

ASSESSING THE EFFICACY AND SAFETY OF NORMAL INTRAVENOUS IMMUNOGLOBULIN PRODUCTS FOR MARKETING AUTHORISATIONS

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Additional Notes	This note for guidance describes the information to be documented for polyvalent IV immunoglobulin preparations (IVIg), including biological data, clinical trials and patient follow-up. These data are necessary for both new applications and variations to marketing authorisations.

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ASSESSING THE EFFICACY AND SAFETY OF NORMAL INTRAVENOUS IMMUNOGLOBULIN PRODUCTS FOR MARKETING AUTHORISATIONS

1 INTRODUCTION

These Guidelines describe the information to be documented for polyvalent IV immunoglobulin preparations (IVIg), including biological data, clinical trials and patient follow-up. These data are necessary for:

- i) products for which an application for a marketing authorisation is to be submitted, referred to as “New products” in the text
- ii) variations to authorised products where a significant change in the manufacturing process has been made (e.g. additional viral removal/inactivation step), referred to as “modified product” in the text.

The clinical trials described in these Guidelines should be performed according to the note for guidance on *Good Clinical Practice*.

1.1 Efficacy

Currently, a number of indications are considered as “well established”. These Guidelines outline the general principles for design of clinical trials in the following claimed indications:

- i) Replacement therapy in:
 - Primary immunodeficiency syndromes:
 - congenital agammaglobulinemia and hypogammaglobulinemia
 - common variable immunodeficiency
 - severe combined immunodeficiencies
 - Wiskott Aldrich syndrome.
 - Myeloma and chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections.
 - Congenital AIDS with recurrent infections.
- ii) 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.
- iii) Kawasaki disease
- iv) Bone marrow transplantation

Biological data and clinical evidence of efficacy and safety in primary/secondary humoral immunodeficiencies and ITP are the key elements required.

v) Other indications

Where the mechanism of action is essentially unknown, relevant clinical data are required. The trials should be carried out with reference to the Notice to Applicants and all relevant EC Guidelines for clinical studies of medicinal products.

1.2 Safety

1.2.1 Immediate adverse events

All adverse events in clinical studies must be recorded and reported.

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

1.2.2 Viral safety

It is mandatory for manufacturers of blood products to improve viral safety by rigorous selection of the donors and screening of the donations, including testing for antibodies to HIV type I and II, to hepatitis C (HCV), as well as HBsAg, and by using in the manufacturing process viral removal/inactivation steps, validated according to the EC Guidelines.

Despite selection criteria for donors and testing of the product at appropriate stages in the manufacturing process (described in Part II-V of the dossier) it is still necessary to follow-up patients treated with the product in clinical trials. For new products, viral safety data must be provided as part of the marketing application dossier. These data should be derived from all patients having entered clinical trials and any other patients having received the product. The company should continue to follow-up patients treated with the product in the long term as a post-marketing surveillance for viral markers.

In view of the difficulty in establishing seroconversion in immunodeficient patients, regular testing for liver function should be carried out; search for viral antigens and use of nucleic acid amplification methods could also be considered.

1.2.3 Other safety issues

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

2. IVIg PRODUCTS FOR WHICH AN APPLICATION FOR A MARKETING AUTHORISATION IS TO BE SUBMITTED

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

2.1 Biological and pharmacokinetic data

2.1.1 Biological (cross-reference to relevant Part II)

Adequate documentation should be provided regarding batch to batch consistency.

Most of the data are provided in Part II of the dossier and follow the European Pharmacopoeia monograph 918, Xth of January 1st, 95. 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 appear along with the cross-reference to Part II, in Part IV of the dossier.

For the values not defined in the European Pharmacopoeia 918, ranges and/or limits are to be defined.

i) Biological characteristics

– General:

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

– Of interest for pharmacodynamic and therapeutic activity

- Distribution of IgG subclasses
- Antibody content:

Bacteria:

Diphtheria
Haemophilus
Pneumococcus
Streptococcus

Virus:

Hepatitis A	range or limit to be defined
Hbs	range or limit to be defined
CMV	range or limit to be defined
Herpes-zoster	range or limit to be defined
Measles	
Parvovirus B19	

- Poliovirus type I

– Of interest for safety profile

- | | |
|----------------------------------|------------------------------|
| • IgA content | range or limit to be defined |
| • Anti-complementary activity | |
| • Anti-A and anti-B isoglutinins | range or limit to be defined |
| • Anti-D antibodies | absence thereof |
| • 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): ability to fix complement, opsonisation, phagocytosis, antibody-dependent complement 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 auto-immune models.

2.1.2 Pharmacokinetics

Pharmacokinetic data are essential to support the pharmacological activity and efficacy of a particular IVIg preparation, and may differentiate one from another. Therefore, they must be provided in each application dossier. Pharmacokinetic data should be derived from patients with hypo- or agammaglobulinemia.

