

AUSTRALIAN PRODUCT INFORMATION

CUVITRU® (Normal Immunoglobulin Subcutaneous [Human] 20%) Injection

1 NAME OF THE MEDICINE

Normal Immunoglobulin Subcutaneous (Human).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition

Name of the components	Nominal values per vial expressed as protein with at least 98% IgG content				
	5 mL	10 mL	20 mL	40 mL	50 mL
Active Ingredient: Normal Immunoglobulin (human) contains at least 98% IgG.	1.0 g	2.0 g	4.0 g	8.0 g	10.0 g

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

Description

The manufacturing processes do not affect the composition of the immunoglobulin in the normal human plasma origin. The distribution of the IgG sub-classes in this product comprises IgG₁ ≥ 56.9%, IgG₂ ≥ 26.6 %, IgG₃ ≥ 3.4%, and IgG₄ ≥ 1.7%.

3 PHARMACEUTICAL FORM

Solution for subcutaneous injection.

Appearance

CUVITRU is a clear and colourless to a pale yellow or light brown solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CUVITRU is indicated as replacement therapy in adult and paediatric patients for:

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

4.2 DOSE AND METHOD OF ADMINISTRATION

For subcutaneous administration only.

CUVITRU should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter and/or discoloration is observed.

Start the infusion promptly after drawing CUVITRU into the syringe. It is suggested to complete the administration within 2 hours due to the potential formation of particles caused by siliconised syringes.

CUVITRU must not be diluted.

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency. Patients should be closely monitored and carefully observed for any adverse reactions throughout the infusion period, particularly patients starting with therapy.

Dosage

The dose and dose regimen is dependent on the indication.

Replacement therapy

In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dose 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 to 2.5 mL/kg) body weight may be required. This may need to be divided over several days, with a maximal daily dose of 0.1 to 0.15 g/kg. After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals to reach a cumulative monthly dose of the order of 0.3 to 1.0 g/kg. Each single dose may need to be injected at different anatomic sites.

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

Table 2: Dosing for patients switching from other Subcutaneous or Intravenous immunoglobulin treatments			
	CUVITRU Dosing Frequency		
	Weekly	Biweekly	Frequent dosing (2-7 times per week)
For patients switching from Immunoglobulin Subcutaneous (Human) treatment (SCIG):	The weekly dose of CUVITRU (in grams) is recommended to be the same as the weekly dose of prior SCIG treatment (in grams) ¹	Biweekly dosing: Multiply the calculated weekly dose by 2	Divide the calculated weekly dose by the desired number of times per week
For patients switching from Immunoglobulin Intravenous (Human) treatment (IVIG)²:	To calculate the initial weekly dose, divide the previous IVIG dose in grams by the number of weeks between intravenous doses ^{1, 2}		
¹ To convert the dose (in grams) to millilitres (mL), multiply the calculated dose (in grams) by 5.			
² Begin treatment with CUVITRU one week after the patient's last IVIG.			

Dose Guidance

A Dose Guidance table has been added below, which shows the suggested dose change (in mL) to achieve a desired IgG trough level change (increase or decrease), once CUVITRU

treatment has been initiated. Calculate the difference between the patient's target serum IgG trough level and the IgG trough level during subcutaneous treatment. Find this difference in the table below, and the corresponding amount (in mL) by which to increase (or decrease) the weekly/biweekly dose based on the patient's body weight. If the difference between measured and target trough levels is less than 100 milligram/dL, then no adjustment is necessary.

However, the patient's clinical response should be the primary consideration which guides dosing.

Table 3: Difference in Volume to be administered weekly/biweekly for intended IgG trough level Change^a						
IgG Trough Levels	Dosing Frequency	Body Weight				
		30 kg	50 kg	70 kg	90 kg	110 kg
100 mg/dL	Weekly	4 mL	6 mL	8 mL	11 mL	13 mL
	Biweekly	7 mL	12 mL	17 mL	21 mL	26 mL
200 mg/dL	Weekly	7 mL	12 mL	17 mL	21 mL	26 mL
	Biweekly	14 mL	24 mL	33 mL	43 mL	52 mL
300 mg/dL	Weekly	11 mL	18 mL	25 mL	32 mL	39 mL
	Biweekly	21 mL	36 mL	50 mL	64 mL	78 mL

^a Derived using a linear approximation of trough levels and weekly dose per kg body mass with a slope of 42.1 kg/L.

