PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

cutaquig®

Immunoglobulin (human) subcutaneous
16.5% Solution for injection (165 mg/mL)
Prescription medication, passive immunizing agent
Presentation sizes: 6 mL, 10 mL, 12 mL, 20 mL, 24 mL, 48 mL
ATC-Code: J06B A01

Manufactured by:
Octapharma Pharmazeutika Produktionsges. m.b.H.
Oberlaaer Strasse 235
1100 Vienna, Austria

Date of Preparation:
FEB 15, 2018

Date of Revision:
AUG 05, 2019

Imported and distributed by:
Octapharma Canada Inc.
308-214 King St W
Toronto, ON M5H 3S6
Canada

Submission Control No: 227006

Date of Approval: August 26, 2019

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
DESCRIPTION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 4
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 7
DRUG INTERACTIONS 9
DOSAGE AND ADMINISTRATION 10
OVERDOSAGE 16
ACTION AND CLINICAL PHARMACOLOGY 16
STORAGE AND STABILITY 17
SPECIAL HANDLING INSTRUCTIONS 18
DOSAGE FORMS, COMPOSITION AND PACKAGING 18

PART II: SCIENTIFIC INFORMATION 19
PHARMACEUTICAL INFORMATION 19
CLINICAL TRIALS 20
DETAILED PHARMACOLOGY 22
TOXICOLOGY 24
REFERENCES 24

PATIENT MEDICATION INFORMATION 26

cutaquig®

Immunoglobulin (human) subcutaneous

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	16.5% Solution for Injection (165 mg/mL)	None of the nonmedicinal ingredients are clinically relevant. For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

DESCRIPTION

cutaquig® (Immunoglobulin (human) subcutaneous, 16.5%) is a sterile liquid preparation of highly purified immunoglobulin G (IgG) with a low viscosity of 11.4 mPa*s (at 20°C).

cutaquig® is manufactured by the cold ethanol fractionation process followed by ultrafiltration and chromatography. The manufacturing process includes treatment with an organic Solvent/Detergent (S/D) mixture composed of tri-n-butyl phosphate (TNBP) and Octoxynol. Viral reduction is achieved through a combination of process steps including cold ethanol fractionation, S/D treatment and pH4 treatment. Other precautions against viral transmission include: selection of plasma donors, screening of donations and plasma pool, as well as quality control measurements of the final product.

cutaquig® is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and other viral diseases (see WARNINGS AND PRECAUTIONS section).

INDICATIONS AND CLINICAL USE

cutaquig® is indicated for the treatment of patients with primary immune deficiency (PID) and secondary immune deficiency (SID) who require immune globulin replacement therapy.

Geriatrics (> 65 years of age):

See subsection Special Populations, under section WARNINGS AND PRECAUTIONS.

Pediatrics (< 18 years of age):

See subsection Special Populations, under section WARNINGS AND PRECAUTIONS.

CONTRAINDICATIONS

- cutaquig® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.
- cutaquig® is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human IgG or to components of cutaquig® such as maltose or polysorbate 80.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- 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. Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment should be administered.
- There is clinical evidence of an association between the administration of immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. Therefore, caution should be exercised when prescribing and administering immunoglobulins.
- Risk factors for thromboembolic events include: advanced age, use of estrogens, in-dwelling central vascular catheters, history of vascular disease or thrombotic episodes, acquired or inherited hypercoagulable states, prolonged periods of immobilization, severe hypovolemia, diseases which increase blood viscosity and cardiovascular risk factors (including obesity, hypertension, diabetes mellitus, history of atherosclerosis and/or impaired cardiac output).
- Thrombosis may occur even in the absence of known risk factors (see WARNINGS AND PRECAUTIONS – Thromboembolism).
- The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patient (see WARNINGS AND PRECAUTIONS - General).

General

Products made from human plasma may contain infectious agents, such as viruses and theoretically, the variant Creutzfeldt-Jakob disease (vCJD) agent that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, 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.

The viral safety of cutaquig® is ensured through a number of steps, such as the virus removal by cold-ethanol fractionation, the S/D treatment and pH4 treatment (see PHARMACEUTICAL INFORMATION section).

Despite these measures, such products can still potentially transmit disease. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections.

Hypersensitivity

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.

In case of hypersensitivity, discontinue the cutaquig® infusion immediately and institute appropriate treatment.

Severe hypersensitivity or anaphylactic reactions up to shock can particularly occur in patients with known allergies to anti-IgA antibodies. Patients with anti- IgA antibodies may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reaction with the administration with cutaquig®. Close medical supervision is required.

In case of severe hypersensitivity/anaphylactic reactions the administration of cutaquig® must be stopped immediately. In case of shock, standard medical treatment should be administered.

Potential complications can often be avoided by ensuring that patients are not sensitive to human normal immunoglobulin, by initially injecting the product slowly.

Patients naive to human normal immunoglobulin or switched from an alternative product should be monitored during and after the first infusion for the first hour, in order to detect potential adverse signs.

Thromboembolism

Thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis have been associated with the use of immunoglobulins.

Since thrombosis may occur in the absence of known risk factors, caution should be exercised in prescribing and administering immunoglobulins. cutaquig® should be administered at the minimum dose and at the minimum rate of infusion practicable. Patients should be adequately hydrated before administration of immunoglobulins.

Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and blood viscosity should be assessed.

Risk factors for thromboembolic events include: advanced age, use of estrogens, in-dwelling central vascular catheters, history of vascular disease or thrombotic episodes, acquired or inherited hypercoagulable states, prolonged periods of immobilization, severe hypovolemia, diseases which increase blood viscosity and cardiovascular risk factors (including obesity, hypertension, diabetes mellitus, history of atherosclerosis and/or impaired cardiac output).

Aseptic Meningitis Syndrome (AMS)

AMS has been reported with use of IVIG or SCIG. The syndrome usually begins within several hours to 2 days following immune globulin treatment. AMS is characterized by the following signs and symptoms: severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting. Patients exhibiting signs and symptoms of AMS should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.

IgA Deficient Patients

Individuals with IgA deficiency can develop anti-IgA antibodies and in very rare cases develop potentially severe hypersensitivity and anaphylactic reactions after administration of blood components containing IgA. Not all patients with anti-IgA antibodies receiving IVIG experience reactions [1], but those patients with high or rising titers of anti-IgA antibodies are thought to have an increased risk of adverse reactions. [2-5]

Patients who have experienced adverse reactions to IVIG have been reported to better tolerate SCIG. [4, 6]

Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be given cutaquig® only under close medical supervision.

Special Populations

Pregnant Women: Animal reproduction studies have not been conducted with cutaquig®. The safety of cutaquig® for use in human pregnancy has not been established in controlled clinical trials. cutaquig® should be given to pregnant women only if clearly needed.

