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4 **Guideline on the clinical investigation of human normal**  
5 **immunoglobulin for intravenous administration (IVIg)**  
6 **Draft**

|                                                      |                             |
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7  
8 This guideline replaces Note for Guidance on the Clinical investigation of human normal  
9 immunoglobulin for intravenous administration (IVIg) (CPMP/BPWG/388/95 rev. 2)

10 Comments should be provided using this [template](#). The completed comments form should be sent  
11 to [BPWPSecretariat@ema.europa.eu](mailto:BPWPSecretariat@ema.europa.eu).

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# 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.

This is the third revision of the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94033/2007 rev. 3). It replaces Version 2 and mainly encompasses the inclusion of multifocal motor neuropathy (MMN), and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and the rewording of the secondary immunodeficiencies.

## 1. Introduction

The purpose of this Guideline is to provide applicants and regulators with harmonised guidance for applications for marketing authorisation for IVIg.

The first use of polyvalent immunoglobulin preparations was as replacement therapy in humoral immunodeficiency situations. As human normal immunoglobulin for intravenous use (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. The therapeutic effect in replacement covers primary immunodeficiencies (PID) and a number of secondary immunodeficiencies (SID). IVIg has also been used in a clinical setting for its immunomodulatory activity. The immunomodulatory indications for IVIGs based on clinical trials with various IVIg products are idiopathic thrombocytopenic purpura (ITP), Guillain Barré syndrome (GBS), Kawasaki disease, multifocal motor neuropathy (MMN), and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

## 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).

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.

86 Quality aspects are also outside the scope of this guideline.

### 87 **3. Legal basis and relevant guidelines**

88 This Guideline should be read in conjunction with the introduction and general principles (4) and part I  
89 of the Annex I to Directive 2001/83 as amended and the following guidance.

- 90 • Guideline on core SmPC for human normal immunoglobulin for intravenous administration  
91 (IVIg)EMA/CHMP/BPWP/94038/2007 Rev. 5
- 92 • Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or  
93 intramuscular administration (SCIg/IMIg) (EMA/CHMP/BPWP/410415/2011 rev 1)
- 94 • Core SmPC for human normal immunoglobulin for subcutaneous and intramuscular use  
95 (EMA/CHMP/BPWP/143744/2011 current version)
- 96 • Guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010).
- 97 • Guideline on good pharmacovigilance practices, Module V – Risk management systems  
98 (EMA/838713/2011)
- 99 • Guideline on "Comparability of Biotechnological Products (ICH Q5E, CPMP/ICH/5721/03)
- 100 • Guideline on Clinical Trials in Small Populations', (CHMP/EWP/83561/2005)
- 101 • Note for Guidance on Studies in Support of Special Populations: Geriatrics (ICH Topic E 7) and the  
102 123 Questions and Answers - EMEA/CHMP/ICH/604661/2009;

103

### 104 **4. Clinical data**

105 Biological data and clinical evidence of **efficacy and safety in primary/secondary humoral**  
106 **immunodeficiencies and ITP** are the key elements required for the licensing of IVIg in the following  
107 claimed indications:

108 IVIg can be used in all age ranges, unless otherwise specified below.

109 Replacement therapy in:

- 110 • Primary immunodeficiency syndromes with impaired antibody production.
- 111 • Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent bacterial  
112 infections, ineffective antibiotic treatment and either proven specific antibody failure (PSAF)\* or  
113 serum IgG level of <4 g/l

114 \* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide  
115 and polypeptide antigen vaccines

116 Immunomodulatory effect in:

- 117 • Primary immune thrombocytopenia\* (ITP) in patients at high risk of bleeding or prior to surgery to  
118 correct the platelet count
- 119 • Guillain Barré Syndrome (GBS)

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\*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"<sup>1</sup>. The acronym will remain the same.

- Kawasaki disease
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN),

In other indications, relevant clinical data are required, see 5.3.5.

## 5. Product 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 IVIg preparations.

### 5.1. 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 in Module 5 of the dossier along with the cross-reference to Module 3 (wherever applicable).

#### 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 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) 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.

## 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, 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. The IgG trough levels obtained and treatment intervals should be compared to either the trough levels and treatment intervals 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, C<sub>max</sub>, T<sub>max</sub>, 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 already stabilised on IVIG treatment (group A) or naïve to IVIG treatment (group B) or the set can contain both patient groups.

