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NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION (IVIg)

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CLINICAL INVESTIGATION OF HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION (IVIg)

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1 INTRODUCTION

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.

This Note for Guidance describes the biological, pharmacokinetic and clinical data required for established indications. The Note for Guidance will be updated whenever new indications for IVIg are demonstrated by clinical trials.

This Note for Guidance describes the information to be documented when an application for a marketing authorisation for IVIg is made, including biological data, 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), referred to as "modified products" in the text.

The clinical trials described in this Note for Guidance should be performed according to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

This Note for Guidance covers normal human immunoglobulin for intravenous administration defined by the European Pharmacopoeia monograph 0918. For other immunoglobulin products (fragmented, chemically modified), the same criteria apply for proof of efficacy and safety.

1.1 Efficacy

Currently, a number of indications are considered as "well established". This Note for Guidance outlines the general principles for design of clinical trials in the following claimed indications:

Replacement therapy in:

Primary immunodeficiency syndromes with hypo- or agammaglobulinemia such as:

- congenital agammaglobulinemia and hypogammaglobulinemia
- common variable immunodeficiency
- severe combined immunodeficiencies
- Wiskott Aldrich syndrome

Myeloma and chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections

Children with congenital AIDS and recurrent infections.

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
- Kawasaki disease

Allogeneic bone marrow transplantation

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

In other indications, relevant clinical data are required.

1.2 Safety

1.2.1 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

Manufacturers of plasma-derived products, including intravenous immunoglobulin, are obliged to optimise viral safety by rigorous selection of donors, screening of donations, including testing for HBsAg, antibody to hepatitis C virus, antibody to HIV 1+2 and by using appropriate viral inactivation/removal methods according to the recommendations in the "Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses" (CPMP/BWP/268/95, February 1996) and "Note for guidance on plasma-derived products" (CPMP/BWP/269/95, rev 2, July 1998).

Three principal complementary approaches are adopted to control potential viral contamination of IVIg products: selecting and testing source material, testing the capacity of the production process to inactivate or remove viruses, and testing the product at appropriate stages of production, including plasma pool testing for hepatitis C virus RNA by nucleic acid amplification technology (CPMP/BWP/390/97, March 1998).

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 still 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.

1.2.3 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.

2 PRODUCTS FOR WHICH AN APPLICATION FOR A MARKETING AUTHORISATION IS TO BE SUBMITTED: "NEW PRODUCTS"

2.1 Biological and pharmacokinetic data

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

2.1.1 Biological (cross reference to relevant Part II)

Adequate documentation with regard to batch to batch consistency is provided in Part II of the dossier and should follow the Ph. Eur. monograph. 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 Part II, in Part IV of the dossier.

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

i) <u>Biological characteristics</u>

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:

  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) <u>Biological activity</u>

- *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 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.

2.1.2 Pharmacokinetics

Pharmacokinetic data are essential to support the pharmacological activity and efficacy of the product, 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.

Pharmacokinetic parameters should be studied in 15 patients with primary immunodeficiency syndromes and possibly in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections. Patients, of whom at least 10 should have primary immunodeficiency, may already be stabilised on treatment.

The pharmacokinetics of the product should be assessed over a period of 6 months (6.5 times the expected half-life). No crossover study is necessary.

- In patients previously treated with another IVIg preparation, trough levels and treatment interval should be documented for the two previous infusions, prior to the introduction of the new IVIg preparation, in order to demonstrate the steady state of the patient. After the introduction of the new product, trough levels (4-6 g/l) and interval to reach trough levels should be measured during 4 to 6 administrations of the new product. These values should be comparable to those following treatment with the previous product. If this is not the case, a formal pharmacokinetic study will be necessary.
- If patients naïve to IVIg are studied, the time to reach steady state (Tss) should be determined. The pharmacokinetic profile should be assessed when Tss is reached, not sooner than 5-6 infusions after beginning of treatment.

2.2 Efficacy

2.2.1 Replacement therapy in primary immunodeficiency syndromes

The 15 patients included in the pharmacokinetic study should be followed over 6 months. Clinical data should be documented including infection rate and use of antibiotics.

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 lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections

The 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. 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.

2.2.3 Replacement therapy in children with congenital AIDS and recurrent infections

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

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 literature data with reference IVIg, performed over a few days in acute phase on at least 15 adult chronic ITP patients, with a platelet count of about 20×10^9/l.

Information required would be:
- platelet count $\geq 50 \times 10^9$/l and duration of platelet response (including % of responders)
- time to reach platelet count $\geq 50 \times 10^9$/l
- maximum platelet level
- regression of haemorrhages

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.

2.2.5 Guillain Barré Syndrome and 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 disease should be provided. The applicability of these data, including the dosage regimen, to the applicant 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.

2.2.6 Allogeneic bone marrow transplantation

Both substitution and immunomodulatory properties of IVIg are required for efficacy in allogeneic bone marrow transplantation. With 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 cannot 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.

2.3 Safety

2.3.1 Adverse events

All adverse events in clinical studies should be recorded in all patients treated, whatever the indication, and reported in accordance with the ICH Guidelines on "Structure and content of clinical study report", CPMP/ICH/137/95 E3. 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 repeated

intervals following the infusion of the new product in the patients included in the pharmacokinetic studies.

Renal function should be monitored, particularly in patients at risk and in those receiving high doses of IVIg.

2.3.2 Viral safety

Compliance with CPMP recommendations with regard to viral safety under 1.2.2 above is necessary for all plasma derived products and is verified by information supplied in Part II 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.

2.3.3. 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.

3 CHANGE IN THE MANUFACTURING PROCESS OF AUTHORISED PRODUCTS: "MODIFIED PRODUCTS"

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

3.1 Biological and pharmacokinetic data

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

3.1.1 Biological

The effects of changes in the manufacturing process (e.g. viral inactivation steps 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 Part II and cross-refer to this in Part IV of the dossier as for new products. If significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics, safety, and efficacy in ITP should also be provided with the application.

3.1.2 Pharmacokinetics

Pharmacokinetic data for modified products should be the same as required for a new product. (See 2.1.2)

3.2 Efficacy

- If the biological, pharmacokinetic and safety data show no change from the parent product:
  - For replacement therapy no further clinical trial would be required.
  - For ITP, since the biological rationale for efficacy is unknown, a further clinical study is required as follows:

    Clinical efficacy data should include an open study comparing literature data with reference IVIg, performed over a few days in acute phase on at least 15 adult chronic ITP patients, with a platelet count of about 20 x 10^9/l.

Information required would be:
- platelet count $\geq$ 50 x 10^9/l and duration of platelet response (including % of responders)
- time to reach platelet count $\geq$ 50 x 10^9/l
- maximum platelet level
- regression of haemorrhages

- For Guillain Barré Syndrome, Kawasaki disease and allogeneic bone marrow transplantation, indications can be granted by reference to the literature, providing that efficacy has been established in ITP for the modified 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 2.2.

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

3.3 Safety

3.3.1 Adverse events

Safety for modified products should be the same as required for the parent product. (See 2.3.1)

3.3.2 Viral safety

Requirements for viral safety are the same as for the parent product. (See 1.2.2 and 2.3.2)