▼ This medicine is subject to additional monitoring **in Australia**. This will allow quick identification of new safety information. Healthcare professionals are asked to report suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – CUTAQUIG® (HUMAN NORMAL IMMUNOGLOBULIN, 16.5%), solution for subcutaneous injection

1 NAME OF THE MEDICINE

Human normal immunoglobulin 16.5% [165 mg/mL], solution for subcutaneous injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cutaquig® contains 165 mg/mL (16.5%) human normal immunoglobulin with a purity of at least 95% immunoglobulin G (IgG) and a broad spectrum of antibodies against infectious agents.

Distribution of the IgG subclasses (approx. values):

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

The maximum IgA content is 600 micrograms/ mL.

Cutaquig® contains all the IgG activities, which are present in the normal population. It is prepared from pooled plasma from not fewer than 1000 donations.

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.

For a full list of excipients, see Section 6.1 List of Excipients.

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 and children in:

- Primary immunodeficiency diseases (PID)
- Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment

4.2 DOSE AND METHOD OF ADMINISTRATION

Cutaquig® should only be administered subcutaneously.

Dose

The dose and dose regimen are dependent on the indication.

Replacement therapy (PID and SID)

Replacement therapy should be initiated under the supervision of a healthcare professional experienced in the treatment of immunodeficiency.

In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline.

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.

After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals (approximately once per week) to reach a cumulative monthly dose of the order of 0.4-0.8 g/kg (2.4 to 4.8 mL/kg).

For more frequent administration than once per week, divide the calculated weekly dose by the desired number of administrations per week (e.g. for 3 times per week dosing, divide weekly dose by 3). For administration every two weeks, double the weekly cutaquig® dose. Doubling the weekly dose of cutaquig® has not been evaluated in clinical studies; however, pharmacokinetic modelling suggests that similar trough levels can be achieved to that of single weekly doses.

To convert the dose (in grams) to millilitres (mL), multiply the calculated dose (in grams) by 6.

Trough levels should be measured and assessed in conjunction with the patient's clinical response. Depending on the desired clinical response (e.g. infection rate), it may be necessary to increase the dose and aim for higher trough levels.

Paediatric population

Cutaquig® has not been studied in children under 2 years of age. 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 22 paediatric subjects (15 children [between 2 and <12 years of age] and 7 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.

Method of administration

For subcutaneous use only. Cutaquig® must not be administered intravenously.

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

Cutaquig® should be brought to room temperature before use.

Cutaquig® contains no antimicrobial agent. Once the container has been opened the contents should be used immediately. Product is for single use in one patient only. Discard any residue.

Cutaquig® may be injected into sites such as abdomen, thigh, upper arm, and lateral hip. The volume of product infused into a particular site may vary.

Infusion recommendations for subcutaneous infusions using a pump:

Volume	If large doses are administered (>15 mL in children and >30 mL in adults) it may be advisable to divide and infuse the dose into multiple sites. There is no limit to number of infusion sites in parallel. Infusions site should be at least 5 cm apart.
Rate	Maximum recommended flow rates per hour per infusion site are as follows: Initial infusion/s: 15-20 mL per hour per site. Subsequent infusions: If well tolerated, increase to 25 mL per hour per site. Thereafter the infusion rate can be further increased as per patient tolerability.

For subcutaneous infusion using a syringe via manual push:

Volume	If large doses are administered (>15 mL in children and >30 mL in adults) it may be advisable to divide and infuse the dose into multiple sites. There is no limit to number of infusion sites in parallel. Infusions site should be at least 5 cm apart.
Rate	Proposed maximum infusion rate is approximately 1-2 mL/min (60-120 mL/hour).

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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The recommended infusion rate must be closely followed (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Patients should be closely monitored and carefully observed for any symptoms throughout the infusion period.

Cutaquig® is for subcutaneous use only and must not be given intravascularly. If cutaquig® is accidentally administered into a blood vessel patients could develop shock. Cutaquig® must not be administered intramuscularly in case of severe thrombocytopenia and in other disorders of haemostasis.

Potential complications can often be avoided by ensuring that patients are:

- not sensitive to human normal immunoglobulin by initially injecting the product slowly.
- carefully monitored for any symptoms throughout the infusion period. In particular, patients naive 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. The treatment required depends on the nature and severity of the adverse reaction.

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.

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

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.

Caution should be exercised in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, and 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.

In patients at risk for thromboembolic adverse reactions, cutaquig® should be administered at the minimum rate of infusion and dose practicable. Patients should be sufficiently hydrated before use of immunoglobulins.

