Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

CUTAQUIG, 165 mg/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (SCIg)

One ml contains:
Human normal immunoglobulin.....165 mg
(purity of at least 95% IgG)

Each vial of 6 ml contains: 1 g of human normal immunoglobulin.
Each vial of 10 ml contains: 1.65 g of human normal immunoglobulin.
Each vial of 12 ml contains: 2 g of human normal immunoglobulin.
Each vial of 20 ml contains: 3.3 g of human normal immunoglobulin.
Each vial of 24 ml contains: 4 g of human normal immunoglobulin.
Each vial of 48 ml contains: 8 g of human normal immunoglobulin.

Distribution of the IgG subclasses (approx. values):

IgG_1 ..... 71%
IgG_2 ..... 25%
IgG_3 ..... 3%
IgG_4..... 2%

The maximum IgA content is 300 micrograms/ml.

Produced from the plasma of human donors.

Excipient(s) with known effect:
This medicinal product contains 33.1 mg sodium per vial of 48 ml and 13.8 mg per vial of 20 ml, see section 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.
The liquid preparation is clear and colourless.
During storage the liquid may turn to slightly opalescent and pale-yellow.
The osmolality of the liquid preparation is 310 to 380 mosmol/kg.
The pH of the solution is 5-5.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Primary immunodeficiency (PID) syndromes with impaired antibody production (see section 4.4).
- 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 <4g/l.*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

4.2 Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Posology
The dose and dose regimen are dependent on the indication.

Replacement therapy
The medicinal product should be administered via the subcutaneous route.

In replacement therapy, the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response.
Cutaquig can be administered at regular intervals from daily up to every other week.
The following dose regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes (as defined in 4.1)
The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l and aim to be within the reference interval of serum IgG for age. A loading dose of at least 0.2 to 0.5 g/kg (1.2 to 3.0 ml/kg) body weight may be required. This may need to be divided over several days, with a maximal daily dose of 0.1 to 0.15 g/kg.

After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals to reach a cumulative monthly dose of the order of 0.4-0.8 g/kg (2.4 to 4.8 ml/kg). Each single dose may need to be injected at different anatomic sites.

Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dose and aim for higher trough levels.

Replacement therapy in secondary immunodeficiencies (as defined in 4.1.)
The recommended dose administered at repeated 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. 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.

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 adjusted to the clinical outcome in replacement therapy indications.

Elderly population
As the dose is given by body weight and adjusted to the clinical outcome of the above-mentioned conditions, the dose in the elderly population is not considered to be different from that in subjects 18 to 65 years of age. In the clinical trials Cutaquig was evaluated in 17 patients older than 65 years. No specific dose-requirements were necessary to achieve the desired serum IgG levels.

Method of administration
For subcutaneous use only.

Subcutaneous infusion for home treatment should be initiated and monitored by a health care professional experienced in the guidance of patients for home treatment. The patient and/or a caregiver must be instructed in the use of the infusion device, the infusion techniques, aseptic handling technique, the keeping of a treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

Cutaquig may be injected into sites such as abdomen, thigh, upper arm, and lateral hip.

Infusion rate
Adjustment of the infusion rate and infusion volume per site is based on subject tolerability.

It is recommended to use an initial administration rate of 15 ml/h/site for patients naïve on SCIG therapy. For patients already on SCIG therapy and switching to Cutaquig it is recommended to use previously used administration rates for the initial

infusions. For subsequent infusions, if well tolerated (see section 4.4), the infusion rate can be gradually increased by approximately 10 ml/h/site every 2-4 weeks in adults (≥ 40 kg) and up to 10 mL/h/site every 4 weeks for paediatrics (<40 kg) (see section 5.1).
Thereafter, if the patient tolerates the initial infusions at the full dose per site and maximum rate, an increase in the infusion rate of successive infusions may be considered until reaching a maximum flow rate of 67.5 ml/h/site for adults and 25 ml/h/site for paediatrics (see section 5.1)

More than one infusion device can be used simultaneously.