Example 1: A patient with a body weight of 70 kg who is on a weekly treatment has a measured IgG trough level of 600 milligrams/dL, and the target trough level is 800 milligrams/dL. The desired target trough level difference is 200 milligrams/dL (800 milligrams/dL minus 600 milligrams/dL). The weekly dose of CUVITRU should be increased by 17 mL.

Example 2: A patient with a body weight of 50 kg who is on a biweekly treatment has a measured IgG trough of 900 milligrams/dL, and the target trough level is 700 milligrams/dL. The desired target trough level difference is 200 milligrams/dL (900 milligrams/dL minus 700 milligrams/dL). The biweekly dose of CUVITRU should be decreased by 24 mL.

Paediatric population

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

No clinical trials have been conducted with CUVITRU in children at age 0 to < 2 years, but experience with immunoglobulins suggests that no harmful effects on treatment of children at age 0 to < 2 years with CUVITRU are to be expected.

Method of administration

Subcutaneous infusion should be commenced and initially monitored by a healthcare professional experienced in the guidance of patients for home treatment with regular follow-ups. Infusion pumps appropriate for subcutaneous administration of immunoglobulins can be used. The patient or caregiver must be instructed in the use of a syringe driver, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

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

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

It is recommended to use an initial administration speed of 10 mL/h/infusion site. If well tolerated, the rate of administration may be increased at intervals of at least 10 minutes to a maximum of 20 mL/h/infusion site for the initial two infusions. More than one pump can be used simultaneously. The amount of product infused into a particular site varies. In infants and children, infusion site may be changed every 5-15 mL. In adults, doses over 30 mL may be divided according to patient preference. There is no limit to the number of infusion sites.

CUVITRU does not contain antimicrobial preservative. It is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

CUVITRU is contraindicated in:

- Patients with known anaphylactic or severe hypersensitivity reactions to the subcutaneous administration of the active substance or any of the excipients.
- Patients with severe IgA deficiency and a history of hypersensitivity to human immunoglobulin treatment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

CUVITRU must not be given intravascularly or intramuscularly.

If CUVITRU is accidentally administered into a blood vessel, patients could develop shock.

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

Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

Potential complications can often be avoided by:

- Initially injecting the product slowly (see Section 4.2 DOSAGE AND ADMINISTRATION)
- Ensuring that patients are 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. Suspicion of severe hypersensitivity or anaphylactic-type reactions requires immediate discontinuation of the injection. The treatment required depends on the nature and severity of the adverse reaction.

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

It is strongly recommended that every time that CUVITRU 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.

Hypersensitivity

True hypersensitivity reactions may occur. They can particularly occur in cases of IgA deficiency with anti-IgA antibodies and these patients should be treated with caution. Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be switched to IGSC, 20% only under close medical supervision. IGSC, 20% contains trace amounts of IgA (contains ≤ 280 mcg/mL IgA).

Human normal immunoglobulin can induce an anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

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, cerebral vascular accident (Stroke), deep vein 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, 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.

Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Renal complications

Severe renal adverse reactions have been reported in patients receiving immune globulin treatment, particularly those products containing sucrose (CUVITRU does not contain sucrose). These include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis.

Factors that increase the risk of renal complications include, but are not limited to pre-existing renal insufficiency, diabetes mellitus, hypovolemia, concomitant nephrotoxic medicinal products, age over 65, sepsis, hyperviscosity and paraproteinaemia.

Aseptic Meningitis Syndrome (AMS)

Aseptic meningitis syndrome (AMS) has been reported to occur in association with immunoglobulin treatment, including CUVITRU (see Section 4.8 Adverse Effects). AMS may occur more frequently in female patients. Discontinuation of Ig treatment may result in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IG treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3 , predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.

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

Haemolysis

CUVITRU contains blood group antibodies that may act as haemolysins and induce in vivo coating of red blood cells (RBC) with immunoglobulin. This may cause a positive direct antiglobulin reaction [DAT, (Coombs test)] and, rarely, haemolysis. Delayed haemolytic anaemia can develop subsequent to IG therapy due to enhanced RBC sequestration. Acute haemolytic anaemia, consistent with intravascular haemolysis, has been reported.

Transmissible agents

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

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

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

Paediatric Use

The listed precautions apply both to adults and children.

