Summary of Product Characteristics

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Yimmugo 100 mg/mL solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Human normal immunoglobulin (IVIg)

2.2 Qualitative and quantitative composition

One mL contains:
Human normal immunoglobulin 100 mg (purity of at least 96% IgG)

Each vial of 50 mL contains: 5 g of human normal immunoglobulin
Each vial of 100 mL contains: 10 g of human normal immunoglobulin
Each vial of 200 mL contains: 20 g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):
IgG1 62%
IgG2 32%
IgG3 4%
IgG4 1%

The maximum IgA content is 500 micrograms/mL.

Produced from the plasma of human donors.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
The solution is clear to slightly opalescent and colourless to pale yellow.
Yimmugo has a pH of 4.4–5.2 and an osmolality of 280–380 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

*R*eplacement 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

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

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain Barré syndrome

- Kawasaki's disease (in conjunction with acetylsalicylic acid; see section 4.2)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

4.2 Posology and method of administration

IVIg therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.

Posology

The dose and dose regimen are dependent on the indication.
The dose may need to be individualised for each patient dependent on the clinical response. Dose based on body weight may require adjustment in underweight or overweight patients.

The following dose regimens are given as a guidance.

Replacement therapy in primary immunodeficiency syndromes
The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/L or within the normal reference range for the population age. 3–6 months are required after the initiation of therapy for equilibration (steady-state IgG levels) to occur. The recommended starting dose is 0.4–0.8 g/kg given once, followed by at least 0.2 g/kg given every 3–4 weeks.

The dose required to achieve a trough level of IgG of 6 g/L is of the order of 0.2–0.8 g/kg/month. The dosage interval when steady state has been reached varies from 3–4 weeks.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Replacement therapy in secondary immunodeficiencies (as defined in section 4.1)
The recommended dose is 0.2–0.4 g/kg every three to four weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

Immunomodulation in:

Primary immune thrombocytopenia
There are two alternative treatment schedules:

- 0.8–1 g/kg given on day 1; this dose may be repeated once within 3 days
- 0.4 g/kg given daily for 2–5 days.

The treatment can be repeated if relapse occurs.
Guillain Barré syndrome
0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).

Kawasaki's disease
2.0 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Chronic inflammatory demyelinating polyneuropathy (CIDP)
Starting dose: 2 g/kg divided over 2–5 consecutive days
Maintenance doses: 1 g/kg divided over 1–2 consecutive days every 3 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Multifocal Motor Neuropathy (MMN)
Starting dose: 2 g/kg divided over 2–5 consecutive days.
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

The dosage recommendations are summarised in the following table:

Indication	**Dose**	**Frequency of infusions**
Replacement therapy:		
Primary immunodeficiency syndromes	Starting dose: 0.4–0.8 g/kg	
	Maintenance dose: 0.2–0.8 g/kg	every 3–4 weeks
Secondary immunodeficiencies (as defined in section 4.1)	0.2–0.4 g/kg	every 3–4 weeks
Immunomodulation:		
Primary immune thrombocytopenia	0.8–1 g/kg	on day 1, possibly repeated once within 3 days
	or	
	0.4 g/kg/d	for 2–5 days
Guillain Barré syndrome	0.4 g/kg/d	for 5 days
Kawasaki's disease	2 g/kg	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Starting dose: 2 g/kg	in divided doses over 2–5 days
	Maintenance dose: 1 g/kg	every 3 weeks in divided doses over 1–2 days
Multifocal Motor Neuropathy (MMN)	Starting dose: 2 g/kg	in divided doses over 2–5 consecutive days
	Maintenance dose: 1 g/kg	every 2–4 weeks
	or	or
	2 g/kg	every 4–8 weeks in divided doses over 2–5 days

Paediatric population
The posology in children and adolescents (0–18 years) is not different to that of adults as the posology for each indication is given by body weight and must be adjusted to the clinical outcome of the above mentioned conditions.

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment unless clinically warranted, see section 4.4.

Elderly
No dose adjustment unless clinically warranted, see section 4.4.

Method of administration
Intravenous use.

Yimmugo should be infused intravenously at an initial rate of not more than 0.3 mL/kg/h for 30 minutes. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, the infusion rate can be gradually increased to a maximum of 2 mL/kg/h for the first infusion. For subsequent infusions, if well tolerated, the infusion rate can be gradually increased to a maximum of 6 mL/kg/h.

Replacement Therapy:
In patients who have tolerated the infusion rate of 6 mL/kg/h well, the rate may be gradually increased to a maximum of 8 mL/kg/h.

4.3 Contraindications

- Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients (see section 4.4 and 6.1).
- Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precautions for use

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal immunoglobulin by initially administering the product slowly (0.3 mL/kg/h corresponding to 0.005 mL/kg/min),
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion in a controlled healthcare setting in order to detect potential adverse signs and to ensure that emergency treatment can be administered immediately should problems occur. All other patients should be observed for at least 20 minutes after administration.