Infusion volume per site
The amount of product infused into a particular site varies. In infants and children, infusion site may be changed every 5-15 ml. In adults doses over 30 ml may be divided according to patient preference. There is no limit to the number of infusion sites. Infusion sites should be at least 5 cm apart.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).
Cutaquig must not be given intravascularly.

It must also not be administered intramuscularly in case of severe thrombocytopenia and in other disorders of haemostasis.

4.4 Special warnings and precautions for use

It is strongly recommended that every time that Cutaquig is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

This medicinal product contains maximally 90 mg of maltose per ml as an excipient. The interference of maltose in blood glucose assays may result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life threatening hypoglycaemia and death. Also, cases of true hypoglycaemia may go untreated if the hypoglycaemic state is masked by falsely elevated glucose readings (see Section 4.5). For acute renal failure see below.

Cutaquig is for subcutaneous use only. If Cutaquig is accidentally administered into a blood vessel patients could develop shock.

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.

Certain 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.

Potential complications can often be avoided by:

- initially injecting the product slowly (see section 4.2).
- ensuring that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human normal immunoglobulin, patients switched from an alternative immunoglobulin 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 order to detect potential adverse signs.

All other patients should be observed for at least 20 minutes after administration.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. The treatment required depends on the nature and severity of the adverse reaction.

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

Hypersensitivity

True allergic reactions are rare. They can particularly occur in patients with anti-IgA antibodies who should be treated with particular caution. Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be treated with Cutaquig only under close medical supervision.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Thromboembolism
Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with preexisting 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 immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity).

Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms.

Aseptic Meningitis Syndrome (AMS)
Aseptic meningitis syndrome has been reported to occur in association with subcutaneous immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following treatment. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.

Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting.

Renal dysfunction/failure
Severe renal adverse reactions have been reported in patients receiving immune globulin treatment, particularly those products containing sucrose (Cutaquig does not contain sucrose). These include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis. Factors that increase the risk of renal complications include, but are not limited to preexisting renal insufficiency, diabetes mellitus, hypovolemia, concomitant nephrotoxic medicinal products, age over 65, sepsis, hyperviscosity and paraproteinemia.

Hemolysis
IgG products can contain blood group antibodies that may act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin (Coombs') test result and, rarely, may cause haemolysis. Monitor Immunoglobulin product recipients for clinical signs and symptoms of hemolysis.

Sodium content
This medicinal product contains 33.1 mg sodium per vial of 48 ml and 13.8 mg per vial of 20 ml, equivalent to 1.7% and 0.7%, respectively of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interference with serological testing
After injection 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 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).

The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19.

There is a 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 listed warnings and precautions apply both to adults and children.

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.

Blood glucose testing
Cutaquigcontains maltose which can be misinterpreted as glucose by certain types of blood glucose testing systems. Due to the potential for falsely elevated glucose readings, only testing systems that are glucose-specific should be used to test or monitor blood glucose levels in diabetic patients.

Paediatric population
The listed interactions apply both to adults and children.

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 and breast-feeding mothers. Immunoglobulin 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 to be expected.

Breast-feeding
Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

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

The ability to drive and operate machines may be impaired by some adverse reactions associated with Cutaquig. 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 such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Local reactions at infusion sites: swelling, soreness, redness, induration, local heat, itching, bruising and rash, may frequently occur. These reactions normally decrease in frequency with ongoing treatment.