Aseptic meningitis syndrome

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 include severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting.

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.

Transmissible agents

Cutaquig® is made from human plasma. 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 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.

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.

Use in the elderly

In the clinical trial cutaquig® was evaluated in 3 patients older than 65 years. Although this is only limited data, it is expected that the same warnings, precautions and risk factors apply to the elderly population.

Paediatric use

Cutaquig® was evaluated in 22 paediatric subjects (15 children [between 2 and <12 years of age] and 7 adolescents [between 12 and <16 years of age]) with primary immunodeficiency disease. Data from these paediatric patients showed a similar safety profile in paediatric and adult patients receiving cutaquig®. Cutaquig® has not been studied in children under 2 years of age.

Effects on laboratory tests

Interference with serological testing
After injection of immunoglobulin the transitory rise of 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 or D may interfere with some serological tests for red cell antibodies, for example the direct antiglobulin test (DAT, e.g. Coombs' Test).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Blood glucose testing
Cutaquig® contains maltose as an excipient (maximally 90 mg of maltose per ml) 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.

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, oral rotavirus, influenza and varicella.

After administration of this 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 a measles vaccine should have their antibody status checked. Refer to the Australian Immunisation Handbook for clinical practice recommendations.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Animal fertility studies have not been conducted with cutaquig®. Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

Use in pregnancy

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 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 fetus and the neonate are to be expected.

Continued treatment of the pregnant woman ensures a passive immunity for the neonate.

Use in lactation

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

4.7 Effects on ability to drive and use machines

Cutaquig® has no or negligible influence on the ability to drive and use machines.

4.8 Adverse effects (Undesirable effects)

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.

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 intravenous immunoglobulin (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 60 subjects. A total of 3534 cutaquig® infusions were administered.

Table 1 below presents adverse drug reactions (ADR) according to the MedDRA system organ classification (SOC and Preferred Term Level).

Within each organ class, adverse reactions are presented in order of decreasing frequency.

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

MedDRA System Organ Class (SOC)	Adverse event	Number (%) of subjects (N=60)	Number (Rate) of AEs (N=3534)
Nervous system disorders	• Headache	2 (3.3)	3 (<0.001)
Gastrointestinal disorders	• Abdominal distension • Abdominal pain • Vomiting	1 (1.7) 1 (1.7) 1 (1.7)	1 (<0.001) 1 (<0.001) 1 (<0.001)
Musculoskeletal and connective tissue disorders	• Myalgia	1 (1.7)	1 (<0.001)
General disorders and administration site conditions	• Injection site reaction** • Pyrexia	45 (75) 2 (3.3)	824 (0.23) 2 (<0.001)
Investigations	• Coombs test positive • Free hemoglobin present • Haptoglobin decreased	1 (1.7) 2 (3.3)1 (1.7)	1 (<0.001) 2 (<0.001) 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.

Post-marketing experience

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, pruritus, flushing, feeling hot, feeling cold, asthenia, fatigue, influenza-like illness, malaise, injection site pain, throat tightness, and hypertension.

In addition to the ADRs observed during clinical trials and after the administration of subcutaneous immunoglobulin products, the following adverse reactions have been experienced during post-approval use of cutaquig®: thromboembolic event (Vascular disorders), aseptic meningitis (Nervous system disorders).

The reporting frequency of post-marketing ADRs is unknown because the reporting is voluntary and from a population of uncertain size.

Paediatric population

Clinical trials with cutaquig® showed a similar safety profile in paediatric and adult patients with PID. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.
For information on viral safety, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Elderly Population

Limited information available in clinical trials showed no difference in the safety profile in patients ≥65 years of age compared to younger patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Consequences of an overdose are not known. In case of overdose the occurrence of adverse drug reactions should be closely monitored and, if necessary, supporting measures should be offered.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, solution for subcutaneous injection.

ATC-Code: J06B A02

Mechanism of action

Cutaquig® contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. It contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations.

Cutaquig® has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range.

Clinical trials

The safety and efficacy of cutaquig® (called octanorm in the trial) was evaluated in a prospective, open-label, non-controlled, single-arm, multicentre Phase 3 study performed in 18 centres in Europe, the USA and Canada.

Treatment of Primary Immunodeficiency Syndromes (PID)
This study aimed to evaluate the pharmacokinetics, efficacy, tolerability and safety of cutaquig® in patients with PID. It was the pivotal study for the approval of cutaquig® for the treatment of PID.