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the IVIg infusion
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics (see section 4.5)

In case of adverse reaction, either the infusion rate must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.
Infusion-related reaction
Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) may be related to the rate of infusion. The recommended infusion rate given under section 4.2 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Adverse reactions may occur more frequently

- in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion
- in patients with an active infection or underlying chronic inflammation

Hypersensitivity
Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients

- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin

In case of shock, standard medical treatment for shock should be implemented.

Thromboembolism
There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Acute renal failure
Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain these excipients may be considered. Yimmugo does not contain sucrose, maltose or glucose.

Aseptic meningitis syndrome (AMS)
AMS has been reported to occur in association with IVIg treatment.
The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL.
AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Haemolytic anaemia
IVIg products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. (See section 4.8.)

Neutropenia/Leukopenia

A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIg. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion-related acute lung injury (TRALI)
In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion-related acute lung injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours after a transfusion, often within 1–2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing
After the administration of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.
Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped hepatitis A virus (HAV) and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

Paediatric population
The special warnings and precautions for use mentioned for the adults should also be considered for the paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines
Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this medicinal product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Loop diuretics
Avoidance of concomitant use of loop diuretics.

Paediatric population
It is expected that the same interaction mentioned for the adults may also occur in the paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women. IVIg products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are expected.

Breast-feeding
The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to breast-feeding mothers. Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns/infants are anticipated.

Fertility
Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

Yimmugo has minor influence on the ability to drive and use machines. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass (see also section 4.4):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

For safety information with respect to transmissible agents, see section 4.4.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Frequency of Adverse Drug Reactions (ADRs) in clinical studies with Yimmugo, indications PID and ITP *(Frequencies are calculated per patients treated (n=101) and per infusions administered (n=1038) respectively.)*

MedDRA System Organ Class (SOC)	**Adverse reaction (MedDRA Preferred Term (PT))**	**Frequency per patient (n=101)**	**Frequency per infusion (n=1038)**
Nervous system disorders	Headache	Very common	Common
	Dizziness	Common	Uncommon
General disorders and administration site conditions	Fatigue	Common	Uncommon
	Chills	Common	Uncommon
	Pyrexia	Common	Uncommon
Gastrointestinal disorders	Nausea	Common	Uncommon
	Abdominal pain upper	Common	Uncommon
	Oral pain	Common	Uncommon
Investigations	Blood pressure increased	Common	Uncommon
	Coombs test positive/ Coombs test direct positive	Common	Uncommon
Skin and subcutaneous tissue disorders	Skin reaction	Common	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Common	Uncommon
	Pain in extremity	Common	Uncommon

Respiratory, thoracic, and mediastinal disorders	Dyspnoea	Common	Uncommon
	Oropharyngeal pain	Common	Uncommon
Blood and lymphatic system disorders	Neutropenia	Common	Uncommon
	(Intravascular) haemolysis	Common	Uncommon
Ear and labyrinth disorders	Vertigo	Common	Uncommon
	Tinnitus	Common	Uncommon
Immune system disorders	Anaphylactic reaction	Common	Uncommon
Psychiatric disorders	Confusional state	Common	Uncommon
Vascular disorders	Flushing	Common	Uncommon

The reported adverse reactions for Yimmugo are in the expected profile for human normal immunoglobulins.

Paediatric population
Frequency, type and severity of adverse reactions in the paediatric population are expected to be the same as in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including infants, elderly patients or patients with cardiac or renal impairment (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02
Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donors. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.
The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Clinical efficacy and safety

PID

In an open-label, prospective, multicentre, multinational trial clinical efficacy, safety, and pharmacokinetic properties of Yimmugo as replacement therapy in patients with PID were investigated in 67 subjects (including 12 children and 6 adolescents). Subjects received a dose between 200 mg to 800 mg per kg body weight (bw) every 3 or 4 weeks, for a treatment period of approximately 12 months. The initial dose and dosage interval was consistent with the subject's prestudy IVIg treatment. The primary efficacy endpoint was the number of serious bacterial infections per subject per year. Secondary efficacy variables included occurrence of any infection of any kind or seriousness, time to resolution of infections, use of antibiotics, the number of days of work/school missed, the number and days of hospitalisations, and the number of episodes of fever. One adult subject experienced one event classified as an acute serious bacterial infection (SBI), resulting in an unadjusted SBI rate of 0.01 per subject-year. The secondary efficacy endpoints supported the efficacy in subjects with PID, in all

different age groups assessed. The mean and median total IgG trough levels remained nearly constant throughout the trial in both schedule groups and stayed well above the targeted minimal trough level of 5–6 g/L.
No fatal AE was observed during the trial. Two treatment-emergent SAEs in adult subjects were assessed as related to Yimmugo (anaphylactic reaction, worsening of neutropenia). The most frequent related infusional AEs were headache (13.4%) and fatigue (4.5%). No non-infusional AE was assessed as related to study medication.