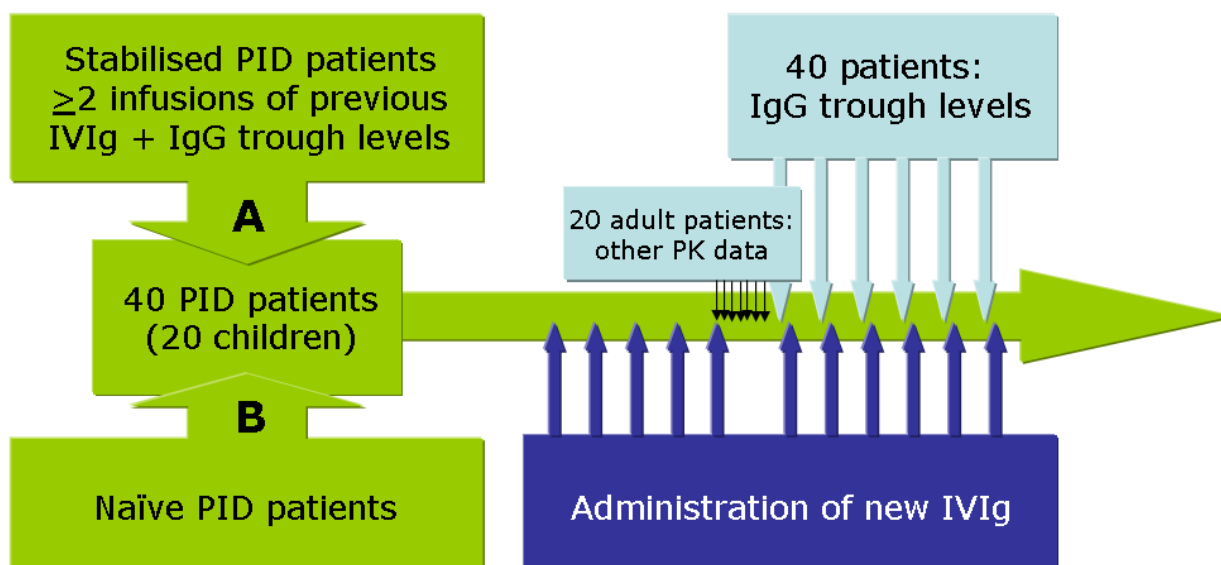
#### Group A) Patients already stabilised on IVIg treatment

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 new IVIg product, trough levels and treatment intervals should be measured.

#### Group B) Patients naïve to IVIg treatment

In patients naïve to IVIg the pharmacokinetic profile should be assessed when steady state (T<sub>ss</sub>) is reached.

### PK study chart



### 5.3. Efficacy

IVIg 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 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 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 (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 7.2), 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**

Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent bacterial infections, ineffective antibiotic treatment and either proven specific antibody failure (PSAF)\* or serum IgG level of <4 g/l

\* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

The above indication would be granted as long as efficacy has been proven in primary immunodeficiency syndromes (see 5.3.1). 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.

### **5.3.3. 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 x 10<sup>9</sup>/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 within 3 days, or 0.4 g/kg/day for 2-5 days). If other dosage regimens are applied for, 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 a response or loss of response after splenectomy and the need of treatment(s) to minimize the risk of bleeding considered as clinically significant by the investigator. 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 x 10<sup>9</sup>/l again after IVIg treatment, 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 the 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:

Number and % of patients with response (R), complete response (CR), no response (NR) and loss of response as well as time to response and duration of response.



These patient parameters are defined according to the proposals of an International Working Group<sup>1</sup>:

- patients with R: platelet count  $\geq 30 \times 10^9/l$  and at least 2-fold increase of the baseline count, confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding.
- patients with CR: platelet count  $\geq 100 \times 10^9/l$ , confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding.
- patients with NR: platelet count  $< 30 \times 10^9/l$  or less than 2-fold increase of baseline platelet count, confirmed on at least 2 separate occasions approximately 1 day apart, or bleeding.
- patients with loss of CR or R: platelet count below  $100 \times 10^9/l$  or bleeding (from CR) or below  $30 \times 10^9/l$  or less than 2-fold increase of baseline platelet count or bleeding (from R). Platelet counts confirmed on at least 2 separate occasions approximately 1 day apart.
- 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).
- 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 (and standard deviation) and median (and minimum and maximum) values for each patient, as well as for summary data.

### **5.3.4. Guillain Barré syndrome (GBS), Kawasaki disease, Multifocal motor neuropathy (MMN), Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)**

In the absence of specific clinical trial data in these indications, the efficacy in primary immunodeficiency syndromes and in ITP should be established.

The dosage regimen 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.

### **5.3.5. 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.

It is recommended to seek Scientific Advice with regard to the study design

## **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).

### **5.4.1. Adverse events**

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

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

296 Comprehensive baseline data and patient histories are essential to compare the safety signals arising  
297 from the studies. The safety signals should be compared with data and frequencies described in the  
298 literature. Any deviation from known signals and rates should be discussed. Adverse events (AEs) and  
299 serious adverse events (SAEs) from all subjects followed throughout the clinical studies should be  
300 recorded and reported regardless of whether the AE is determined to be related to the product or not.