CUVITRU was evaluated in pivotal clinical studies which included a total of 53 paediatric subjects with PID: 25 paediatric subjects in Study 170903 (5 aged 2 to <6 years, 8 aged 6 to <12 years and 12 aged 12 to <18 years old) and 28 paediatric subjects in Study 170904 (1 aged <6 years, 14 aged 6 to <12 years and 13 aged 12 to < 18 years old). CUVITRU has not been evaluated in patients aged < 2 years.

Use in the Elderly

CUVITRU was evaluated in pivotal studies which included a total of 12 subjects of the age 65 years and older. No differences in safety or efficacy were observed for this group.

Monitor patients who are at an increased risk for developing renal failure or thrombotic events. Do not exceed the recommended dose and infuse at the minimum infusion rate practicable.

Effects on laboratory tests

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

Administration of CUVITRU can lead to false positive readings in assays that depend on detection of beta-D-glucans for diagnosis of fungal infections; this may persist during the weeks following infusion of the product.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of CUVITRU 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.

Paediatric population

The listed interactions apply both to adults and children.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

CUVITRU contains a human plasma derived native protein, which is not anticipated to have an adverse effect on fertility.

Use in pregnancy

The safety of CUVITRU product for use in human pregnancy has not been established in controlled clinical trials and therefore it should only be given with caution to pregnant women. Immunoglobulin products have been shown to cross the placenta, increasingly during the third trimester.

Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Physicians should balance the potential risks and only prescribe CUVITRU, if clearly needed.

Use in lactation

During breast-feeding immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

Physicians should balance the potential risks and only prescribe CUVITRU, if clearly needed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The ability to drive and operate machines may be impaired by some adverse reactions associated with CUVITRU. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

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

Local reactions at infusion site: swelling, soreness, redness, induration, local heat, local pain, itching, bruising and rash, may frequently occur.

For safety information with respect to transmissible agents, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Tabulated list of adverse reactions

The safety of CUVITRU administered subcutaneously was evaluated in two prospective, open-label, non-controlled, multi-centre studies in 122 subjects with PID.

CUVITRU treatment was well tolerated with local adverse reactions (ARs) mostly mild in intensity. One subject discontinued treatment due to a local AR. 112 out of 122 subjects treated with CUVITRU completed a study.

There were no deaths or serious adverse events related to treatment with CUVITRU in the clinical studies.

Table 4 presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Table 4: Frequency of Adverse Reactions (ADRs) in clinical studies with CUVITRU			
MedDRA System Organ Class (SOC)	Adverse reaction	Frequency per subject^a	Frequency per infusion^b
NERVOUS SYSTEM DISORDERS	Headache	Very Common	Common
	Dizziness	Common	Uncommon
	Burning sensation	Uncommon	Rare
	Migraine	Common	Rare
	Somnolence	Common	Rare
VASCULAR DISORDERS	Hypotension	Common	Rare
GASTROINTESTINAL DISORDERS	Diarrhoea	Very Common	Common
	Nausea	Very Common	Uncommon
	Abdominal pain lower	Uncommon	Rare
	Abdominal pain	Common	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritus	Common	Rare
	Urticaria	Common	Rare
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Myalgia	Common	Uncommon
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Local reaction:	Very Common	Common
	• Infusion site erythema (including Injection site erythema)	Very Common	Common
	• Injection site pain (including Infusion site discomfort and Infusion site pain)	Very Common	Common
	• Infusion site swelling	Common	Uncommon
	• Injection site pruritus (including Infusion site pruritus)	Common	Uncommon
	• Infusion site urticaria	Common	Uncommon
	• Infusion site bruising	Common	Rare
	• Infusion site oedema	Uncommon	Rare
	Fatigue	Very Common	Uncommon

	Pain	Common	Rare
INVESTIGATIONS	Anti-GAD antibody positive	Uncommon	Rare
	Coombs direct test positive	Uncommon	Rare

Legend: Frequency categorisation is based upon the following scale: Very Common ($\geq 1/10$); Common ($\geq 1/100 - < 1/10$), Uncommon ($\geq 1/1,000 - < 1/100$), Rare ($\geq 1/10,000 - < 1/1,000$), Very Rare ($< 1/10,000$).

^a The frequency per subject is calculated using the number of subjects associated with all AEs irrespective of relatedness to CUVITRU.

^b The frequency per infusion is calculated using the number of infusions associated with all AEs irrespective of relatedness to CUVITRU.