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

Tabulated list of adverse reactions
Clinical safety data of Cutaquig in subjects with PID are based on the pivotal open-label, single-arm, prospective, multicentre Phase III study (n=75, 4462 infusions), the prospective, open-label, single-arm, multicentre phase III extension study (n=27, 2777 infusions) and the open-label, three-arm, multicentre phase III study (n=64, 1338 infusions).
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies per patient 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).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequency of Adverse Reactions (ADRs) per subject and per infusion in the clinical studies with Cutaquig:

MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency/infusion**	**Frequency/subject**	
Nervous system disorders	Headache	Uncommon	Common	
	Dizziness	Rare	Uncommon	
Gastrointestinal disorders	Nausea	Uncommon	Common	
	Abdominal distension	Rare	Common	
	Abdominal pain	Rare	Common	
	Vomiting	Rare	Common	
	Retching	Rare	Uncommon	
Hepatobiliary disorders	Hypertransaminasaemia	Rare	Uncommon	
Skin and subcutaneous tissue disorders	Rash	Rare	Uncommon	
	Skin reaction	Rare	Uncommon	
Musculoskeletal and connective tissue disorders	Myalgia	Rare	Common	
	Arthralgia	Rare	Uncommon	
General disorders and administration site conditions	Injection site reaction	Very common	Very common	
	Pyrexia	Rare	Common	
	Chills	Rare	Common	
	Fatigue	Uncommon	Common	
	Chest discomfort	Rare	Uncommon	
	Influenza-like illness	Rare	Uncommon	
	Malaise	Rare	Uncommon	
	Pain	Rare	Uncommon	
Investigations	Free haemoglobin present	Rare	Common	
	Coombs test positive	Rare	Uncommon	
	Haptoglobin decreased	Rare	Uncommon	
	Haemoglobin increased	Rare	Uncommon	
	Blood creatinine increased	Rare	Uncommon	

The following adverse reactions have been identified during post-approval use of Cutaquig. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
This list does not include reactions already reported in the clinical trials with Cutaquig:

MedDRA System Organ Class (SOC)	**Adverse reaction (PT)**	
Immune system disorders	Hypersensitivity (e.g., erythema, urticaria)	
Vascular disorders	Thromboembolism, thrombosis (e.g., deep vein thrombosis, cerebrovascular accident), hypertension	
Skin and subcutaneous tissue disorders	Pruritus	
Musculoskeletal and connective tissue disorders	Back pain	

The following additional adverse reactions have been reported during post approval use of subcutaneous immunoglobulin products: face oedema, tremor, pallor, bronchospasm, dyspnoea, cough, diarrhoea, flushing, feeling hot, feeling cold, asthenia, injection site pain, throat tightness, aseptic meningitis.

Paediatric population
Frequency, type and severity of adverse reactions in children 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
Earlsfort Terrace
IRL – Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Consequences of an overdose are not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration, ATC code: J06BA01.

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 donations. 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.

In a clinical trial a total of 75 (37 adults, 12 young children [≥2 and <6], 14 older children [≥6 and < 12], 12 adolescents [≥12 and <17]) subjects with primary immune deficiency syndromes were treated with Cutaquig during up to 64 weeks.
The mean dose administered each week per patient was 0.187 g/kg in adult patients, 0.150 g/kg in young children, 0.164 g/kg in older children and 0.170 g/kg in adolescents. Subjects received a total of 4462 weekly Cutaquig infusions.
No serious bacterial infections were reported neither during the wash-in/wash-out period nor during the efficacy period in subjects receiving Cutaquig within the clinical study.
Cutaquig was evaluated in 38 paediatric subjects (26 children [between 2 and <12 years of age] and 12 adolescents [between 12 and <16 years of age]) with primary immunodeficiency disease. No paediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

The extension study was a prospective, open-label, single-arm, multicenter phase 3 safety follow up study that enrolled 27 subjects (17 adults, 2 young children [≥2 and <6], 4 older children [≥6 and < 12], 4 adolescents [≥12 and <17]) with primary immunodeficiency. Twenty-one subjects were initially treated in the pivotal study and 6 subjects were newly enrolled. Subjects were observed over a period of up to 4.5 years for subjects previously enrolled in the pivotal study and 12 months for de novo subjects. Subjects received Cutaquig on a weekly (25 subjects) or an "every other week" schedule (2 subjects). The mean average actual dose of Cutaquig infused per patient was 0.127 g/kg in young children, 0.210 g/kg in older children, 0.160 g/kg in adolescent patients and 0.166 g/kg in adult patients. Subjects received a total dose of 2777 infusions (2740 weekly and 37 biweekly). One SBI (serious bacterial infection) of the infection type bacteraemia/sepsis was reported.

