

# 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 (SCLg)

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<sub>1</sub> ..... 71%

IgG<sub>2</sub> ..... 25%

IgG<sub>3</sub> ..... 3%

IgG<sub>4</sub>..... 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.

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.

#### *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 trial Cutaquig was evaluated in 3 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. From infusion 7 on, if well tolerated (see section 4.4), the infusion rate can be gradually increased to 25 ml/h/site.

Recommended infusion rate per hour for all sites combined: 30 ml/h for first 6 infusions, then gradually increase to 50 ml/h and, if well tolerated to 80 ml/h.

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 interactions**

#### 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

Cutaquig contains 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 are based on the pivotal Phase III open-label, single-arm, prospective, multicentre study of Cutaquig in subjects with PID, previously treated with IVIG for at least 6 months. This study was conducted in Europe and North America. In this study, the safety of Cutaquig was evaluated in 75 subjects. A total of 4462 Cutaquig infusions were administered. 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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 study with Cutaquig:

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency/infusion	Frequency/subject
Nervous system disorders	Headache	Rare	Common
Gastrointestinal disorders	Abdominal distension	Rare	Common
	Abdominal pain	Rare	Common
	Vomiting	Rare	Common
Musculoskeletal and connective tissue disorders	Myalgia	Rare	Common
General disorders and administration site conditions	Injection site reaction	Very common	Very common
	Pyrexia	Rare	Common
Investigations	Coombs test positive	Rare	Common
	Free hemoglobin present	Rare	Common
	Haptoglobin decreased	Rare	Common

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.

MedDRA System Organ Class (SOC) according to the sequence:	Adverse reaction (PT)
Nervous system disorders	Dizziness
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Pruritus
General disorders and administration site conditions:	Fatigue

The following additional adverse reactions have been reported during post approval use of subcutaneous immunoglobulin products: face oedema, tremor, pallor, bronchospasm, dyspnoea, cough, diarrhoea, urticaria, rash, flushing, feeling hot, feeling

cold, asthenia, influenza-like illness, malaise, injection site pain, throat tightness, aseptic meningitis, hypertension and thromboembolic events.

#### 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](http://www.hpra.ie)  
e-mail: [medsafety@hpra.ie](mailto: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 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.

#### 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<sub>IV</sub>), after the 11th infusion of Cutaquig (first SC profile: PK<sub>SC1</sub>) and after the 28th infusion of Cutaquig (second SC profile: PK<sub>SC2</sub>). 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 C<sub>max</sub> was lower after SCIG (13.2±3.4 g/l and 13.5±3.7 g/l for PK<sub>SC1</sub> and PK<sub>SC2</sub>, 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<sub>SC1</sub> and PK<sub>SC2</sub>, 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: 1<sup>st</sup> May 2020

#### **10 DATE OF REVISION OF THE TEXT**

May 2022