Half-life should be studied in 15 patients with primary immunodeficiency due to primary immunodeficiency syndromes and possibly in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections. Patients, of whom at least 10 should have primary immunodeficiency, may already be stabilised. The pharmacokinetics should be assessed over a period of 6 months (6.5 times the expected half-life). No cross-over study is necessary.

The IgG concentration should be determined before injection of the recommended dose of the IVIg. Pharmacokinetic profile should be assessed by repeated sampling during the first infusion, and followed by trough levels (measured before the next injection). In patients naïve to IVIg, the Time to reach Steady State (T_{SS}) could be determined.

2.2 Efficacy

2.2.1 Replacement therapy in primary immunodeficiency syndromes

Clinical data should include an open study comparing historical data with reference IVIg in at least 15 patients, whatever the primary immunodeficiency syndrome. Evaluation criteria would be: number of days out of school/work, number of days of hospitalisation. Trough levels of IgG and T_{SS} when possible, should be documented over 6 months. Trough levels should be no less than 4 to 6g/L.

The results regarding efficacy would apply to all types of primary immunodeficiency syndrome due to deficiency of functional IgG.

2.2.2 Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections

Indication in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections would be granted, as long as efficacy has been proven in primary immunodeficiency syndromes.

2.2.3 Replacement therapy in congenital AIDS with recurrent infections

Indication in congenital AIDS with recurrent infections would be granted, as long as efficacy has been proven in primary immunodeficiency syndromes.

2.2.4 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 efficacy of the preparation in this indication.

- Clinical efficacy data should include an open study comparing historical data with reference IVIg, performed over a few days in acute phase on at least 15 adult chronic ITP patients, with a platelets count below $20 \times 10^9/L$.
- Information required would be:
 - response of platelet count $\geq 50 \times 10^9/L$.
 - regression of haemorrhages
 - duration of platelet response.
- Standard doses should be studied (1g/kg b.w./day for 2 days, or 0.4g/kg b.w./day for 5 days) Other dosage regimens should be documented.

2.2.5 Kawasaki disease

It is no longer ethical to conduct placebo controlled trial in this indication and it can be granted by reference to the literature, providing that efficacy in primary immunodeficiency syndromes and in ITP has been established for the relevant IVIg.

2.2.6 Allogenic Bone Marrow Transplantation

IVIg effect in BMT requires both substitution and immunomodulatory activities. In reference to this indication, specific data are not required as long as efficacy has been proven in primary immunodeficiency syndromes and in ITP for the relevant IVIg.

2.2.7 Other indications

Other possible indications can not be granted without relevant 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. These trials should be carried out with reference to the Notice to Applicants and all relevant EC Guidelines for clinical studies of medicinal products.

2.3. Safety

2.3.1 Immediate safety events

All adverse events in clinical studies should be recorded in all patients treated, whatever the indication, and reported in reference with the note for guidance on *Structure and Content of Clinical Study Reports*. Data from at least 30 patients or 180 infusions are required.

Safety evaluation should include monitoring of short term tolerance (blood pressure, heart rate, temperature, respiratory rate, and monitoring of other adverse events) at 30 minutes intervals for 4 hours and at 12 and 24 hours following the injection of the new product in patients, such as patients included in the pharmacokinetic studies or patients included in clinical studies for efficacy. Renal function should be monitored.

2.3.2 Viral safety

For new products, some viral safety data should be provided as part of the marketing application. These data should be derived from all patients having entered efficacy clinical trials and for a minimum of 3 batches of the IVIg preparation. Each patient should preferably be treated with one batch only. The company should continue to follow-up patients treated with the product in the long term as a post-marketing surveillance for viral markers. Updated data should be provided on a yearly basis after the marketing authorisation has been granted.

Blood sampling for the viral safety study should include: one pre-infusion sample for every parameter, and appropriately thereafter for up to 6 months following exposure to any new batch of the preparation. Sera from these points should be stored at -70°C as well as being tested as set out below for each patient group.

The monitoring of viral safety depends on the category of patients receiving the new product (immunocompetent or non-immunocompetent patients). Non-immunocompetent patients who are primary recipients of IVIg may not have formed detectable antibodies against human viruses which may be transmitted through IVIg. All safety data obtained in various populations receiving the new product should be presented together but identifying immunocompetent and non-immunocompetent patients. This will provide a basis for an overall safety assessment for all clinical studies.

Passive transmission of HBs, HBc, HAV and parvovirus B19 antibodies by the IVIg preparation may be difficult to differentiate from transmission of infection, and this should be discussed.

i) Immunocompetent patients

- Transaminases: the baseline should be properly established before the first infusion and all samples taken before each infusion for the 6 months after the first infusion.
- Seroconversion for:
 - HAV Ab (IgM); HIV 1-2 Ab: at weeks 12 and 24
 - HBsAg; HBc Ab and HCV Ab: at weeks 16 and 24
 - Parvovirus B19: a sample before and at week 1 after the first infusion must be taken.