To monitor the safety, tolerability, and efficacy of Cutaquig a prospective, open label, three-arm multicentre phase III study enrolled 64 PID subjects (59 adults, 1 young child [≥2 and <6], 2 older children [≥6 and < 12], 2 adolescents [≥12 and <17]) aged 5 to 74 years.

After completing the 4-week stabilisation period, subjects entered the treatment period with a follow up of 24 weeks and were assigned to one of the 3 cohorts:

- Cohort 1 assessed increased volume per site with up to a maximum of 100 ml/site.
- Cohort 2 assessed increased infusion flow rate per site up to a maximum of 100 ml/hr/site or the maximum flow rate achievable by the pump.
- Cohort 3 assessed Cutaquig on a every other week schedule at the equivalent of twice the patient's body-weight dependent (mg/kg) weekly dose.

The co-primary endpoint was to compare total IgG trough levels from weekly infusions to every other week infusions and to assess safety and tolerability of increased infusion volumes and increased infusion rates at each infusion site and every other week dosing.

Overall, subjects received a total of 1338 infusions (386 in Cohort 1, 396 in Cohort 2, 556 in Cohort 3). In Cohort 1 (n=15 adults) the mean maximum realised volume per site was 69.4 ml/site with a maximum volume of 108 ml/site. One-third of subjects (5/15; 33.3%) attained ≥90% of the allowed maximum volume of 100 ml/site, a further third attained between 50% and <90% of the allowed maximum, and one third attained <50% of the allowed maximum. The median maximum realized flow rate per subject was 56.9 ml/h, ranging from 34.0 ml/h to 94.7 ml/h

In Cohort 2 (n=15, [13 adults, 1 older child [≥6 and < 12], 1 adolescents [≥12 and <17]) the mean maximum realised flow rate per site was 42.1 ml/hr/site with a maximum flow rate of 67.5 ml/h/site. 73.3% attained a maximum flow rate per site of <50% of the allowed maximum of 100 ml/h/site and the remaining 26.7% attained between 50% and 75% of the allowed maximum. The median maximum realized flow rate per subject was 135.0 ml/h, ranging from 51.4 ml/h to 192.0 ml/h.

In Cohort 3 (n=34, [31 adults, 1 young child [≥2 and <6], 1 older children [≥6 and < 12], 1 adolescents [≥12 and <17]), a decrease in mean (SD) total IgG trough levels was seen with every other week dosing (9.927 [2.0146] g/l) compared to weekly dosing (10.364 [1.9632] g/l) (p = 0.0017; 1-sided 97.5% lower confidence limit [LCL] =-0.799). The median maximum realized flow rate per subject was 93.5 ml/h, ranging from 24.3 ml/h to 145.9 ml/h.

The mean average actual dose of Cutaquig administered per body weight was 0.143 g/kg in Cohort 1, 0.157 g/kg in Cohort 2 and 0.256 g/kg in Cohort 3, respectively.

There were no SBIs reported during the study and the overall rate of SBI was 0.00 per person-year (98% CI upper limit [alternative method] = 0.135 [0.614 in Cohort 1, 0.602 in Cohort 2, and 0.244 in Cohort 3.])

Paediatric population
No differences were seen in the pharmacodynamic properties between adult and paediatric patients.