Continued treatment of the pregnant woman is important to ensure that the neonate is born with appropriate passive immunity [7]. Immunodeficient women who are pregnant may be at greater risk for infection since placental transfer of the IgG to the fetus may deplete already limited maternal stores. Therapeutic replacement therapy doses may in fact need to be increased to confer adequate humoral protection to the mother and newborn. [7]

Nursing Women: cutaquig® has not been evaluated in nursing mothers.

After administration of IVIG products, IgGs are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate. As the route of administration is irrelevant for the passive transfer of antibodies once they are in the circulation, and due to the similar metabolism of IVIG and SCIG products, this transfer is also expected to apply to cutaquig®.

Pediatrics (< 18 years of age): The Pivotal Phase III study was conducted in 59 PID patients, of which 22 subjects were pediatric patients of < 18 years of age. There were no apparent differences in the safety and efficacy profiles of pediatric subjects as compared with adult subjects being treated with cutaquig®. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

cutaquig® was not studied in neonates or infants.

Geriatrics (> 65 years of age): In the Pivotal Phase III study, 3 patients over 65 years of age were evaluated. The pivotal clinical study did not include sufficient number of subjects over the age of 65 years to determine whether they respond differently from younger patients. No overall differences in safety or efficacy are to be expected between these subjects and younger subjects.

Monitoring and Laboratory Tests

Patients may need to be monitored for the following reactions reported to occur with IVIG treatment, including: renal dysfunction/failure, hyperproteinaemia, thrombotic events, aseptic meningitis syndrome (AMS), and transfusion-related acute lung injury (TRALI).

For Drug-Laboratory Interactions, see the appropriate sub-section under section DRUG INTERACTIONS.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

No related serious adverse drug reactions were observed in subjects treated with cutaquig® during the clinical studies evaluating its safety.

The most common related adverse drug reactions reported in patients treated with cutaquig® were local reactions at the site of injection and pyrexia.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 59 subjects. A total of 2666 cutaquig® infusions were administered. Overall, there were no safety concerns with the use of cutaquig® in the study population.

Local reactions were the most common AEs experienced by 42 subjects (71.2%) and occurred at a rate of 0.24 per infusion. Almost all local AEs (99.7%) were mild or moderate in intensity.

Systemic (or non-injection site) AEs were possibly related to study drug and temporally associated (i.e., during infusion or within 72 hours after the end of infusion) in 8 subjects (13.6%). All systemic AEs were either mild or moderate in intensity.

Table 1 Causally and temporally associated (72 hrs) AEs*

AEs	Number (%) of subjects (N=59)	Number (rate) of AEs (N=2666)
Local reaction**	42 (71.2)	656 (0.25)
Systemic reaction, any	8 (13.6)	10 (0.004)
Pyrexia	2 (3.4)	2 (<0.001)
Headache	1 (1.7)	2 (<0.001)
Abdominal distension	1 (1.7)	1 (<0.001)
Abdominal pain	1 (1.7)	1 (<0.001)
Vomiting	1 (1.7)	1 (<0.001)
Myalgia	1 (1.7)	1 (<0.001)
Coombs test positive	1 (1.7)	1 (<0.001)
Free haemoglobulin present	1 (1.7)	1 (<0.001)

* Excluding infections
** Local reaction included the following events with more than 2 occurrences that took place at the injection/infusion/puncture site: erythema, redness, swelling, pruritus, oedema, pain, mass, bruising, induration, haematoma, rash, tenderness, and warmth.

Local reactions at the site of injection can be expected with all SCIG infusions. In the study, the incidence of local reactions decreased over time; approximately 38% of subjects experienced a local reaction after the first 4 cutaquig® infusions; 18% of subjects experienced a local reaction during the last 4 infusions.

Abnormal Hematologic and Clinical Chemistry Findings

There were no unexpected safety concerns regarding clinical laboratory parameters over the course of the studies. The observed cases of abnormal values were isolated and did not indicate any trend.

There were no clinically relevant changes in vital signs, and most physical examination findings were normal at baseline and at the completion visit.

Post-Market Adverse Drug Reactions

No post-marketing safety experience is available for cutaquig®.

IgG Adverse Drug Reactions

The following adverse reactions have not been observed in the cutaquig® clinical studies but they have been reported during post approval use of IVIG products and therefore could also occur following cutaquig® administration.

- Blood and lymphatic system: Pancytopenia, leukopenia, haemolytic anaemia, hemolysis.
- Immune system: Anaphylactic shock, anaphylactic reaction, hypersensitivity reaction, allergic reaction, angioneurotic oedema, face oedema.
- Psychiatric system: Agitation.
- Neurological: Loss of consciousness, cerebrovascular accident, aseptic meningitis, seizures, migraine, tremor, paraesthesia, dizziness.
- Cardiovascular: Cardiac arrest, thromboembolism, thrombosis, vascular collapse, tachycardia, palpitations, hypotension, hypertension.
- Respiratory system: TRALI, acute respiratory distress, respiratory failure, pulmonary embolism, apnea, cyanosis, hypoxia, pulmonary edema, bronchospasm, dyspnoea, cough, wheezing.
- Gastrointestinal: Hepatic dysfunction, diarrhoea, nausea.
- Skin: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, (bullous) dermatitis, eczema, urticaria, rash (erythematous), pruritus, alopecia.
- Musculoskeletal: Back pain, arthralgia, pain in extremity.
- Renal: (acute) renal failure.
- General/Body as a Whole: Chills, chest pain or tightness, hot flush, flushing, hyperhidrosis, fatigue, flu-like symptoms, malaise.
- Investigations: Hepatic enzymes increased, blood glucose false positive.

DRUG INTERACTIONS

Overview

The passive transfer of antibodies with immunoglobulin administration may interfere, for a period of at least 6 weeks and up to 3 months, with the response to live virus vaccines such as measles, mumps, rubella, or 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. The immunizing physician should be informed of recent therapy with cutaquig® so that appropriate measures may be taken.

Because vaccination in patients with PID is an evolving field, we recommend you refer to the relevant vaccination guidelines[1].

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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 patients receiving cutaquig®.

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell alloantibodies (Coombs test).

DOSAGE AND ADMINISTRATION

Dosing Considerations

The recommended weekly dose of cutaquig® is 0.1–0.2g/kg body weight (BW) administered subcutaneously.

For dosing frequencies greater than once per week (2 to 3 times per week), divide the calculated weekly dose by the desired number of administration per week (e.g., for 3 times per week dosing, divide weekly dose by 3).

To convert a cutaquig® dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 6.

[1] Canadian Immunization Guide 7th edition. Available at http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-07-eng.php

Recommended Dose and Dosage Adjustment

Loading Dose

If a loading dose is required, cutaquig® may be given at least 0.2 to 0.5 g/kg BW divided over several days.

Patients that were previously on IVIG replacement therapy

To calculate the initial weekly dose of cutaquig®, divide the previous IVIG monthly dose in grams by the number of weeks between doses during the patient's IVIG treatment (i.e., 3 or 4).