If the pre-treatment sample has no anti-B19 Ab (IgM or IgG), the week 1-sample should be tested with gene amplification method.

In patients parvovirus B19 seropositive in the pre-treatment sample, no further investigation is required.

ii) Non-immunocompetent patients

- Transaminases: the baseline should be properly established before the first infusion and all samples taken before each infusion for the 6 months after the first infusion.
- Antigen detection for
 - HIV and HBs: at week 8 after the first infusion.

- HCV: nucleic acid amplification method before the first infusion and at weeks 8 and 16 after the first infusion.
- Parvovirus B19: before the first infusion and at week 1 after the first infusion using either nucleic acid amplification method or Ag detection.

3. CLINICAL TRIALS WITH AUTHORISED PRODUCTS WHERE A SIGNIFICANT CHANGE IN THE MANUFACTURING PROCESS HAS BEEN MADE (E.G. ADDITIONAL VIRAL REMOVAL/INACTIVATION STEP)

Appropriate viral removal/inactivation steps in the manufacturing process for IVIg are mandatory, to increase the viral safety of these products.

Little data exist on the effect of some viral inactivation steps or other purification steps on IgG integrity and function, or on IVIg immunomodulatory activity. Thus, it is important to include full data on antibody integrity and function, in Part II and cross-refer to this in Part IV of the dossier as for new products. Data on pharmacokinetics and on immediate safety should also be provided with the application.

3.1 Pharmacokinetics

Pharmacokinetic data must be provided in each application dossier, from patients with primary immunodeficiency syndromes

Half-life should be studied in 15 patients with primary immunodeficiency due to primary immunodeficiency syndromes and possibly in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections. Patients, of whom at least 10 should have primary immunodeficiency, may already be stabilised. The pharmacokinetics should be assessed over a period of 6 months (6.5 x expected half-life). No cross-over study is necessary.

The IgG concentration should be determined before injection of the recommended dose of the IVIg. Pharmacokinetic profile should be assessed by repeated sampling during the first infusion, and followed by trough levels (measured before the next injection). In patients naïve to IVIg, the Time to reach Steady State (T_{SS}) could be determined.

3.2 Immediate safety

Immediate safety for modified products should be the same as required for a new product, that is: all adverse events in clinical studies should be recorded in all patients treated, whatever the indication, and reported in reference with the note for guidance on *Structure and Content of Clinical Study Reports*. Data from at least 30 patients or 180 infusions are required.

Safety evaluation should include monitoring of short term tolerance (blood pressure, heart rate, temperature, respiratory rate, and other adverse events) at 30 minutes intervals for 4 hours and at 12 and 24 hours following the injection of the modified product in patients, such as patients included in the pharmacokinetic studies or patients included in clinical studies for efficacy. Renal function should be monitored.

3.3 Efficacy

3.3.1 Products for which biological, pharmacokinetic and immediate safety data are demonstrative of identity to the parent product

Where biological data, pharmacokinetics and immediate safety profile show identity to the parent product, further efficacy data will be required with the application in order to verify efficacy of the modified preparation.

Requirements on efficacy data will be as follow:

3.3.1.1 Replacement therapy in primary immunodeficiency due to Primary immunodeficiency syndromes

No further clinical trial would be required, as long as biological data, pharmacokinetics and immediate safety data have been provided and show identity to the parent product.

3.3.1.2 Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections.

No further clinical trial would be required, as long as biological data, pharmacokinetics and immediate safety data have been provided and show identity to the parent product.

3.3.1.3 Replacement therapy in congenital AIDS with recurrent infections

No further clinical trial would be required, as long as biological data, pharmacokinetics and immediate safety data have been provided and show identity to the parent product.

3.3.1.4 ITP

Clinical efficacy data should include an open study comparing historical data with reference IVIg, performed over a few days in acute phase on at least 15 adult chronic ITP patients, with a platelets count below $20 \times 10^9/L$.

Information required would be:

- response of platelet count $\geq 50 \times 10^9/L$.
- regression of haemorrhages
- duration of platelet response.

3.3.1.5 Kawasaki disease

This indication can be granted by reference to the literature, providing that biological data, pharmacokinetics and immediate safety data have been provided and show identity to the parent product, and that efficacy has been established in ITP for the modified product.

3.3.1.6 Bone Marrow Transplantation

No further clinical trial would be required, providing biological data, pharmacokinetics and immediate safety data have been provided and show identity to the parent product, and that efficacy has been established in ITP for the modified product.

3.3.1.7 Other indications

For modified preparations only the four established indications, foreseen in the core SPC, would be granted, unless relevant clinical data was submitted, either with the modified or with the parent preparation.

Providing that the modified product satisfies the above requirements, no further clinical trial would be required for the other indications.

3.3.2 Products for which biological data, pharmacokinetics or immediate safety profile are different from the parent product

If the biological data, pharmacokinetics or immediate 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 2.2.

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