Authorised medicines and regulatory considerations by EMA

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Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Claudia Gramiccioni, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (Resolution n. 37 dated 13/10/2020).

N.B. I am not receiving any compensation

Scope

1. To present the current regulatory requirements for the clinical development of immunoglobulins in support of a marketing authorisation application.

Updated firstly in

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

16 December 2021
EMA/CHMP/BPWP/94033/2007 rev. 4
Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg)

16 December 2021
EMA/CHMP/BPWP/94038/2007 Rev. 6
Committee for Medicinal Products for Human Use (CHMP)

Date for coming into effect	1 January 2022

2. To present:

- the Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)

and

- the Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCIg/IMIg)

Both under public consultation until 31 May 2025

3. To analyze the authorized medicinal products and their therapeutic indications

IVIg Therapeutic Indications

Replacement therapy in adults, children, and adolescents (0–18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial 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.

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

If the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard is met and added to the product specification(FDA, 2018).

Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (0–18 years) in:

- primary immunodeficiency syndromes (PID) with impaired antibody production
- secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial 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.

Immunomodulation in adults and children and adolescents (0–18 years) in:

- primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct platelet count
- Guillain-Barré syndrome
- Kawasaki disease (in conjunction with acetylsalicylic acid)

Authorised IVIg

CP	Notes
Flebogamma DIF	2-18 years Measles pre-/post exposure prophylaxis
Kiovig	
Privigen	
Deqsiga (pending)	

DCP/MRP	Notes
Octagam 5%	Measles pre-/post exposure prophylaxis
Intratect	
Octagam 10%	Measles pre-/post exposure prophylaxis
Iqymune	
Globiga	Measles pre-/post exposure prophylaxis
Gamunex	Measles pre-/post exposure prophylaxis
Yimmugo	
Ig vena	

IVIg vs SC/IM Ig

Administration	IV infusion	SC infusion or rapid push
Infusion frequency	Less frequent, every 3–4 wk	Can be given every day to twice weekly
Volume	Larger	Smaller (minimal change to intravascular volume in high-risk patients)
Time needed	2–6 h	30–90 min (infusion) 5–20 min (push)
High-dose therapy	Possible	Limited by volume tolerated per site and number of sites
IgG level measurement	IgG trough, drawn at the end of 3- to 4-wk infusion cycle	IgG steady state, can be drawn anytime
Pharmacokinetics	Rapid increase in serum level at initiation Fluctuating serum IgG level Wear-off effects from low trough levels	— Steady serum IgG level No wear-off effects
Infusion	Requires IV access Requires trained medical personnel	SC infusion; preferred in poor venous access Can be administered by self, partner, or parent
Infusion location	Hospital, clinic, infusion center, home	Home

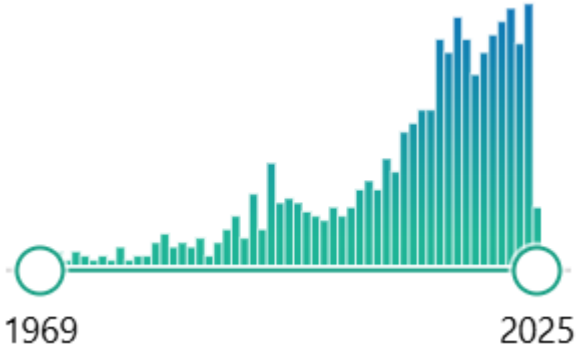
Side effects		
Infusion site reactions	Uncommon	Common but usually not serious and tend to decrease over time: swelling, erythema, itching for few hours to few days
Systemic reactions	Common, especially during first few infusions	Uncommon
Patient satisfaction	Preferred by patients not favoring self-administration	Improved quality of life (flexibility, independence, portability)
Cost	Higher (product, IV supplies, facility fee, nursing charges)	Lower (product and infusion supplies, pump)