For dosing frequencies greater than once per week (2 to 3 times per week), divide the calculated weekly dose by the desired number of administration per week (e.g., for 3 times per week dosing, divide weekly dose by 3).

Patients that were previously on SCIG replacement therapy

For patients already on SCIG treatment the dosing recommendation is to start with an initial cutaquig® dose that is equal to the previous SCIG dose.

The previous weekly SCIG dose should be maintained for weekly dosing.

For dosing frequencies greater than once per week (2 to 3 times per week), divide the calculated weekly dose by the desired number of administration per week (e.g., for 3 times per week dosing, divide weekly dose by 3).

Dose Adjustment

Over time, the dose may need to be adjusted to achieve the desired clinical response and serum IgG trough level. However, the patient's clinical response should be the primary consideration in dose adjustment.

Measles Exposure

Individuals already receiving weekly replacement SCIg at 200 mg/kg body weight or higher are considered protected against measles if the last dose of SCIg was received within one week prior to measles exposure.

For all other PID patients a total weekly dose of 200 mg/kg bodyweight for 2 consecutive weeks should be given as soon as possible. This dosing regimen should provide a serum level > 240 mIU/mL of measles antibodies.

Missed Dose

A missed dose should be administered as soon as possible to ensure an adequate IgG serum level.

Administration

For subcutaneous use. Subcutaneous infusion for home treatment should include proper patient instruction for safe and effective infusions.

The following information is guidance based on the results of clinical trials:

Injection Sites

cutaquig® can be infused in the following areas: abdomen, thigh, upper arm, and/or upper leg/hip area. cutaquig® may be infused into multiple injection sites. Injection sites should be at least 2 inches apart (5 cm).

For subcutaneous infusions using a pump

Volume	For patients not already on SCIG therapy, the maximum initial volume per injection site should not exceed 25 mL. The volume may be gradually increased to a maximum of 40 mL/site as tolerated.
Rate	Maximum recommended flow rates per hour per infusion site are as follows: First 6 infusions: 15-20 mL per hour per site. Subsequent infusions: 25 mL per hour per site. Maximum recommended flow rates per hour for all sites: First 6 infusions: 30mL per hour for all sites. From infusion no. 7 a gradual increase to 50 mL per hour for all sites, subsequently to 80 mL per hour for all sites, and if tolerated to gradually up to 100 mL per hour for all sites.

For subcutaneous infusions using a syringe via manual rapid push

Volume	For patients not already on SCIG therapy, the maximum initial volume per injection site should not exceed 25 mL. The volume may be gradually increased to a maximum of 40 mL/site as tolerated.
Rate	Proposed maximum infusion rate is approximately 1-2 mL/min (60-120 mL/hour).

Administration/Handling instructions

cutaquig® is for subcutaneous administration only. Do not inject into a blood vessel.

Follow the administration guidance below and use aseptic technique when administrating cutaquig®.

1. **Getting ready for infusion**

- Choose and prepare a clean work area (Figure 1).

Figure 1

- Gather your infusion supplies:
  - Syringe(s)
  - Infusion pump (optional)
  - Needle (for drawing up product from the vial)
  - Infusion set
  - Infusion tubing and Y-connector (if required)
  - Alcohol & alcohol wipes
  - Gauze or transparent dressing
  - Tape
  - Sharps container
  - Treatment diary and pen
- Wash your hands thoroughly and let them dry (Figure 2). Use disinfectant gel as per the pump manufacturer's instructions.

Figure 2

2. Checking & opening the vials

- Inspect each vial carefully for:
  - Correct labelled dose based on prescription,
  - Appearance of the solution (clarity and color),
  - Protective cap,
  - Expiry date and batch number.
- Remove the protective cap.
- Disinfect the rubber stopper by using a sterile wipe and allow it to dry (Figure 3).

Figure 3

3. Preparing and filling the syringe

- Open sterile syringe and needle.
- Attach the needle to the syringe with a screw action.
- Draw back on the plunger to fill the syringe with air which should be roughly equal to the amount of solution needed from the vial.
- Insert the needle into the vial and turn the vial upside down. Inject air - ensuring the tip of the needle is not in the solution to avoid foaming.
- Next, making sure the needle remains always in the solution, slowly draw up the cutaquig® (Figure 4).

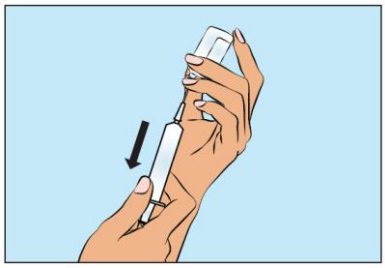

Figure 4

- Withdraw the needle from the vial.
- This procedure might be repeated if you need to use more than one vial.
- When finished remove the needle and dispose it into the sharps bin.
- Immediately proceed to the next step as the IgG solution should be used promptly.

4. Preparing the infusion pump (optional)

- Prepare the infusion pump (if using) by following the manufacturer's instructions.

5. Prepare tubing

- Prime (fill) the infusion tubing. To prime the tubing, connect the syringe filled with cutaquig® to the infusion tubing and gently push on the syringe plunger to fill the tubing with cutaquig®.
- Stop priming before cutaquig® fluid reaches the needle.
- If using a pump, insert syringe filled with cutaquig® into the pump.

6. Deciding on infusion sites and inserting the infusion needle(s)

- cutaquig® can be infused in the following areas: abdomen, thigh, upper arm, and/or upper leg/hip area (Figure 5).

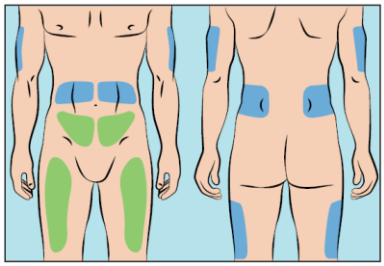

Figure 5

- The infusion sites should be at least 5 cm apart.
- Never use the same infusions site during consecutive infusions.
- Avoid inserting the needle into scars, tattoos or injured/inflamed skin areas.
- Clean your skin at your selected infusion site(s) with an antiseptic skin wipe allow each site to dry before proceeding.
- Pinch the skin between your thumb and forefinger around the injection site (Figure 6) and insert the needle into the skin – subcutaneous tissue (Figure 7). The angle of the needle will depend on the type of infusion set being used.

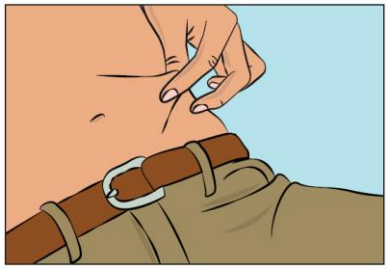

Figure 6

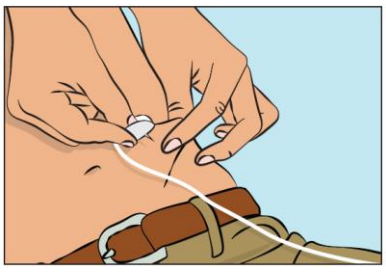

Figure 7

7. Checking the infusion

- The immunoglobulin should not be infused into a blood vessel.
- Secure the needle in place by applying sterile gauze and tape or a transparent dressing (Figure 8).