5.2 Pharmacokinetic properties

In a clinical Phase III trial, a pharmacokinetic (PK) sub-study was conducted in 37 PID subjects. Blood samples for PK study were collected prior to switching to Cutaquig (IVIG profile: PK_{IV}), after the 11th infusion of Cutaquig (first SC profile: PK_{SC1}) and after the 28th infusion of Cutaquig (second SC profile: PK_{SC2}). The objective of the PK sub-study was to compare the AUCs following the IV and SC administration, using a dose correction factor (DCF) of 1.5. By means of a population PK model PK parameter were estimated and simulations were performed.

Absorption and distribution
Following subcutaneous administration of Cutaquig, peak serum levels are achieved after approximately 2 days.

Due to gradual absorption, SCIG administration leads to flatter profiles and lower fluctuations at steady state compared to IVIG treatment: Mean Cmax was lower after SCIG (13.2±3.4 g/l and 13.5±3.7 g/l for PK_{SC1} and PK_{SC2}, respectively) compared to the end of infusion level after IVIG treatment (18.0±4.5 g/l). Correspondingly, mean serum IgG and IgG subclass trough levels were higher after SC treatment (11.5 and 11.7 g/l for PK_{SC1} and PK_{SC2}, respectively; the overall range from 6.5 to 18.9 g/l compared with that at the end of the IVIG period (10.1 g/l; range: 6.5 g/L to 14.3 g/l).

SC bioavailability was calculated to be 75% corresponding to a dose correction factor of 1.3 for achievement of equal AUC exposure after body weight based SCIG compared to IVIG treatment.

The PK-based modeling and simulation performed on the data from the clinical study with weekly Cutaquig dosing, indicated that body weight-adjusted dosing without a DCF for the lower SC bioavailability would suffice to maintain systemic IgG exposure in the therapeutic range, for dose intervals up to 1 week, including more frequently than once a week (e.g. daily) administrations.
Longer dose intervals (esp. at lower IgG baseline levels) increase the risk of falling below IgG trough levels of 5 g/l.
Example: Assuming an IgG baseline level of 4.0 g/l and a dose conversion factor of 1.0 from IVIG to SCIG treatment, the fraction of patients falling below IgG trough level of 5 g/l was predicted to increase to 4 % at a dose interval of 2 weeks compared to 1.4 % at dose intervals ≤ Q1W.

Elimination
IgG and IgG-complexes are broken down in cells of the reticuloendothelial system. Median half–life of IgG after Cutaquig administration in PID subjects was estimated to be ~16 (9.2-36.3) days, as calculated in population PK model, assuming zero endogenous production of IgG.

Paediatric population
No clinically relevant differences were seen in the pharmacokinetic parameters between adult and pediatric PID study patients.

The PK-based modeling and simulation performed on the data from the clinical study with weekly Cutaquig dosing, indicates that body weight-adjusted dosing will suffice to maintain systemic IgG exposure in the therapeutic range irrespective of age.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of human plasma. Non-clinical data reveal no special hazard for humans based on conventional non-clinical studies on safety pharmacology and local tolerance. Since clinical experience provides no evidence for carcinogenic or mutagenic potential of immunoglobulins, no experimental studies in heterologous species were performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltose, 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.

6.3 Shelf life

3 years
Once a vial has been opened, the solution should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Within its shelf-life, the product may be stored at room temperature (do not store above 25°C) for up to 9 months without being refrigerated again during this period, and must be discarded if not used after this.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

6, 10, 12, 20, 24 or 48 ml of solution in a vial (Type I glass) with a bromobutyl rubber stopper – pack size 1, 10 or 20.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The medicinal product should be brought to room or body temperature before use.

Products should be inspected visually for particulate matter and discoloration prior to administration. 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

Octapharma (IP) SPRL
Allée de la Recherche 65
1070 Anderlecht
Belgium

8 MARKETING AUTHORISATION NUMBER

PA2219/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st May 2020
Date of last renewal: 03rd February 2024

10 DATE OF REVISION OF THE TEXT

November 2023