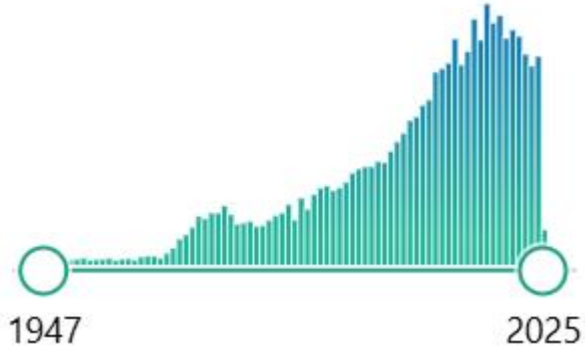
Sriaroon P. Immunology and Allergy Clinics of North America 2015, 35(4):713-730

Human normal immunoglobulin for for subcutaneous and/or intramuscular administration (SCIg/IMIg)

Replacement therapy in primary/secondary humoral immunodeficiencies

912 results





Immunomodulation

14,346 results

Rationale for updating

Second revision of the Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) (EMA/CHMP/BPWP/410415/2011 rev 2)
to be consistent, where applicable,
with the revised guideline for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 current version).
It clarifies the indication wording of secondary immunodeficiencies (SID) and includes the indication for maintenance treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Consequent revision of:
Guideline on core SmPC (EMA/CHMP/BPWP/143744/2011 rev.2)

This guideline describes the information to be documented when an application for a marketing authorisation for SCIg/IMIg is made, including biological data, pharmacokinetics, clinical trials and patient follow-up.

Products for which an application for a marketing authorisation is to be submitted

Authorised products where a significant change in the manufacturing process has been made (e.g. additional viral inactivation/removal steps or new purification procedures).

Biological data

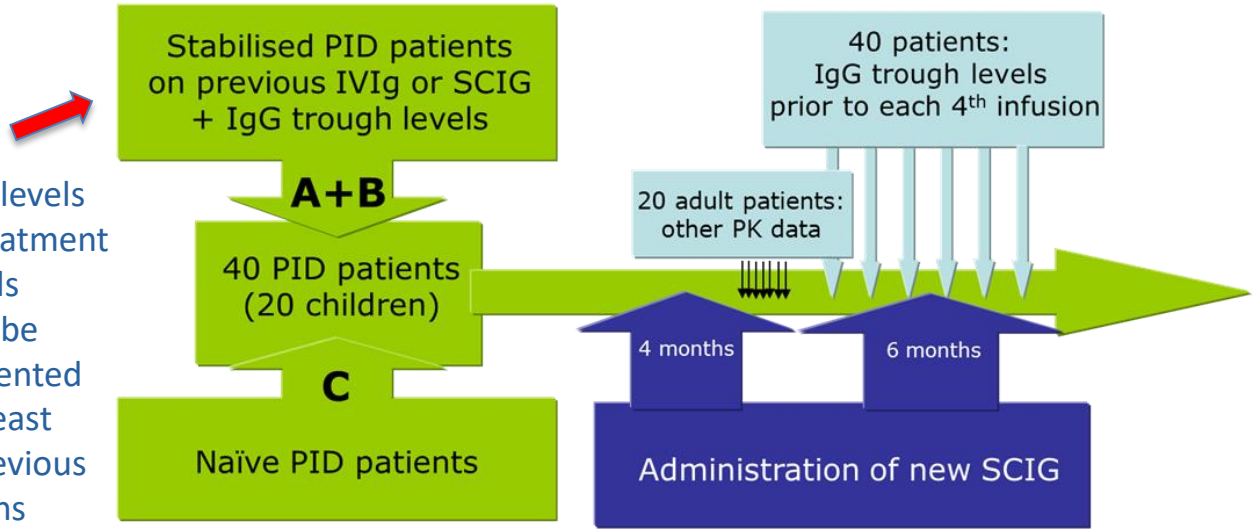
Batch to batch consistency has to be provided in Module 3 (Ph. Eur. Monograph 2788).
Additional specific data may be needed to support the pharmacodynamic and therapeutic activities as well as the safety profile of the SCIg preparation.
The relevant data should be summarised in Module 5 (with cross-reference to Module 3).
For example 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.

Pharmacokinetics

It may differentiate one product from another.
Therefore, PK data must be provided in each application dossier

trough levels and treatment intervals should be documented for at least two previous infusions



IgG trough levels assessed prior to each infusion over a period of 6 months, starting after 4 months treatment on the new SCIg product. The results should be compared to trough levels of at least two previous infusions of the former SCIg or IVIg product (Group A + B). For Group C, descriptive comparison to published literature.