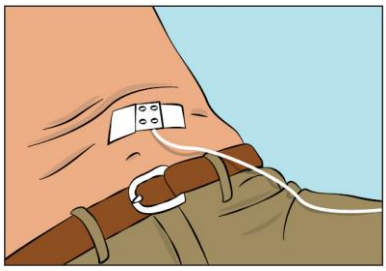

Figure 8

8. Starting the infusion

- Start the infusion.
- If an infusion pump is used for infusion, follow the manufacturer's instructions.
- If administration is done by the manual rapid push method using a syringe, start to push the plunger gently and infuse at a rate that is comfortable for you.

9. Recording the infusion

- On each vial of cutaquig® you will find a peel off label giving the batch number details. Stick this label in your patient's treatment diary or infusion log book. Record details of the dose, date, time, infusion site location and any infections, side effects or other comments.

10. After the infusion is complete

Remove the needle(s) and immediately place into the sharps container.

OVERDOSAGE

Consequences of an overdose are not known with cutaquig®.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action / Pharmacodynamics

Immunoglobulin replacement therapy is the standard treatment for patients with primary and secondary immunodeficiency. Providing passive immunity by administering exogenous IgG controls most recurrent infections.

cutaquig® supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents; it has a distribution of immunoglobulin subclasses closely proportional to that in native human plasma. The mechanism of action in PID has not been fully elucidated, however adequate doses may restore abnormally low immunoglobulin G levels to the normal range and thus help in preventing infections.

Pharmacokinetics

A pharmacokinetic (PK) sub-study of the pivotal Phase III study was conducted in a subset of subjects at various time-points. The objective of the PK sub-study was to compare the AUC under SCIG treatment with that of IVIG. Bioavailability was calculated: the geometric mean of the ratio (SC:IV) was 1.0303, (90% CI: 0.9722, 1.0918), thus confirming bioequivalence between SCIG and IVIG treatment.

Trough levels of serum IgG (total and subclasses) and of specific antibodies were also monitored throughout the study.

Plasma IgG and IgG subclass trough levels were nearly constant during the course of the study, with higher mean levels after the SCIG PK assessment (12.66 g/L) compared with those following IVIG (9.73 g/L). At the IVIG PK assessments, the minimum individual trough levels were 5.1 g/L predose and 5.8 g/L on the last day; at the SCIG PK assessments at predose and 7 days post-dose the minimum individual trough level of total IgG was 7.2 and the maximum trough level was 21.0 g/L. By weekly infusion from week 2 onwards, the minimum trough levels ranged between 6.1 and 8.4 g/L. The mean C_{max} was 14.0 g/L and was reached after a median of 2.05 days.

Key Pharmacokinetic Parameters for cutaquig®

Parameter[#]	**IVIG** (n=22)	**cutaquig®** (n=18)
C_{max} [g/L]	18.9	14.0
C_{min} [g/L]	10.1	11.9
T_{max} [h]	2.8	49.3
AUC_{tau} [g*hr/L]	7709	2406
$T_{1/2}$ [days]	38.4	not evaluable

[#]For T_{max}, median is given; for all other parameters, mean values are presented.

STORAGE AND STABILITY

cutaquig® can be stored at +2 °C to +8 °C for up to 24 months from the date of manufacture. Within its shelf-life, the product may be stored at room temperature up to +25 °C for up to 6 months without being refrigerated again during this period, and must be discarded if not used after this. Do not use after expiry date.

Do not freeze. Keep the vial in the outer carton to protect it from light. Keep in a safe place out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

Prior to administration, visually inspect each vial of cutaquig® for particulate matter, whenever the solution and container permit. Do not use if the solution is cloudy or contains particulates.

- Check the product expiration date on the vial label. Do not use beyond the expiration date.
- Do not mix cutaquig® with other products.
- Do not shake the cutaquig® vial.
- Use aseptic technique when preparing and administering cutaquig®.
- The cutaquig® vial is for single-use only. Discard any unused product after each infusion in accordance with local requirements.

Any unused product or waste material should be disposed of in accordance with local requirements for blood products.

DOSAGE FORMS, COMPOSITION AND PACKAGING

cutaquig® is supplied in a single-use vial containing the labeled amount of functionally active IgG. The components used in the packaging of cutaquig® are latex-free.

cutaquig® is a 165 mg/mL solution for subcutaneous injection. The following dosage forms are available:

Size	Grams Protein
6 mL	1
10 mL	1.65
12 mL	2
20 mL	3.3
24 mL	4
48 mL	8

One millilitre of solution contains 165 mg of protein of which ≥ 96% is human immunoglobulin G.

Quantitative composition:	per mL
Human normal immunoglobulin G (IgG)	165 mg
Maltose	79 mg
Polysorbate 80	40 µg
Water for injections	*ad* 1 mL

Package sizes: 1 vial, 10 vials

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Immunoglobulin (human) subcutaneous

Chemical name: Immunoglobulin G

Molecular formula and molecular mass: The antibody molecule consists of four polypeptide chains, two identical light polypeptide chains (L) and two identical heavy polypeptide chains (H). The four chains are covalently bonded together by disulfide bonds. The amino terminal end is characterized by sequence variability (V) in both the heavy and light chain. The rest of the molecule has a relatively constant (C) structure. The constant region of the heavy chain is further divided into three structurally discrete regions: CH1, CH2 and CH3. The globular regions, which are stabilized by intra chain disulphide bonds, are referred to as "domains". The sites at which the antibody binds antigen are located in the variable domains. The molecular weights range from 146 to 170 kD.

Structural formula: cutaquig® consist mainly of human immunoglobulin G which is a glycoprotein. Each immunoglobulin molecule is bifunctional, one region of the molecule is engaged in specific binding to antigen while a different region mediates binding of the immunoglobulin to host tissues.

Physicochemical properties: Immunoglobulins have a common structure with four polypeptide chains. Two heavy chains and two non-glycosylated light chains. Human IgG is divided in four subclasses IgG_1, IgG_2, IgG_3 and IgG_4 due to minor differences in the amino sequence. The isoelectric point varies between 5.0 and 9.5. Cleavage of an immunoglobulin molecule with proteolytic enzymes such as papain, in the hinge region, yields two Fab fragments (fragment antigen binding) and one Fc fragment (fragment crystallisable). The Fab fragments contain the antigen binding part. The Fc fragment contains the lower parts of the heavy chains and is essential for a number of biological actions, e.g. complement fixation, binding to cell surface Fc receptors and ability to cross the placenta.