In this clinical trial, 60 patients received cutaquig® treatment over a period of about 15 months, comprising a 12-week wash-in/wash-out period followed by a 12-month efficacy phase. The study population comprised 4 young children (2 years of age to <5 years), 11 children (5 years of age to <12 years), 7 adolescents (12 years of age to <16 years) and 38 adults (16 years of age to ≤75). Each patient who stayed in the study for the whole period received 64 cutaquig® SC weekly infusions. The first primary objective was to assess the efficacy of cutaquig® in preventing serious bacterial infections (SBI, defined as bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, or visceral abscess) compared with historical control data. The second primary objective was to evaluate the PK characteristics of cutaquig® and to compare the AUC with that of IVIG.

In the 12-week wash-in/wash-out phase, weekly (±2 days) SC doses of cutaquig® were given, at 1.5 times the previous IVIG dose adjusted for weekly dosing. After completion of the 12-week wash-in/wash-out phase, patients entered the efficacy phase during which treatment continued. The final examinations were performed 1 week after the end of the last infusion or 1 week after premature withdrawal of a patient from the study.

No SBIs were observed during the study. There was 1 infection (reported as severe) which resulted in hospitalisation. A total of 192 non-serious infections were observed in 51 patients in the primary observation period and 245 infections in 53 patients over the whole treatment period. The rate of other infections per person-year was 3.434 overall. Three-quarters of the infections in the primary period were mild and one-quarter moderate in intensity; there was 1 severe infection. Other efficacy parameters calculated per patient year, such as days with use of antibiotics, absences from school or

work, and episodes of fever were also in line with what has been published for other SCIGs previously developed.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following subcutaneous administration of cutaquig®, peak serum levels are achieved after approximately 2 days.

Elimination

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Primary Immunodeficiency Disease (PID)

In a clinical trial a total of 60 subjects with primary immune deficiency syndromes were treated with cutaquig® up to 64 weeks. The mean dose administered each week was 0.176 (range: 0.06-0.39) g/kg. Subjects received a total of 3534 weekly cutaquig® infusions.

The pharmacokinetics were evaluated in a subset of 22 subjects (19 adult subjects and 3 paediatric subjects) with PID. By weekly infusion from week 2 onwards, the minimum trough levels ranged between 6.1 and 8.4 g/L, median IgG trough levels were at 11.5 g/L. The mean Cmax was 13.5 g/L and was reached after a median of 2.02 days (see Table 2).

Table 2 Key Pharmacokinetic Parameters for Total IgG in 22 PID Patients

Parameter	Cutaquig® (N=22)
C_{max} [g/L]	13.5
C_{min} [g/L]	11.6
C_{avg} [g/L]	13.7
T_{max} [h]#	48.4
AUCτ [h*g/L]	2293

N = number of patients; AUCτ = area under the concentration-time curve (where τ is the dosing interval); C_{max} = maximum plasma concentration; C_{avg} = average plasma concentration; C_{min} = minimum plasma concentration; T_{max} = time to maximum plasma concentration

T_{max} is presented as median, all other parameters are presented as mean values

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Clinical experience provides no evidence for genotoxic potential of immunoglobulins.

Carcinogenicity

Clinical experience provides no evidence for carcinogenic potential of immunoglobulins.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Maltose
Polysorbate 80
Water for Injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, cutaquig® must not be mixed with other medicinal products.

6.3 SHELF LIFE

Shelf life is 2 years.

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.
Do not use after the expiry date.

Once removed from refrigeration, the product may be stored below 25°C for a single period of 6 months. In this case, the product expires at the end of the 6-month period - the new date of expiry should be noted on the outer carton. At the end of this period, the product may not be refrigerated again. Do not use after the expiry date given on the label.

6.5 NATURE AND CONTENTS OF CONTAINER

The primary containers are type I glass vials that are closed with a bromobutyl rubber stopper.

The product is supplied in the following vial sizes in packs of 1, 10 or 20:

- 6 mL containing 1 g of human normal immunoglobulin
- 10 mL containing 1.65 g of human normal immunoglobulin
- 12 mL containing 2 g of human normal immunoglobulin
- 20 mL containing 3.3 g of human normal immunoglobulin
- 24 mL containing 4 g of human normal immunoglobulin

- 48 mL containing 8 g of human normal immunoglobulin

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS registry number: 308067-58-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Octapharma Australia Pty. Ltd.

Jones Bay Wharf
42/26-32 Pirrama Road
Pyrmont NSW 2009
Australia

Medical Enquiries: 1800 780 169 (Australia toll free)

Email: aumedinfo@octapharma.com

9 DATE OF FIRST APPROVAL

03 May 2021

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

cutaquig® is a registered trademark of Octapharma AG.