Other PK parameters: Plasma concentration-time curve, AUC, Cmax, Tmax in a sub-set of 20 adult PID patients assessed by repeated blood sampling after approximately 4 months of the product until immediately before the next infusion.

Efficacy as replacement therapy

Primary (PID) and Secondary (SID) Immunodeficiency Syndromes

Open label, single-arm clinical trial of one-year duration in at least 40 patients with PID from the PK study (approximately half children and adolescents)

Primary efficacy objective: rate of acute serious bacterial infections less than 1.0 per person per year

Secondary endpoints: PK parameters, e.g. IgG trough levels, all other infections, antibiotic treatment, days lost from school/work, hospitalisations and fever episodes.

The efficacy results from this study would apply to all types of PIDs due to deficiency of functional IgG.

If efficacy is proven in PIDs, indication granted for SIDs

Main updates - Secondary Immunodeficiencies

Change	Rationale
Section 4: "Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/L. Proven specific antibody failure (PSAF) = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines". **Section 5.3.2:** The above indications would be granted as long as efficacy has been proven in primary immunodeficiency syndromes (see 5.3.1); if efficacy has been demonstrated in PIDs, no further studies are required to demonstrate efficacy in SIDs. Dosage regimens different from the standard dosages stated in the core SmPC should be supported by clinical data.	According to the current "Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) - Rev. 6" (EMA/CHMP/BPWP/94038/2007 Rev. 6) and to what already evaluated and authorized for several SCIg, in the frame of specific centralized or decentralized procedures.

Corresponding update of Core SmPC	Rationale
Section 4.1: "Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/L. Proven specific antibody failure (PSAF) = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines". **Section 4.2:** The recommended dose administered at regular intervals (approximately once per week) is to reach a cumulative monthly dose of the order of 0.2-0.4 g/kg (1.2 – 2.4 ml/kg). Each single dose may need to be injected at different anatomic sites. IgG trough levels should be measured and assessed in conjunction with the incidence of infection. The dose should be adjusted as necessary to achieve optimal protection against infections; an increased dose may be required in patients with persisting infection, and a decreased dose can be considered when the patient remains infection free.	The posology has been established on the basis of cumulative montly dose of IVIg considered protective in the same indication and according to what already evaluated and authorized for several SCIg, in the frame of specific centralized or decentralized procedures.

Efficacy in immunomodulation

Chronic inflammatory demyelinating polyradiculoneuropathy a as maintenance therapy (CIDP)

Efficacy in primary immunodeficiency syndromes established

The only currently demonstrated immunomodulatory indication for SCIgs, based on phase III clinical trials conducted with several SCIg products.

Extrapolation to maintenance therapy for CIDP is possible without perform separate clinical trials in this indication, if adequately justified.

The other immunomodulatory indications for IVIgs are not yet approvable for SCIgs as no clinical data are available.

The dosage regimen should however be justified. If other dosage regimens than the ones provided in the guideline on core SmPC are requested, they should be supported by relevant clinical data.

Main updates – Inclusion of CIDP

Change	Rationale
Section 4: Inclusion of the indication "Immunomodulation in: • chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), as maintenance therapy after stabilisation with IVIg". **Section 5.3.3:** If the efficacy in primary immunodeficiency syndromes is established, then an extrapolation to maintenance therapy for CIDP after stabilisation with IVIg might be possible without the need to perform separate clinical trials in this indication, if adequately justified. The dosage regimen should, however, be justified. If other dosage regimens than the ones provided in the guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCIg/IMIg) are requested, they should be supported by relevant clinical data.	Inclusion of CIDP **on the basis of phase III clinical trials**. The other "established" immunomodulatory indications for IVIgs are not yet established for SCIgs.

Corresponding update of Core SmPC	Rationale
Section 4.1: According to the text of Guideline **Section 4.2:** *Immunomodulatory therapy in CIDP* Treatment is initiated 1 week after the last IVIg infusion. The recommended subcutaneous dose is 0.2 to 0.4 g/kg body weight per week administered in 1 or 2 sessions over 1 or 2 consecutive days. The initial subcutaneous dose may be a 1:1 conversion from the previous IVIg dose (calculated as weekly dose). Example: a 1 g/kg IVIg dose given every 3 weeks would convert into a 0.33 g/kg dose given once a week. The weekly dose can be divided into smaller doses and administered by desired number of times per week. For dosing every two weeks, the weekly dose should be doubled.	The posology has been established according to what already evaluated and authorized for other SCIg, in the frame of specific centralized or decentralized procedures.