Pharmaceutical Standard: ATC-Code: J06B A01

Product Characteristics

cutaquig® is a ready-to-use, sterile, 16.5% protein liquid preparation of polyvalent human immunoglobulin G (IgG) for subcutaneous administration. cutaquig® is prepared by cold-ethanol fractionation of donated human fresh frozen plasma. Each preparation is made from a pool of at least 3,500 donations of human fresh frozen plasma. Residual ethanol is removed via ultra-/diafiltration. Viral inactivation is accomplished by a S/D method and a specific pH4

treatment. Residual S/D reagents are removed by oil extraction (TNBP) and C18 chromatography (Octoxynol). A second ultra-/diafiltration step removes all ions such as sodium and increases the protein content. The whole manufacturing process is carried out at a low pH in order to maintain the nativity of the IgG molecules. After addition of maltose and polysorbate 80 the 16.5% IgG solution is sterile filtered and filled into non-siliconized depyrogenated glass vials.

In the manufacturing process of cutaquig® a heparin sepharose column is implemented to reduce the possible content of procoagulant factors. Furthermore a sensitive batch release test is implemented (Factor XIa-like activity) to detect increased thromboembolic potential. Blood group A and B antibodies (isoagglutinins A and B) are reduced by the ethanol precipitation steps.

Viral Inactivation

The plasma used for the manufacture of cutaquig® is obtained from collection centers that are inspected by Octapharma and are US FDA licensed. All operations and procedures of the plasma centers are reviewed with particular emphasis on donor selection, plasma testing, and proper documentation. All single donations are tested and must be HBsAg-, anti-HCV-, and anti-HIV-1/2-negative as well as negative for Syphilis. The test interval is complying with US regulations. Further, only donations that are tested negative for HIV, HBV, HCV and HAV and below the acceptance limit for Parvo B19 by Polymerase Chain Reaction (PCR) in minipools are accepted. Additionally, the plasma pool used for the production of cutaquig® is tested for HCV by PCR techniques and re-tested for HBsAg and anti- HIV-1/2. Only preparations, which are negative in all these tests, are used for further manufacture.

The pathogen safety of cutaquig® is ensured through three dedicated- and contributing manufacturing steps. In particular, the S/D treatment inactivates enveloped viruses such as HIV, hepatitis B (HBV) and hepatitis C (HCV) virus. The pH4 treatment is effective against both enveloped and non-enveloped viruses, such as hepatitis A virus (HAV). In addition, the manufacturing process comprises an unspecific and highly robust pathogen removal step, i.e. cold-ethanol fraction (removal of fraction I+III) reducing the burden of non-enveloped and enveloped viruses as well as potentially present transmissible spongiform encephalopathy (TSE) agents (prions).

CLINICAL TRIALS

Clinical data are available from one pivotal study conducted in North America and Europe.

Study demographics and trial design

The study was a prospective, open-label, non-controlled, single-arm, multicentre Phase 3 study to evaluate the pharmacokinetics (PK), efficacy, tolerability and safety of subcutaneous human immunoglobulin (cutaquig®) in patients with primary immunodeficiency diseases (PID).

The study was conducted in 59 adult and pediatric patients who received weekly SC infusions with cutaquig® during a 12-week wash-in/wash-out period followed by a 12-month efficacy period (primary observation period) during which the efficacy, pharmacokinetics, safety, tolerability and quality of life (QoL) parameters of cutaquig® were evaluated.

During the 12-month primary observation period the mean weekly dose was 176 mg/kg BW, with individual doses ranging from 60 to 390 mg/kg BW. The median duration of infusion per week was 1.5 hours.

All enrolled patients (n=59) were included in the Safety Analysis Set and the Full Analysis Set (FAS). Four patients were excluded from the Per-Protocol (PP) Set because they terminated early before the start of the primary treatment period.

Overall, 32 female patients and 27 male patients participated in this study. The youngest patient enrolled in the study was 2 years old and the oldest was 73 years old. The mean age in the adult group (16–75 yrs) was 47 years.

The majority of patients (51 patients; 86.4%) had a history of CVID, 3 patients had X-linked agammaglobulinaemia and 5 had other primary immunodeficiencies. The most common previous IVIG schedule was a 4-weekly one (47 patients; 79.7%). The mean dose over the last 6 infusions was 442 mg/kg BW.

Primary objectives

The first primary objective of the study was to assess the efficacy of cutaquig® in preventing serious bacterial infectiona (SBI) compared with historical control data. This criterion was clearly met, as no SBIs were reported at any time during the study.

The second primary objective was to evaluate the PKs of cutaquig® and to compare the area under the curve (AUC_{SC}) with that of IVIG (AUC_{IV}). Bioavailability was calculated (AUC_{SC2}/AUC_{IV}) and the geometric mean was 1.0303, (90% CIs: 0.9722, 1.0918), thus confirming bioequivalence.

Secondary objectives

Secondary objectives of the study included: the number of episodes of any other infections, along with type and severity of infection and time to resolution; number of days of use and annual rate of antibiotics; absence and number of days of absence from work/school/ kindergarten/day care; hospitalisations due to infections and number of days and annual rate of hospitalisation; number of episodes of fever; and QoL assessments.

The rate of other (non-serious) infections per person-year was 3.3 overall (upper 95% CI: 4.697). Two-thirds of the infections in the primary observation period were mild and one-third moderate in intensity. The median time to resolution of infections was 10 days, with longer times for moderate infections (15 days) than for mild infections (8 days).

Just under half of patients used antibiotics during the primary observation period. There were regional differences, with higher antibiotic use in North America than in Europe. The number of treatment episodes per person-year was 2.2 and the number of treatment days per person-year was 45.8 in the primary observation period.

During the primary observation period 3 (5.1%) patients each had 1 episode of fever, giving 0.076 episodes of fever per person-year.

During the primary observation period 9 patients (16.4%) had 16 absences from work or school due to infections with a total of 73 days of absence. The total number of days absent from work or school per person-year was 1.9.

There were no hospitalisations due to infection during the study.

QoL parameters: Overall, there were no major changes in the mean and median CHQ-PF50 scores over time. The aggregated component score of physical health showed a slight improvement and the psychosocial summary score showed a slight worsening.

Mean SF-36v2 scores ranged between 42 and 53. The summary mental health score was 52.5 at the End of Study Visit and the physical health score was 48.6. Overall there were increases (i.e., improved QoL), albeit slight, between Week 1 and the End of Study Visit in mean scores for both summary scores (physical health and mental health) and also for all eight scales.

DETAILED PHARMACOLOGY

Non-clinical Pharmacology Studies

cutaquig® is a 16.5% human plasma-derived normal immunoglobulin solution (SCIG) intended to be used as a replacement therapy at normal physiological levels. Hence, the standard pharmacodynamic studies generally carried out for new substances in commonly used species are not applicable to this product.

