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Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)

Draft

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Adoption by CHMP	
Date for coming into effect	

This guideline replaces Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (CPMP/BPWG/388/95 rev.1).

Important note

Draft guideline CPMP/BPWG/388/95 rev.2 was released for public consultation in August 2009. The purpose of this second public consultation is to specifically seek comments on the ITP section (7.3.3) where there are significant changes in the recommendations from the previous draft revision in order to encompass the recommendations by Rodeghiero F. *et al.* Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386-2393.

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Please do not provide comments on other parts of the guideline that were already provided during the 2009 consultation. These are being taken into account in this on-going revision process and an overview of all comments received with outcomes will be published at the time of finalisation of the guideline.

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

Keywords	*IVIg, human normal immunoglobulin, primary immunodeficiency syndromes, hypogammaglobulinaemia, primary immune thrombocytopenia (= idiopathic thrombocytopenic purpura) (ITP), Guillain Barré syndrome, Kawasaki disease, multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis exacerbations.*

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 (background)

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.

Timeline of first revision was as follows:

• Discussion in Blood Products Working Group	June 1999
• Release for consultation	June 1999
• Deadline for comments	December 1999
• Discussion in Blood Products Working Group	May 2000
• Final adoption by Committee for Medicinal Products for Human Use (CHMP)	December 2000

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 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.
- Children and adolescents with congenital AIDS and recurrent bacterial infections.
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).

Immunomodulatory effect in:

- Primary immune thrombocytopenia[*] (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.

[*] The term idiopathic thrombocytopenic purpura has been exchanged for primary immune thrombocytopenia according to the recommendations of an International Working Group (IWG) in "Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children"[1]. The acronym will remain the same.

6. Safety

6.1. Adverse events

All adverse events in clinical studies must be recorded and analysed with regard to causality, seriousness, outcome and expectedness (see 7.4.1.). 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.

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

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 6.2.1 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. Product for which and 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 requirements.

However, specific data are needed to support the pharmacodynamic and therapeutic activities as well as the safety profile of the IVIg preparation. The data should include the following parameters and be summarised along with the cross-reference to Module 3 (wherever applicable), in Module 5 of the dossier.

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; rubella, 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 or adolescents 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, starting after 5-6 administrations of the product (6.5 times the expected half-life). 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 immediately before the next infusion. The other PK parameters obtained should be discussed by the applicant in the light of the literature data.

PK population

Pharmacokinetic data set can be derived from patients with primary immunodeficiency syndromes (PID) who are either in group A) already stabilised on IVIG treatment or in group B) naïve to IVIG treatment or the set can contain both patient groups.

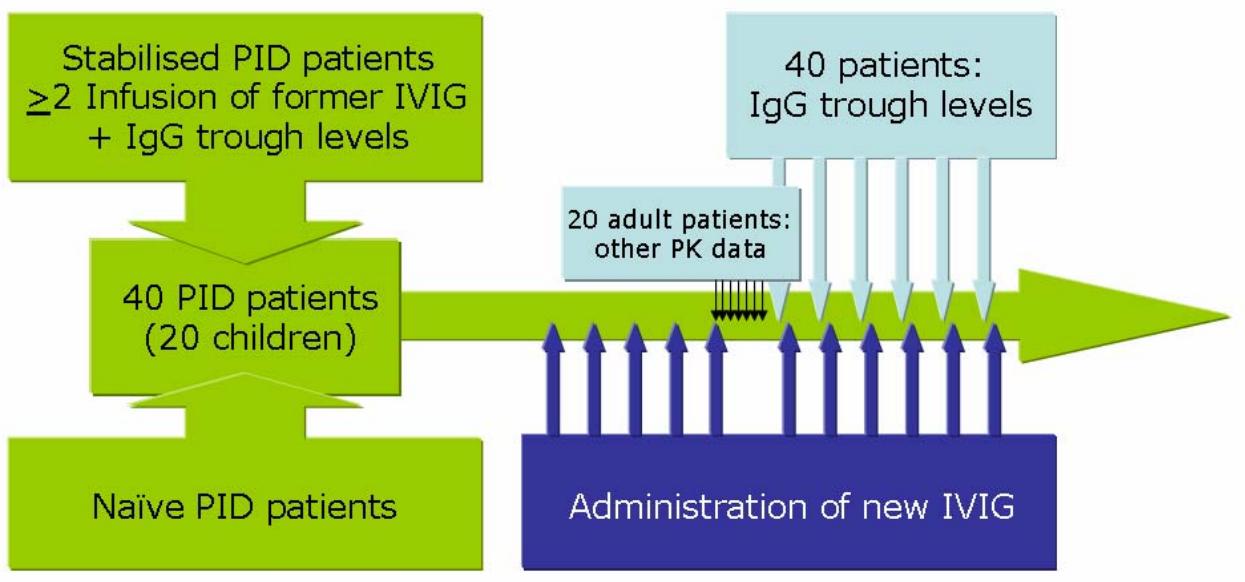
A) Patients already stabilised on IVIg treatment

