



London, 25 July 2002
EMEA/CPMP/BPWG/283/00

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF
HUMAN NORMAL IMMUNOGLOBULIN FOR SUBCUTANEOUS AND
INTRAMUSCULAR USE
(CPMP/BPWG/283/00)**

DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP	September 2000 November 2000 February 2001
TRANSMISSION TO CPMP	March 2001
RELEASE FOR CONSULTATION	March 2001
DEADLINE FOR COMMENTS	End September 2001
DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP	February 2002 June 2002
TRANSMISSION TO CPMP	July 2002
ADOPTION BY CPMP	July 2002
DATE FOR COMING INTO OPERATION	January 2003

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1. INTRODUCTION

In 1952 Bruton identified the first case of antibody deficiency and introduced IgG replacement therapy. Initially this normal immunoglobulin therapy was given by intramuscular injection (IMiG). Later, due to modifications of the manufacturing process, immunoglobulin preparations could be administered intravenously (IVIg). Nowadays, the established indications for the use of normal immunoglobulins are the substitution of antibodies and immunomodulation in auto-immune-related illnesses. For the majority of these patients, treatment is based on IVIGs, which have almost completely replaced IMIGs.

However, in the last ten years IMiG preparations were re-introduced for clinical use as subcutaneous applications (SCIg), as the subcutaneous route offers the advantage of being applicable in the home setting. The main indication therefore, is primary immunodeficiencies, where the therapy regimen remains more or less constant and predictable, once the patients have attained steady state IgG serum levels. Initial treatment (i.e. until reliable steady state IgG serum levels are reached) is usually performed by a clinician using IVIg or SCIg. After carefully selecting suitable patients (guardians) for home therapy and a specified training period, the treatment can be continued at home. Subcutaneous home therapy presents a well tolerated treatment, an increase in health-related quality of life for the patient and reduces the costs in the healthcare sector. In addition, compared to the intravenous route very few adverse systemic reactions have occurred; the need for venepuncture is circumvented, which is a particular advantage in children with poor venous access and the efficacy in maintaining normal range serum IgG levels has been demonstrated in various studies.

This Note for Guidance describes the information to be documented when an application for a marketing authorisation for normal immunoglobulin for subcutaneous/intramuscular use (SC/IMiG) 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 significant change in the manufacturing process has been made (e.g. additional viral inactivation/removal steps or purification procedures), referred to as “modified product” 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 does not cover specific immunoglobulins.

IMiG preparations which fulfil the Ph. Eur. specification as to the anti-HAV content of at least 100 IU/ml can be used in hepatitis A prophylaxis.

1.1 Efficacy

Replacement therapy

Although IgG replacement therapy was initially administered intramuscularly, this route of administration can now be considered outdated as the required doses to achieve adequate trough levels cannot be administered safely or without extreme discomfort for the patient.

Replacement therapy is considered an indication for SC/IMiGs provided that the subcutaneous route is used; a prerequisite being that adequate data on efficacy and safety are submitted.

In exceptional cases, where intravenous or subcutaneous administration may not be applicable, low doses of SC/IMIg are administered by the intramuscular route. This may however not ensure sufficiently high trough levels.

Replacement therapy is indicated in primary immunodeficiency syndromes such as:

- congenital agammaglobulinemia and hypogammaglobulinemia
- common variable immunodeficiency
- severe combined immunodeficiencies
- IgG subclass deficiencies with recurrent infections

Replacement therapy is also indicated in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections

Normal immunoglobulin for subcutaneous use in replacement therapy is used in children. Therefore, when applying for approval, data on efficacy and safety in children under the age of 12 years should also be included.

Indications for intramuscular administration

In the following indications for intramuscular administration, no clinical efficacy data are required:

SC/IMIg with a minimum antibody content for HAV of 100 IU/ml:

- Short term Hepatitis A prophylaxis in travellers who present less than 2 weeks before possible exposure. It is recommended to give the immunoglobulin in combination with a Hepatitis A vaccine.