However, three pharmacological studies were performed in different animal species: one efficacy study and two safety pharmacology studies as follows:

The objective of a Non-GLP study was to test efficacy of cutaquig® given subcutaneously in three different dose levels (660, 330 and 165 mg/kg) in the mouse sepsis model induced by Streptococcus pneumoniae ATCC 6301 in CD1 female mice.

The test item and the negative control (human serum albumin) were each administered by subcutanous injection to mice 48 hours before intraperitoneal challenge with different dilutions of S. pneumoniae. Animals were observed for six days following inoculation and mortality was recorded. The concentration of Streptococcus pneumoniae was determined by the dilution plate method. Mice were inoculated with a bacterial load ranging from 3.9x105 to 0.39 CFU (colony forming units) per mouse.

cutaquig® showed strong, dose dependent protection following intraperitoneal infection with a range of inoculum sizes. Complete protection against infection with *S. pneumoniae* ATCC 6301 was observed up to 39 CFU/mouse for 165 and 330 mg/kg, and up to $3.9x10^3$ CFU/mouse for 660 mg/kg cutaquig®.

Partial protection was also seen at the inoculum sizes $3.9x10^4$ and $3.9x10^5$, however without statistically significant difference in survival rates vs. human serum albumin control.

In conclusion, cutaquig® at doses of 165, 330 and 660 mg/kg s.c. showed a strong, dose dependent effect in *S. pneumoniae* ATCC6301 induced intraperitoneal sepsis in mice.

cutaquig® was screened for its potential thrombogenic properties in a venous stasis model in rabbits based on Wessler et al. (1959).[8]

The Wessler test has been used extensively for 50 years as a laboratory measure of in vivo hypercoagulability. The test, in which induced hypercoagulability is enhanced by local venous stasis, has proved invaluable for assessing the thrombogenicity of varoius blood- and plasma-derived products.

Two batches of cutaquig® were tested at a dose of 400 mg/kg BW and intravenously injected as a bolus. FEIBA (human plasma fraction with Factor VIII inhibitor bypassing activity from Baxter) served as a positive control item to ensure the sensitivity of the test system. Physiologic saline served as a negative control substance. 5 animals per group were tested.

Prior to the injection of the test items, the animals were anaesthetized with intravenous sodium pentobarbital. A 1 to 2 cm length of the external vena jugularis was freed from its surrounding structures and its tributaries were ligated. The test items were administered within 15 seconds into a marginal vein of the contra-lateral ear. Within 25 seconds after completion of the injection, the previously exposed vena jugularis was gently ligated (over a length of 1 - 2 cm). This ligated vein segment remained in situ for 10 minutes. The segment was then removed from the animal; its content was emptied into a Petri dish containing 30 mL of a 5% sodium citrate solution and the content of the dish was then examined using a scale as described in the mentioned literature source. Both batches of cutaquig® did not show any thrombogenic effect.

The aim of a GLP-study was to assess the cardiovascular effects and the potential for QT interval prolongation of cutaquig® in telemetered Beagle dogs following a single subcutaneous administration of 500 mg/kg BW. Four animals were employed. Cardiohaemodynamic parameters, physical activity and body temperature were measured 24 hours prior to dosing (baseline and predose) and 72 hours post dosing. Haemodynamic data, physical activity and body temperature were reported in 5-minute intervals. Electrocardiography (ECG) data were reported in 4-hour intervals (baseline) and for the time-points 5, 15 and 30 min and 1, 2, 3 and 4 hours after dosing. Treatment values were compared to the corresponding predose values. None of the animals died prematurely. No test item-related local or systemic intolerance reactions were noted. No test item-related influence was noted on any of the following parameters: systolic, diastolic or mean arterial blood pressure, heart rate, RR interval, QRS interval, QT interval, QTc value (van de Water), QTc value (Fridericia), PQ interval, physical activity or body temperature. No signs were noted for a prolongation of the QT interval or the QTc values.

In conclusion, single subcutaneous administration of 500 mg/kg BW cutaquig® had no effect on blood pressure or ECG parameters and no potential for a QT interval prolongation in telemetered dogs.

Non-clinical Pharmacokinetic Studies

Pharmacokinetic studies with human proteins in animals are not predictive for the human situation. Human proteins undergo rapid clearance in animals resulting in a shortened half-life as compared to the half-life in human beings. Therefore, animal pharmacokinetics studies with the final product are not performed.

Human Pharmacokinetics and Pharmacodynamics

Please refer to ACTION AND CLINICAL PHARMACOLOGY section.

TOXICOLOGY

Animal Toxicity Studies

IgG is a normal constituent of human plasma. In animals, single dose toxicity testing is of no relevance since the high doses required would result in IgG overload. As proteins of human origin are immunogenic to animals, repeated dose and reproduction toxicity testing in animals would not generate useful data. Therefore, single and repeated dose as well as reproduction toxicity studies with the final product are not performed.

Since the clinical experience does not provide any evidence of tumorigenic or mutagenic effects of IgG, experimental studies, particularly in heterologous species, are not considered to be necessary.

However, a local tolerance study was performed in rabbits as follows:

The aim of this experiment was to obtain information on the local tolerance of cutaquig® in comparison with the reference item, a 20% subcutaneous human normal immunoglobulin, in rabbits after single subcutaneous injection. The test item cutaquig® was used as supplied and the reference item was diluted with sterile 0.9% NaCl solution to a final concentration of 16.5%. The volume administered was 5.0 mL/animal. Two male and 2 female animals were employed per item. The test or reference item was administered once under the dorsal skin on the left side of each animal. In addition, a 0.9% aqueous NaCl solution was administered in the same manner and same volume on the right side of each animal and served as a control. Ninety-six hours after administration all animals were sacrificed and the injection sites were examined macro- and microscopically.

No test item-related macroscopic changes were noted. The histomorphological examination of 16 skin localizations in rabbits from a local tolerance test after subcutaneous administration of cutaquig® and a comparator did not reveal any morphological changes in the skin considered to be test item-related. No signs of systemic toxicity occurred.

In conclusion, subcutaneous injection of 5.0 mL cutaquig®/animal did not reveal any test item-related histopathological changes 96 hours after administration.

REFERENCES

1. Berger M. Subcutaneous Administration of IgG. ImmunolAllergy ClinNorth Am. 2008;28(4):779-802.
2. Ferreira A, Garcia Rodriguez MC, Lopez-Trascasa M, Pascual SD, Fontan G. Anti-IgA antibodies in selective IgA deficiency and in primary immunodeficient patients treated with gamma-globulin. Clin ImmunolImmunopathol. 1988;47(2):199-207.