Table 5: Most Frequent Local Adverse Reactions ^a Reported in 5% of Subjects in Clinical Studies with CUVITRU								
Adverse Reaction	Pivotal Phase III North America (170904)				Pivotal Phase III Europe (170903)			
	Total Number of Adverse Reactions		By Subject n (%) ^b N=74	By Infusion n (rate) ^c N=4327	Total Number of Adverse Reactions		By Subject n (%) ^b N=48	By Infusion n (rate) ^c N=2349
	Mild	Moderate			Mild	Moderate		
Infusion site pain (including Infusion site discomfort and Injection site pain)	33	3	15 (20.3%)	36 (0.008)	34	0	10 (20.8%)	34 (0.014)
Infusion site erythema (including Injection site erythema)	22	1	8 (10.8%)	23 (0.005)	54	0	10 (20.8%)	54 (0.023)
Infusion site pruritus (including Injection site pruritus)	7	1	4 (5.4%)	8 (0.002)	30	0	7 (14.6%)	30 (0.013)
Infusion site swelling	1	0	1 (1.4%)	1 (<0.001)	46	0	4 (8.3%)	46 (0.020)

^a Causally Related and/or Temporally Associated (Within 72 Hour) AEs (Excluding Infections).

^b Total number of affected subjects divided by the total number of subjects under treatment.

^c Total number of AEs divided by the total number of infusions under treatment.

Paediatric population

The safety profile in the paediatric population was similar to that in adult subjects.

Post-Marketing Adverse Reactions

Nervous System Disorders: Meningitis aseptic.

Class Reactions

The following additional adverse reactions have been identified and reported during the post-marketing use of another subcutaneous immune globulin product: anaphylactic reaction, paraesthesia, tremor, tachycardia, dyspnoea, laryngospasm, chest discomfort, injection site reactions (such as induration, warmth).

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:

<http://www.tga.gov.au/reporting-problems>

4.9 OVERDOSE

Consequences of an overdose are not known.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

IgG antibodies are protein molecules that are capable of specific interaction with molecules that are part of the membranes of infectious agents, foreign or abnormal cells, or toxic materials (antigens). Antibodies are produced by B lymphocytes, often with the help of T lymphocytes, macrophages, or dendritic cells. Following an initial interaction, some of the B-cells differentiate to memory cells, which upon encountering with the same infectious agent later in life, are capable of rapidly reproducing and producing increased quantities of the IgG antibodies specific to the same infectious agent.

The IgG molecules have two distinct and separable functions. One function is to bind specifically to the epitope in the antigen through the Fab end of the molecule, which is formed by the combination of the heavy and light chains. The other end of the IgG molecule, the Fc portion, can activate complement, bind to receptors on phagocytic cells to promote engulfment of the antigen/antibody complexes, and binding to the neonatal receptor which modulates the catabolism of IgG. In addition, binding of the Fc portion of the IgG molecule to regulatory receptors on B cells, T cells, and macrophages can modulate the activity of those cells, which may be useful in the control of autoimmune disease.

Thus, the mode of action of subcutaneous immunoglobulin (IGSC) mimics the action of the normal plasma immunoglobulin in a healthy adult individual having a broad spectrum of antibodies against infectious agents. As the active ingredient in CUVITRU, IgG 20% w/v, is a plasma-derived immunoglobulin isolated from pooled plasma of healthy donors, this product can be classified as a replacement therapy in patients who are unable to produce sufficient amount of IgG antibodies. Adequate doses of this medicinal product may restore the abnormally low IgG levels of immune deficient patients to a normal range.

The active ingredient in CUVITRU is a human plasma-derived Immunoglobulin, concentration of 200 mg/mL (20% w/v), produced from large pools of human plasma by a modified Cohn-Oncley cold ethanol fractionation, yielding an intermediate immunoglobulin G (IgG), referred to as Precipitate G. During the cold ethanol plasma fractionation manufacturing process, the level of viral burden in a plasma pool has been largely reduced to a certain extent, as demonstrated by viral spiking experiment. Precipitate G is further purified by means of a weak cation-exchange and anion-exchange chromatography.

To reduce further a possible viral transmission to a minimal level, a triple step of viral inactivation (TVR inactivation), [solvent detergent (S/D), nano-filtration (35nm), and incubation at a low pH and elevated temperature (30°C to 32°C, pasteurisation for 21 to 23 days) has been incorporated into the downstream purification. Thus, the active ingredient formulated in CUVITRU has been subjected to a rigorous elimination for both lipid and non-lipid enveloped viruses.