For long-term hepatitis A prophylaxis, active immunisation is recommended.

- Hepatitis A prophylaxis in persons exposed less than 2 weeks previously .

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 normal immunoglobulin, are obliged to optimise viral safety by three principal complementary approaches:

- rigorous selection of donors and screening of donations, including testing for HBsAg, antibody to hepatitis C virus (HCV) and HIV 1+2,
- screening plasma pools for HBsAg, antibodies to HCV and HIV 1+2, and HCV RNA by nucleic acid amplification technology (CPMP/390/97, March 1998),
- the use of 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 the current edition of the “Note for guidance on plasma-derived medicinal products” (CPMP/BWP/269/95).

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 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 on 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 SC/IMIg.

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 SC/IMIg 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 SC/IMIg 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 0338, ranges and/or limits are to be defined.

i) Biological characteristics

General

IMIGs are required to have a protein concentration of 160 g/l with a minimum immunoglobulin content of 90% and contain at least two antibodies (one antiviral and one antibacterial) for which an international standard is known and whose concentration has increased ten-fold compared to the original material.

- 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; cytomegalovirus; varicella-zoster; measles; rubella; parvovirus B19; poliomyelitis virus type I,
 - For products with clinical indications for prophylaxis of Hepatitis A:
antibody content of at least 100 IU/ml (hepatitis A),

Other

- Anti-A and anti-B haemagglutinins
- Haemolysins (usually anti-A and anti-B)
- Anti-D antibodies

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 cell-mediated cytotoxicity (ADCC).

2.1.2. Pharmacokinetics

As described in section 1.1, the use of a SC/IMiG in replacement therapy is considered appropriate provided that the subcutaneous route of administration of the product is used. For this, pharmacokinetic 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 when replacement therapy is applied for. Pharmacokinetic data should be derived from patients with hypo- or agammaglobulinemia. Pharmacokinetic data for at least 15 patients, including 10 PID patients should be provided. No crossover study is necessary.

The design of the following pharmacokinetic studies is based on a weekly dosage regimen. If a different dosage regimen is proposed, the study design should be adjusted accordingly.

In patients receiving IViG or SCiG, trough levels should be documented over a 3 month period prior to the introduction of the new SC/IMiG product. Three months after the introduction of the SC/IMiG, trough levels should be measured every week and treatment intervals recorded in order to obtain data for 6 weeks of the new product's use in steady state. 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.

2.2. Efficacy

2.2.1. Replacement therapy in primary immunodeficiency syndromes and in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections

i) Subcutaneous administration

Clinical efficacy data must be provided for those patients included in the subcutaneous pharmacokinetic study. In addition, efficacy data should be provided for not less than 10

children. All patients should be followed over 6 months. This should include data from the home setting.

Patients should be monitored regularly for intervals of administration, clinical data should be documented including infection rate, use of antibiotics and compliance.

Information should be provided on the selection of suitable patients (guardians) and on the length and nature of the training period for home therapy.

ii) Intramuscular administration

No efficacy data are required.

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.

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 during and after the first three administrations of the new product to the patients included in the pharmacokinetic studies.
- all adverse events occurring until the end of the study. These should be documented either by the treating physician in the clinical setting or by the patient in the home setting.

Injection site reactions should be documented.

i) Subcutaneous administration

Data from at least 30 patients, including children, followed for 3 to 6 months should be provided, including patients who are monitored at regular intervals in the home setting and patients monitored in the pharmacokinetic study.

ii) Intramuscular administration

For hepatitis A prophylaxis all available data should be provided, otherwise post-marketing surveillance should be instituted, particularly focussing on the short term tolerance

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.

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 SC/IMIg preparations.

3.1.1 Biological

The effects of changes in the manufacturing process (e.g. viral inactivation steps or 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 primary immunodeficiency 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, no further clinical trial would be required for replacement therapy.

If the biological data, 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)