ITP

In an open-label, prospective, randomized, multicentre, multinational trial efficacy and safety of Yimmugo was investigated in 34 adult subjects with ITP. Subjects were randomized in a 1:1 ratio to receive Yimmugo at a total dose of 2 g/kg bw administered either as two daily doses of 1 g/kg bw given on 2 consecutive days or 0.4 g/kg bw per day for 5 consecutive days (i.e., a total dose of 2 g/kg bw per treatment course). 18 of the 34 subjects (52.9%) achieved response, defined as platelet count of ≥30 × 10^9/L and at least a 2-fold increase of the baseline count, confirmed on at least two separate occasions at least 7 days apart, and absence of bleeding. 18 of all 19 subjects with baseline platelet counts <20 × 10^9/L achieved an increase in platelet count to at least 50 x 10^9/L within 7 days after the first infusion, for a response rate of 94.7 %. Additionally, the maximum platelet count, the time to reach a platelet count of at least 30 x 10^9/L, the duration of that response (i.e., the number of days the platelet count remained in excess of 30 x 10^9/L), and the regression of haemorrhages in subjects who had bleeding at baseline were observed. There were no clinically relevant differences between the 2-day and 5-day treatment groups. After Yimmugo administration, the mean platelet count over time showed a pattern typical for treatment with IVIg (i.e. continuous increase from baseline through Day 8 followed by decrease).
No fatal and no related serious AE occurred during the trial. The most frequent non-serious ADRs were headache and (intravascular) haemolysis; both with a frequency of 14.7%, which represents 5 subjects each. The most frequent infusional ADR was headache (14.7% of all subjects). Non-infusional ADRs occurred in 14.7% of subjects: haemolysis (8.8%), intravascular haemolysis (2.9%), and Coombs test positive (2.9%).

Paediatric population
The overall benefit-risk profile of Yimmugo in subjects with PID was favourable in all age groups assessed.

5.2 Pharmacokinetic properties

Absorption

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration.

Distribution

It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3–5 days equilibrium is reached between the intra- and extravascular compartments.

Elimination

The half-life may vary from patient to patient. The pharmacokinetic parameters for Yimmugo were determined in a clinical trial in 55 PID patients. In this trial the mean half-life was 24.2–31.1 days depending on the treatment schedule (see table below). IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Pharmacokinetic parameters of Yimmugo in PID patients

	Q3W Schedule			**Q4W Schedule**		
	n	**Mean (SD)**	**gMean (CV [%])**	**n**	**Mean (SD)**	**gMean (CV [%])**
C_{max} (g/L)	10	30.0 (7.65)	29.1 (27.6)	45	26.5 (6.08)	25.9 (22.4)
t_{max} (day)*	10	0.22 (0.06 – 0.28)		45	0.20 (0.06 – 7.03)	
AUC_{tau} (day × g/L)	10	374.3 (110.69)	358.8 (32.0)	42	398.5 (99.27)	388.0 (23.2)
$t_{1/2}$ (day)	7	24.2 (5.899)	N/D	25	31.1 (12.899)	N/D

*For t_{max}, median (minimum - maximum) values are shown.
Abbreviations: AUC_{tau} = area under the concentration-time curve calculated from start to end of the dosing interval; C_{max} = maximum serum concentration; CV = coefficient of variation; gMean = geometric mean; N = total number of subjects; n = number of subjects with data; N/D = not determined; Q3W = 3-week (schedule); Q4W = 4-week (schedule); SD = standard deviation; $t_{1/2}$ = terminal elimination half-life; t_{max} = time to maximum serum concentration.

Paediatric population
No differences were seen in the pharmacokinetic parameters between adult and paediatric study patients with PID.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body.

Repeated dose toxicity testing and embryo-foetal toxicity studies are impracticable due to induction of, and interference with antibodies. Effects of the product on the immune system of the newborn have not been studied.

Since clinical experience provides no hint for tumorigenic and mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary.
A single dose toxicology study has been performed in rats including safety pharmacology endpoints. Under the conditions of this study, the single intravenous infusion administration of Yimmugo was not associated with any adverse findings.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, polysorbate 80, water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, nor with any other IVIg products.

6.3 Shelf life

30 months.

During the shelf-life, the product may be kept at room temperature (up to 25 °C) for a single period not exceeding 6 months. Once the medicinal product has been taken out of the refrigerator, it must not be returned to the refrigerator. Please record the beginning of storage at room temperature on the product carton. Store in the original package in order to protect from light.

After first opening, an immediate use is recommended.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original package in order to protect from light.

For storage at room temperature, see section 6.3.

6.5 Nature and contents of container

Colourless glass vials (Type II glass) with bromobutyl rubber stopper and a flip off cap (plastic).

Pack with 1 vial with 50 mL, 100 mL or 200 mL solution.
Pack with 3 vials with 100 mL or 200 mL solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The product should be brought to room or body temperature before use.
The solution should be clear or slightly opalescent and colourless to pale yellow. Solutions that are cloudy or have deposits should not be used.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0592/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd August 2024

10 DATE OF REVISION OF THE TEXT