Indications for intramuscular use (IMIg)

Hepatitis A prophylaxis

If minimum antibody content for HAV of 100 IU/ml, it is also used in adults and children and adolescents (0-18 years) for:

- Pre-exposure prophylaxis, preferably in combination with vaccination, in unvaccinated individuals travelling in less than 2 weeks to areas at risk of hepatitis A.
- Post-exposure prophylaxis in unvaccinated individuals within 2 weeks of hepatitis A virus (HAV) exposure.

For long term hepatitis A prophylaxis, vaccination is recommended.

Clinical data not required.

The Monograph for Human normal immunoglobulin (0338) should be adhered to.

Safety

AEs and SAEs from clinical studies should be recorded and reported (causality, seriousness, severity, outcome and expectedness).

Separate evaluation of the safety dataset in children and adolescents, to be compared to the adult dataset: relevant discrepancies listed in the SmPC.

Separate safety evaluation of the excipients

Monitoring of short term and local tolerance (blood pressure, heart rate, temperature, and monitoring of other adverse events, skin reactions) at repeated intervals after the infusion

Post-marketing safety data collection in children should be required in the RMP

Viral Safety

Reference to Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95 rev.3) and Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010).

All available data gathered on patients treated in clinical trials should be provided.

Similar principles should apply for all transmissible agents including TSE and other emerging pathogens.

Transfer effect of passive transmission of haemagglutinins (anti-A/anti-B), and anti-D should be evaluated by searching for haemolysis and performing a Direct Antiglobulin Test (DAT – Direct Coombs Test)

Other Changes on Guideline on Clinical Investigation

“New products”

- 5.4.4. *Other transmissible agents*

Similar principles t
viral safety sho
transmissible
Transmissible
encephalopathy
emerging pathoge
Manufacturers should follow the respective guidance documents and position statements.

Formal update of Sections

- ***3 Legal basis and relevant guidelines***
- ***5.4.1 Adverse events***
- ***7 References***

“ Change in the manufacturing process of authorised products ”

- 6.2 Biological data

the manufacturing
eps, changes in pH,
new purification
characteristics and
investigated.
vide full data on
antibody integrity and function as for new product (see section 5.1).

Other Changes on Guideline on core SmPC

- **Section 4.1:** Addition of warning on age ranges in case of safety issues due to excipients (sorbitol and fructose intolerance);
- **Section 4.2:** Addi[illegible]y, renal or haepatic impairment;
- **Section 4.4:** Additi[illegible]n traceability, deletion of warning on sodi[illegible]
- **Section 4.6:** Updat[illegible]
- **Section 4.8:** In the table on AEs, addition of the specification of frequency per patient and per infusion;
- **Section 6.6:** Addition of the sentence on the appearance of the solution.

Formal revision of all sections, review by QRD members to be in line with the QRD template

Main comment during GCG revision

The proposal have been discussed by the drafting group and considered not acceptable for the following reasons:

even if, on the basis of some literature data, this route of administration is considered outdated and not practical, it is still useful in some conditions, such as, for example, in pre- and post- exposure hepatitis A prophylaxis and in international travellers (ACIP recommendations), that is actually an authorised therapeutic indication if the SCIg/IMIg has a minimum antibody content for HAV of 100 IU/ml. Therefore this route of administration has been considered still valid in some circumstances.

Request to consider the removal of IM administration since outdated

Moreover, it has to be noted that a warning, informing that IM administration is outdated in other therapeutic indications, such as replacement therapy, as the required doses cannot be administered safely or without excessive and unnecessary discomfort for the patient, is reported at the end of Section 1 of Guideline on Clinical Investigation.

Authorised SC/IMIg

CP	Notes
Hizentra	Already updated
Hyqvia	Already updated

DCP/MRP	Notes
Octanorm	
Cuvitru	
Cutaquig	Already updated for primary and Secondary Immunodeficiencies. Not updated for Immunomodulatory indications
Xembify	

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