301 Safety evaluation should include monitoring of short term tolerance (blood pressure, heart rate,  
302 temperature, and monitoring of other adverse events) at repeated intervals following the infusion of  
303 the new product. All AEs that begin during or within 72 hours after an infusion should be classified and  
304 analysed as infusional AEs.

305 AEs should be evaluated with regard to the infusion rates. Renal function should be monitored,  
306 particularly in patients at risk and in those receiving high doses of IVIg.

307 All safety data should include a separate evaluation of the safety dataset in children and adolescents.  
308 This should be compared to the adult dataset and relevant discrepancies listed in the SmPC.

309 Post-marketing safety data collection in children should be proposed in the risk management plan.

310 A separate safety evaluation of the excipients should be provided, which should encompass a summary  
311 of the non-clinical and literature data.

#### 312 **5.4.2. Safety with respect to transmissible agents**

313 Compliance with CHMP recommendations with regard to viral safety and other transmissible agents is  
314 necessary for all plasma-derived products and is verified by information supplied in Module 3 of the  
315 dossier.

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

#### 318 ***Viral Safety***

319 Manufacturers of plasma-derived products, including IVIg, are obliged to optimise viral safety by  
320 selection of donors, screening of individual donations and plasma pools for specific markers of infection  
321 and the inclusion of effective steps for the inactivation/removal of viruses in the manufacturing  
322 processes.

323 The above-mentioned procedures are now considered to be highly effective and demonstrative of the  
324 viral safety of the product with respect to enveloped viruses.

325 These procedures may be of limited value against non-enveloped viruses, such as hepatitis A virus and  
326 parvovirus B19. There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus  
327 B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an  
328 important contribution to the viral safety.

329 The applicant is nevertheless required to provide all available data gathered on patients treated with  
330 the product in clinical trials. Investigators should continue with their normal clinical practice of  
331 monitoring patients. The applicant should demonstrate that there are systems in place to collect  
332 information on patients treated with the product and to respond rapidly to any reports of infection with  
333 a full investigation.

334 For products with an entirely novel manufacturing process other principles may apply. These  
335 applications should be discussed with the Regulatory Authorities prior to submission.

### **Other transmissible agents**

Similar principles to those outlined above for viral safety apply to safety with regard to other transmissible agents including TSE and other emerging pathogens. Manufacturers should follow the respective guidance documents and position statements.

### **5.4.3. 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 Coombs' test) in the patient.

### **5.5. Studies in paediatric patients**

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.

### **5.6. Studies in elderly patients**

Separate efficacy studies in the elderly population are not considered needed, but Applicants are encouraged to include elderly patients in studies with their IVIG product.

## **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.

### **6.1. General aspects**

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. 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 a significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics and safety in PID patients is required. In addition, since the biological rationale for efficacy in ITP is not completely elucidated, efficacy and safety in ITP patients should also be provided with the application.

371 If the biological data and/or pharmacokinetics data are significantly different from the parent  
372 preparation, then the product should comply with the requirements for a new product as defined in  
373 section 5.

374 **6.2. Biological data**

375 The effects of changes in the manufacturing process (e.g. viral inactivation steps, changes in pH,  
376 changes of excipients, changes in dimer content or new purification procedures) on the biological  
377 characteristics and activity of the product should be investigated.

378 Thus, it is important to provide full data on antibody integrity and function as for new products (see  
379 section 5.1).

380 **6.3. Pharmacokinetics**

381 Plasma concentration-time curve, half-life, area under the curve, volume of distribution, C<sub>max</sub>, T<sub>max</sub>,  
382 and elimination rate constant(s) should be measured in 20 adult PID patients assessed by repeated  
383 blood sampling after approximately 5-6 administrations of the product until immediately before the  
384 next infusion. These PK parameters should be compared to data obtained with the predecessor  
385 product.

386 **6.4. Efficacy and safety**

387 For ITP, since the biological rationale for efficacy is not completely elucidated, a further clinical study is  
388 required as outlined above in 5.3.3.

389 The remaining indications that were granted for the parent product (i.e. prior to the changes in the  
390 manufacturing procedures) can be granted by reference to the literature, provided that efficacy has  
391 been established in ITP for the changed product.

392 PID patients included in the limited PK study (5.2) and ITP patients should be evaluated for safety  
393 according to the principles outlined in 5.4.

394 Requirements for viral safety and other transmissible agents are the same as for the parent product  
395 (see 5.4.2).

396

397 **Definitions**

398 CIDP    Chronic inflammatory demyelinating polyradiculoneuropathy

399 GBS     Guillain Barré Syndrome

400 ITP     Primary immune thrombocytopenia

401 MMN    Multifocal motor neuropathy

402 **References**

403        1    Rodeghiero F. *et al.* Standardization of terminology, definitions and outcome criteria in immune  
404            thrombocytopenic purpura of adults and children: report from an international working group.  
405            Blood. 2009; 113:2386-2393