3. de Albuquerque CR, Sato MN, da Silva Duarte AJ. IgG anti-IgA subclasses in common variable immunodeficiency and association with severe adverse reactions to intravenous immunoglobulin therapy. JClinImmunol. 2000;20(1):77-82.
4. Horn J, Thon V, Bartonkova D, Salzer U, Warnatz K, Schlesier M, et al. Anti-IgA antibodies in Common Variable Immunodeficiency (CVID): Diagnostic workup and therapeutic strategy. ClinImmunol. 2007;122(2):156-62.
5. Salama A, Schwind P, Schonhage K, Genth R, Cotting C, Hustinx H, et al. Rapid detection of antibodies to immunoglobulin A molecules by using the particle gel immunoassay. Vox Sang. 2001;81(1):45-8.
6. Eijkhout HW, van den Broek PJ, van der Meer JWM. Substitution therapy in immunodeficient patients with anti-IgA antibodies or severe adverse reactions to previous immunoglobulin therapy. Netherlands Journal Of Medicine. 2003;61(6):213-7.
7. Gardulf A, Andersson E, Lindqvist M, Hansen S, Gustafson R. Rapid subcutaneous IgG replacement therapy at home for pregnant immunodeficient women. JClin Immunol. 2001;21(2):150-4.
8. Wessler S, Reimer SM, Sheps MC. Biologic assay of a thrombosis-inducing activity in human serum. Journal of applied physiology. 1959;14:943-6.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

cutaquig®
Immunoglobulin (human) subcutaneous
16.5% Solution for injection (165 mg/mL)

Read this carefully before you start taking cutaquig® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about cutaquig®.

Serious Warnings and Precautions

- 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. Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment should be administered.
- There is clinical evidence of an association between the administration of immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. Therefore, caution should be exercised when prescribing and administering immunoglobulins.
- Risk factors for thromboembolic events include: advanced age, use of estrogens, in-dwelling central vascular catheters, history of vascular disease or thrombotic episodes, acquired or inherited hypercoagulable states, prolonged periods of immobilization, severe hypovolemia, diseases which increase blood viscosity and cardiovascular risk factors (including obesity, hypertension, diabetes mellitus, history of atherosclerosis and/or impaired cardiac output).
- Thrombosis may occur even in the absence of known risk factors.

What is cutaquig® used for?

cutaquig® is used to treat primary immunodeficiency (PID) and secondary immunodeficiency (SID) in people who need immune globulin replacement therapy. People with PID and SID can get many infections. cutaquig® helps to lower the number of infections.

How does cutaquig® work?

Normally, our immune system protects us against infections by recognizing potentially harmful bacteria and viruses that enter our body every day. In response, the immune system produces

special proteins called antibodies (Immune Globulins or Immunoglobulins) that fight these infective agents. When our immune system is not working properly, it is unable to produce these antibodies.
This product can help prevent infections by providing a protective role of these antibodies in patients who suffer from a poorly functioning immune system.

What are the ingredients in cutaquig®?

Medicinal ingredients: Human normal immunoglobulin G (IgG)

Non-medicinal ingredients: Maltose, Polysorbate 80, Water for Injections

cutaquig® comes in the following dosage forms:

cutaquig® is a 165 mg/mL solution for subcutaneous injection, provided in the following dosage forms:

Size	Grams Protein
6 mL	1
10 mL	1.65
12 mL	2
20 mL	3.3
24 mL	4
48 mL	8

Do not use cutaquig® if:

- You are hypersensitive to this drug or to any ingredient in the formulation or component of the container.
- You have experienced anaphylactic or severe systemic reactions to the administration of human normal immunoglobulin or to components of cutaquig®

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take cutaquig®. Talk about any health conditions or problems you may have, including:

- If you have a history of allergic or other reactions to immunoglobulins.
- If you have a history of (cardio)vascular disease.
- If you have a history of thromboembolic events (e.g. deep vein thrombosis, blockage of blood vessels, blood clots, stroke).
- If you have hypertension or diabetes mellitus.
- If you have a kidney disease.
- If you have been previously advised that you have IgA deficiency.
- If you are pregnant or think you may be pregnant.

- If you are nursing.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with cutaquig®:

cutaquig® should not be mixed with other products.

The passive transfer of antibodies by cutaquig® may interfere with the response to live virus vaccinations.

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.

How to take cutaquig®:

Detailed patient handling instructions for administration of cutaquig®

cutaquig® is for subcutaneous administration only. Do not inject into a blood vessel.

Only use cutaquig® at home once you have been properly instructed and trained by your healthcare professional.

Follow the administration guidance below step by step and use aseptic/sterile technique when administrating cutaquig®. Use gloves if you have been told to do so when preparing the infusion.

1. **Prepare the necessary number of cutaquig® vials**
    - If stored in the fridge put the vials at room temperature at least 90 minutes prior to infusion.
    - Do not heat the vials or put them into the microwave.
    - Do not shake the vials to avoid foaming.

2. Getting ready for infusion

- Choose and prepare a clean work area using antiseptic wipes or disinfecting solution (Figure 1).

Figure 1

- Gather your infusion equipment:
  - Syringe(s)
  - Infusion pump (optional)
  - Needle (for drawing up product from the vial)
  - Infusion set
  - Infusion tubing and Y-connector (if required)
  - Alcohol & alcohol wipes/antiseptic wipes
  - Gauze or transparent dressing and tape
  - Sharps container
  - Treatment diary and pen
- Wash your hands thoroughly and let them dry (Figure 2). Use disinfectant gel as has been shown to you during training.

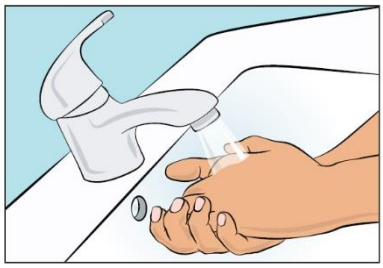

Figure 2

- If necessary program the pump according to the user manual and as you have been shown during the training by your healthcare professional.

3. Checking & opening the vials

- Inspect each vial carefully for:
  - Correct labelled dose based on your prescription,

- Check the appearance of the solution (it should be clear and colorless),
- Make sure the protective cap has not been broken or is missing,
- Check the expiry date and batch number.
- Do not use the solution if it is cloudy or contains particles.

- Remove the protective cap.
- Disinfect the rubber stopper by using an antiseptic wipe and allow it to dry (Figure 3).

Figure 3

4. Preparing and filling the syringe

- Open sterile syringe and needle.
- Attach the needle to the syringe with a screw action.
- Draw back on the plunger to fill the syringe with air which should be roughly equal to the amount of solution needed from the vial.
- Insert the needle into the vial and turn the vial upside down. Inject air - ensuring the tip of the needle is not in the solution to avoid foaming.
- Next, making sure the needle remains always in the solution, slowly draw up the cutaquig® (Figure 4).