Pharmacodynamic properties

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

Mechanism of action

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

Paediatric population

There are no theoretical or observed differences in the action of immunoglobulins in children compared to adults.

Clinical trials

The efficacy of CUVITRU was investigated in two prospective uncontrolled multi-centre phase 2/3 studies in adult and paediatric subjects with PID. The pivotal study 170903 conducted in Europe was designed to examine CUVITRU efficacy when administered at the same weekly-equivalent dose as with the previously used IG product. In the supportive study conducted in North America, Study 170904, subjects received CUVITRU at a dose adjusted to achieve the bioavailability of IGIV, 10%.

Study 170903

A prospective, open-label, non-controlled, multi-centre study was conducted to evaluate the efficacy, safety, tolerability, and PK parameters of CUVITRU in subjects with PID aged 2 years and older at time of screening. The study consisted of 2 parts. In study part 1, subjects were treated with IGSC 16% for 12 weeks or with IGIV 10% for 13 weeks. Administration, dosage frequency, and dose were dependent on the pre-study treatment. However, the dose range had to be within 0.3-1.0 g/kg BW per 4 weeks.

During study part 2, subjects received weekly CUVITRU infusions for 51 weeks at the dose used during study part 1, adjusted to a weekly equivalent dose if necessary. PK assessments were performed before the end of study part 1 and after approximately 5 months in study part 2 in subjects aged ≥ 12 years. For younger subjects (aged 2 to < 12 years) only IgG trough levels were assessed to avoid multiple blood draws. The geometric mean of CUVITRU trough levels was 827 mg/dL [95% CI: 748-913]. Human and population PK parameters for CUVITRU were calculated from levels of Immunoglobulin G (IgG) measured during each part of the study.

CUVITRU was administered at the same weekly-equivalent dose as with the previously used IG product (mean (\pm SD) dose: 0.125 ± 0.042 g/kg/week). CUVITRU administered at this dose was shown to be effective in PID subjects aged ≥ 2 years.

One acute serious bacterial infection (ASBI) of pneumonia was reported in a 12-year old subject with a more severe form of hypogammaglobulinaemia (XLA) while receiving CUVITRU. The point estimate of the annualised rate of ASBIs was 0.022 (upper limit of 99% CI: 0.049) during CUVITRU treatment. This annual rate of ASBIs was lower than 1.0 ASBIs /year, ($p < 0.0001$), the threshold specified as providing substantial evidence of efficacy.

The summary of infections and associated events for subjects in study 170903 during subcutaneous treatment with CUVITRU are summarised in Table 6.

Table 6: Summary of Infections and Associated Events	
Parameters	Results
Number of subjects	48
Annual rate ^a of any infections (rate per subject-year)	4.38 (95% CI: 3.38 to 5.56)
Days on antibiotics (rate per subject-year)	18.11 (95% CI: 13.01 to 24.41)
Days off work/school/unable to perform normal daily activities due to illness or infection (rate per subject-year)	15.55 (95% CI: 10.06 to 22.75)
Number of hospitalisations due to infections (rate per subject-year)	0.04 (95% CI: 0.02 to 0.08)
Number of days in hospital due to infections (rate per subject-year)	0.11 (95% CI: 0.05 to 0.21)
^a Rate = number of infections divided by the total number of subject-years under treatment.	

Study 170904

A prospective, open-label, non-controlled, multi-centre clinical study was conducted to determine the efficacy, tolerability and PK of CUVITRU in 77 adult and paediatric subjects with PID. Efficacy was determined in 53 adults aged 16 years or older, 6 adolescents aged 12 to <16 years, and 15 children aged 2 to <12 years. CUVITRU was administered to 74 subjects with a mean dose of 222 mg/kg/week \pm 71 mg/kg/week for a median treatment duration of 380.5 days (range: 30 - 629 days) and a mean (\pm SD) of 413.1 \pm 116.5 days. The median duration of treatment did not vary significantly between age groups. The total exposure to CUVITRU was 83.70 subject-years and 4327 infusions.

