalent immunoglobulin preparations was as replacement therapy in humoral immunodeficiency situations. As human normal immunoglobulin for subcutaneous and intramuscular (SCIg/IMIg) 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, SCIg/IMIg 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, SCIg/IMIg has also been used in a clinical setting for its immunomodulatory activity. However, contrary to the "established immunomodulatory indications" for IVIgs, SCIgs do not yet have clearly "established" indications in this area, investigation for some auto-immune disorders are on-going and some of the chronic neurological disorders have now become the focus of attention due to possible advantages home treatment would provide.

Timeline history of guideline: The original guideline (CPMP/BPWG/283/00) came into operation in January 2003. Revision 1 updates the guideline to be consistent where applicable with the updated guideline for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94033/2007 rev. 2).

2. Scope

This guideline describes the information to be documented when an application for a marketing authorisation for SCIg/IMIg 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 normal human immunoglobulin for subcutaneous and/or intramuscular administration defined by the relevant European Pharmacopoeia monographs. The Guideline does not relate to fragmented or chemically modified products.

Quality aspects are also 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 normal immunoglobulin for subcutaneous and intramuscular use (CPMP/BPWG/282/00), currently under revision.
- 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. Possible indications

Indications for subcutaneous administration (SCIg)

Although IgG replacement therapy was initially administered intramuscularly, this route of administration can now be considered outdated for replacement therapy as the required doses to achieve adequate trough levels cannot be administered safely or without extreme discomfort for the patient; replacement therapy is therefore considered an indication for SCIgs in the following situations. SCIg can be used in all age ranges.

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.

Indications for intramuscular administration (IMIg)

Hepatitis A prophylaxis

If the SC/IMIg has a minimum antibody content for HAV of 100 IU/ml it is also used for:

- Short term hepatitis A prophylaxis in travellers who present less than 2 weeks before possible exposure
- Hepatitis A prophylaxis in persons exposed less than 2 weeks previously.

The indications listed above are considered as "established" for SCIg/IMIg and this guideline outlines the general principles for design of clinical trials.

Other indications

In other indications, relevant clinical data are required, see 5.3.4.

5. 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 SCIg preparations.

5.1. Biological data

Adequate documentation with regard to batch to batch consistency is provided in Module 3 of the dossier and should adhere to the Ph. Eur. Monograph 2788 requirements.

Additional data may be needed to support the pharmacodynamic and therapeutic activities as well as the safety profile of the SCIg preparation.

For example 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.

5.2. Pharmacokinetics

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

Pharmacokinetic data set can be derived from patients with primary immunodeficiency syndromes (PID) who are either already stabilised on SCIg treatment **(Group A)** or on IVIg treatment **(Group B)** or are naïve to Ig treatment **(Group C)** or the set can contain patients from the various groups. Groups A- C)

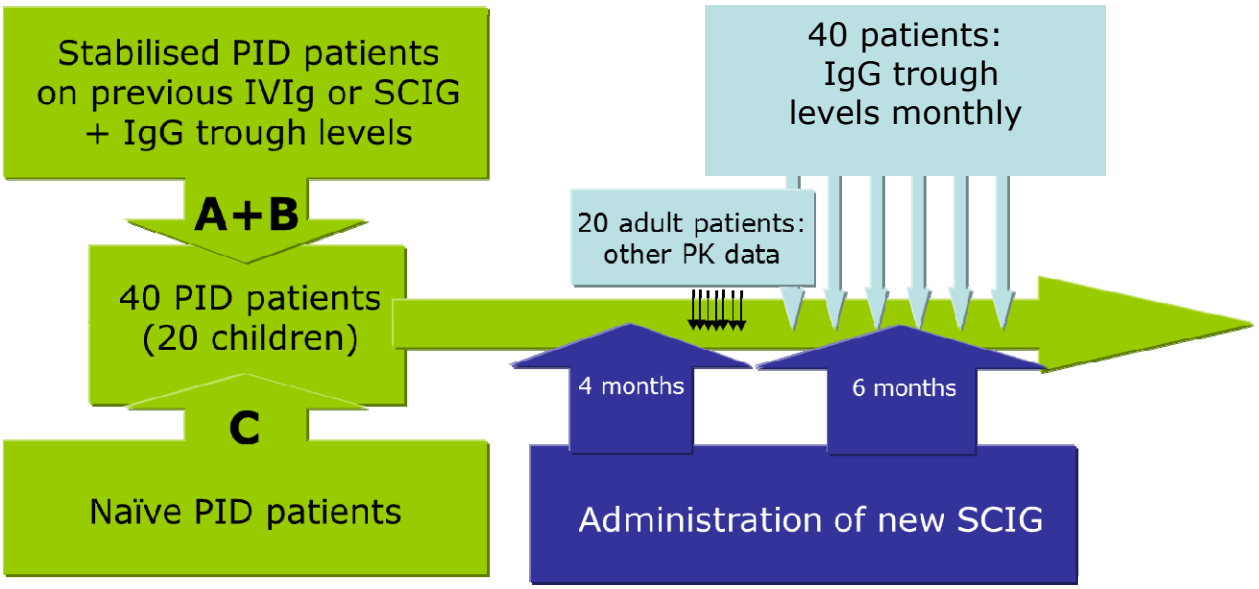
PK parameters

1. IgG trough levels should be studied in 40 PID patients, 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 on a monthly basis over a period of 6 months, starting after 4 months treatment on the new SCIg product. The monthly IgG trough levels obtained should be compared to trough levels of at least two previous infusions of the former SCIg or IVIg product (Group A + B). For Group C a descriptive comparison to published literature is requested.

2. Other PK parameters including area under the curve, Cmax, and Tmax should be measured in a sub-set of 20 adult PID patients assessed by repeated blood sampling after approximately 4 months 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.

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.

PK study chart



5.3. Efficacy

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

5.3.1. Replacement therapy in primary immunodeficiency syndromes

Efficacy should be confirmed 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 (from the PK study) should be included; approximately half of these patients should be children and adolescents with an age distribution representative of this patient population. 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 per subject per year (with the aim to achieve 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 section 5.2), all other infections, antibiotic treatment, days lost from school/work, hospitalisations and fever episodes.

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

5.3.2. 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.

The above indications would be granted as long as efficacy has been proven in primary immunodeficiency syndromes (see 5.3.1). If dosage regimens different from those in the core SmPC are requested, they should be supported by clinical data.

5.3.3. Hepatitis A prophylaxis

Clinical data are not required. The Monograph for Human normal immunoglobulin (0338) should be adhered to.

5.3.4. Other Indications

In general, 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 SCIg preparation with placebo or with an established therapy are thus required to substantiate marketing authorisation in other indications, following the relevant guidelines where available.

5.4. 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).

5.4.1. Adverse events

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

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 and local tolerance (blood pressure, heart rate, temperature, and monitoring of other adverse events, skin reactions) 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.

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 if applicable (e.g. for new excipients, new route of administration, considerably higher quantities administered compared with previous uses).

5.4.2. 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 SCIg/IMIg, 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.

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

5.4.3. 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 SCIg.

5.5. Special populations

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.

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

6. 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.

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.

6.1. Pharmacokinetics

If a PK study is needed, plasma concentration-time curve, area under the curve, Cmax, Tmax, and trough level should be measured in 20 adult PID patients assessed by repeated blood sampling after approximately 4 months of the product until immediately before the next infusion. These PK parameters should be compared to data obtained with the "pre-change" product.

PID patients included in the PK study should be evaluated for safety according to the principles outlined in 5.4.

Definitions

CLL Chronic lymphocytic leukaemia

MM Multiple myeloma