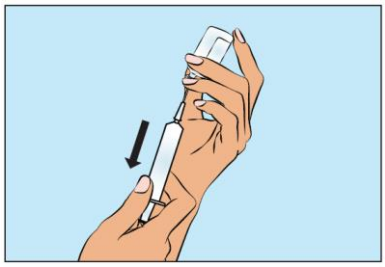

Figure 4

- Withdraw the needle from the vial.
- This procedure might need to be repeated if you need multiple vials for the calculated dose.
- When finished remove the needle and dispose it into the sharps bin.
- Immediately proceed to the next step as the IgG solution should be used promptly.

5. Preparing the infusion pump (optional)

- Prepare the infusion pump (if using) by following the manufacturer's instructions

6. Prepare tubing

- Prime (fill) the infusion tubing. To prime the tubing, connect the syringe filled with cutaquig® to the infusion tubing and gently push on the syringe plunger to fill the tubing with cutaquig® (Figure 5).

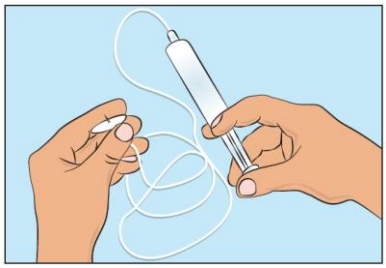

Figure 5

- Stop priming before cutaquig® fluid reaches the needle.
- If using a pump, insert syringe filled with cutaquig® into the pump.

7. Deciding on infusion sites and inserting the infusion needle(s)

- cutaquig® can be infused in the following areas: abdomen, thigh, upper arm, and/or upper leg/hip area (Figure 6).

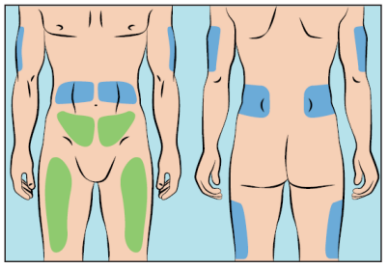

Figure 6

- The infusion sites should be at least 5 cm apart.
- Use different infusions sites than you used for the previous administration.
- Avoid inserting the needle into scars, tattoos, stretch marks or injured/inflamed/red skin areas.
- Clean your skin at your selected infusion site(s) with an antiseptic skin wipe and let the skin dry.

- Pinch the skin between your thumb and forefinger around the injection site (Figure 7), carefully remove the needle cover and insert the needle into the skin (Figure 8). The angle of the needle will depend on the type of infusion set being used.

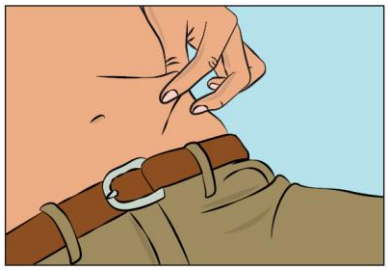

Figure 7

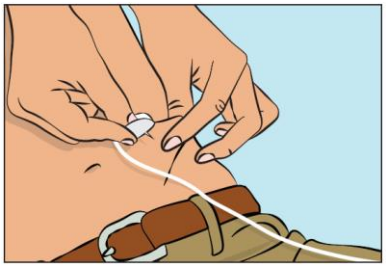

Figure 8

8. Checking the infusion

- The solution should not be infused into a blood vessel.
- Secure the needle in place by applying sterile gauze and tape or a transparent dressing (Figure 9).

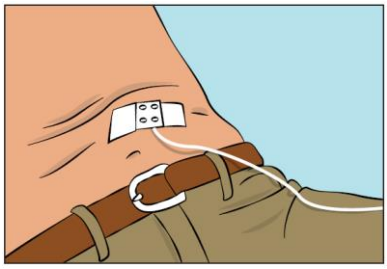

Figure 9

9. Starting the infusion

- Start the infusion.
- If an infusion pump is used for administration, follow the manufacturer's instructions.
- If administration is done by the manual rapid push method using a syringe, start to push the plunger gently and infuse at a rate that is comfortable for you.

10. Recording the infusion

- On each vial of cutaquig® you will find a peel off label giving the batch number details. Stick this label in your patient's treatment diary or infusion log book. Record details of the dose, date, time, infusion site location and any infections, side effects or other comments in connection with this infusion.

11. After the infusion is complete

- Gently remove the needle(s) and immediately place into the sharps bin.
- If necessary press a small piece of gauze on the needle site and apply a dressing.
- Throw away all used disposable supplies as well as any unused product and the empty vial(s) as recommended by your healthcare professional and according to local requirements.
- Tidy up and securely store all the reusable equipment (e.g. pump) until the next infusion.

Usual dose:

Your doctor or healthcare professional will individualize your dose based on your clinical response to cutaquig® therapy and on serum immunoglobulin G (IgG) trough levels.

Doses may be adjusted over time to achieve the desired clinical response and serum IgG levels.

In case of measles exposure your dose might need to be adjusted for 2 consecutive weeks. Please consult your doctor or healthcare professional, if you have been exposed to measles.

Overdose:

Consequences of an overdose are not known with cutaquig®.

If you think you have taken too much cutaquig®, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Inform your doctor or health care professional if you missed a dose. A missed dose should be administered as soon as possible to ensure an adequate IgG serum level.

What are possible side effects from using cutaquig®?

These are not all the possible side effects you may feel when taking cutaquig®. If you experience any side effects not listed here, contact your healthcare professional. Please also see WARNINGS AND PRECAUTIONS.

No related serious adverse drug reactions were observed in subjects treated with cutaquig® during the clinical studies evaluating its safety.

Injection site reactions (such as redness, swelling, itching, pain, tenderness, and feeling of warmth) are a common occurrence with SCIG infusions and this side effect is expected. Overall the adverse events were mild or moderate in intensity.

Other side effects have also been observed less frequently: fever, headache, abdominal pain, vomiting, fatigue, and muscle pain.

Tell your doctor right away or go to the emergency room if you have hives, trouble breathing, wheezing, dizziness, or fainting. These could be signs of a bad allergic reaction.

Tell your doctor right away if you have any of the following symptoms. They could be signs of a serious problem.

- Severe headache with nausea, vomiting, neck stiffness, fever, and sensitivity to light. These could be signs of a brain swelling called meningitis.
- Pain, swelling, warmth, redness, or a lump in your legs or arms, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body, sudden confusion, or trouble speaking. These could be signs of a blood clot.
- Fever over 100ºF (37.8°C). This could be a sign of an infection.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
cutaquig® can be stored at +2 °C to +8 °C for up to 24 months from the date of manufacture. Within its shelf-life, the product may be stored at room temperature up to +25 °C for up to 6 months without being refrigerated again during this period, and must be discarded if not used after this. Do not use after expiry date.

Do not freeze. Keep the vial in the outer carton to protect it from light. Discard any remaining contents after use.

Keep out of reach and sight of children.

If you want more information about cutaquig®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.octapharma.ca, or by calling 1-888-438-0488.

This leaflet was prepared by Octapharma Pharmazeutika Produktionsges.m.b.H

Last Revised <AUG-05-2019>