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.

PK chart study



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 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 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, adolescents 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 (> 12 months duration) adult ITP patients with a baseline platelet count of $<30 \times 10^9$/l. The results should be compared to data from the literature. 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.

Baseline data on splenectomy and co-medication (especially affecting bleeding or platelets) should be provided. Patients included in the study may have refractory ITP i.e. the failure to achieve at least a response or loss of response after splenectomy and the need of treatment(s) to minimize the risk of clinically significant bleeding. In clinical practice refractory patients may need on demand IVIG to temporarily increase the platelet count sufficiently to safely perform invasive procedures or in case of major bleeding or trauma; the platelet count to be reached will depend on the nature of the invasive procedure

Corticosteroids are permitted if the patient is either on long-term stable doses of corticosteroids or the platelet count falls below 30×10^9/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:

Platelet counts should be confirmed on at least 2 separate occasions (at least 7 days apart when used to define complete response (CR) and response (R) or 1 day apart when used to define no response (NR) or loss of response.

- Number and % of patients with CR: platelet count $\geq 100 \times 10^9$/L and absence of bleeding
- Number and % of patients with R: platelet count $\geq 30 \times 10^9$/L and at least 2-fold increase the baseline count and absence of bleeding
- Time to response: time from starting treatment to time of achievement of CR or R (Late responses not attributable to the investigated treatment should not be defined as CR or R)
- Number and % of patients with NR: platelet count $< 30 \times 10^9$/L or less than 2-fold increase of baseline platelet count or bleeding
- Number and % of patients with loss of CR or R: platelet count below 100×10^9/L or bleeding (from CR) or below 30×10^9/L or less than 2-fold increase of baseline platelet count or bleeding (from R)

Duration of response

- Measured from the achievement of CR or R to loss of CR or R

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.

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 [†]. 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), This should include a justification for the
  - scope of the confirmatory dataset (sample size, dose, time frame, patient population),
  - choice of the neurological scale and clinically meaningful differences within the chosen scale

[†] 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.

- comparator arm,/ or lack of comparator
- wash-out period of previous medication and/or stable co-medication

- 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).

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 should be provided; which should encompass a summary of the non-clinical and literature data.

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 Direct Antiglobulin Test (DAT; direct Coomb's test) in the patient.

7.5. Paediatrics regulation

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.

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 or the safety of the product.

If a significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics in PID patients and efficacy and safety in ITP patients should also be provided with the application.

8.1. General aspects on clinical trials

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.

If the biological and pharmacokinetics are significantly different from the parent preparation, then the product should comply with the requirements for new product as defined in section 7.

8.2. 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.

8.3. Pharmacokinetics

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 immediately before the next infusion. These PK parameters should be compared to data obtained with the predecessor product.

8.4. Efficacy and safety

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.

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.

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

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

Definitions

CIDP Chronic inflammatory demyelinating polyradiculoneuropathy

GBS Guillain Barré Syndrome

ITP Primary immune thrombocytopenia

MMN Multifocal motor neuropathy

References

[1] Rodeghiero F. et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386-2393