Initially subjects received immune globulin 10% intravenously (IGIV) every 3 or 4 weeks at a monthly dose equivalent to that received prior to the study for 13 weeks. The objective of part 1 of the study was to determine AUCIV of total IgG following IGIV administration. In part 2 of the study, subjects received CUVITRU subcutaneously at an adjusted dose of 145% of the IGIV dose. The objective of part 2 was to determine AUCSC of total IgG following weekly CUVITRU administration and to calculate an adjusted dose to be used in part 3. The dose adjustment factor was assessed to be 145% of the IGIV 10% dose by comparing the AUCSC with the AUCIV, 0- τ (standardised to 1 week) of part 1 for the first 15 subjects that completed part 2. Subjects who completed part 1 after this assessment was available, went directly into part 3. In part 3 of the study, subjects were treated weekly for 12 weeks at the adjusted dose. The ratio of serum IgG trough levels for part 1 and 3 were compared to the expected trough level determined in part 2 to establish the individually adapted dose for part 4 for each subject. In part 4 of the study, subjects were infused weekly with CUVITRU at the individually adapted dose for 40 weeks. During part 4, an additional pharmacokinetic assessment was performed. Follow-up with the subject either by diary system or by investigator occurred 3-5 days after every infusion in each study part to document adverse events. Adverse events were assessed using the subject's eDiary – all subjects received eDiary tablet to continuously record home treatments, adverse events, and additional information as they occurred.

One acute serious bacterial infection (ASBI) of pneumonia was reported in a 78-year old subject who had specific antibody deficiency and allergic bronchopulmonary aspergillosis while receiving CUVITRU. The point estimate of the annualised rate of ASBIs was 0.012 (upper limit of 99% CI: 0.024) during CUVITRU treatment. This annual rate of ASBIs was lower than 1.0 ASBIs /year ($p < 0.0001$), the threshold specified as providing substantial evidence of efficacy.

The summary of infections and associated events for subjects during subcutaneous treatment with CUVITRU is summarised in Table 7.

Parameters	Results
Number of subjects	74
Total number of subject-years on treatment	83.70
Annual rate of any infections (per subject-year)	2.41 (95% CI: 1.89 to 3.03)
Days on antibiotics (rate per subject-year)	57.59 (95% CI: 40.71 to 78.59)
Days off work/school/unable to perform normal daily activities due to illness or infection (rate per subject-year)	1.16 (95% CI: 0.70 to 1.79)
Number of hospitalisations due to infections (rate per subject-year)	0.012 (95% CI: 0.006 to 0.022)
Number of days in hospital due to infections (rate per subject-year)	0.06 (95% CI: 0.03 to 0.11)

In the clinical study 170904, across all age groups, the median maximum infusion rate was 60 mL/h/site. This infusion rate was achieved in 57.3% (2480/4327) of completed CUVITRU infusions. CUVITRU infusion rate of 60 mL/h/site was achieved in 28.6% (6/21) of paediatric subjects (2 years to <16 years of age), in 88.7% (47/53) of adults (16 years of age and older) and in 71.6% (53/74) of all subject. For more than half of CUVITRU infusions (2393/4327), a volume of 30 to 39 mL (1096/4327 infusions) or 40 to 49 mL (1297/4327 infusions) was infused per site. For 320/4327 of CUVITRU infusions, a volume of 60 mL/site or more was infused. Infusion parameters resulted in a median of 2 infusion sites (range: 1 to 4) per CUVITRU administration. During CUVITRU treatment, 84.9% (3662/4314) of infusions were administered using 1 infusion site (18.5%; 798/4314) or 2 infusion sites (66.4%; 2864/4314) across all ages. The median duration of infusions was less than 1 hour (0.95 h; range: 0.2-6.4 hours). During all treatment periods, 99.8% of infusions were completed without a reduction, interruption, or discontinuation for tolerability reasons. Infusion characteristics did not significantly differ between adult and paediatric subjects.

Throughout the study, health-related quality of life was assessed using the Paediatric Quality of Life Inventory™ (PEDS-QL) questionnaire (paediatric subjects) or the self-administered SF-36 survey (adult subjects). Quality of life was analysed separately for the age groups 2 to 4 and 5 to 7 years (PEDS-QL, observer: parent), 8 to 12 and 13 years (PEDS-QL, observer: subject) and 14 years and older (SF-36, observer: subject). Treatment satisfaction was measured using the Life Quality Index questionnaire (LQI) and the Treatment Satisfaction Questionnaire for Medication (TSQM-9). The LQI was assessed for the age group 2 years to 12 years (observer: parent) and the age group 13 years and older (observer: subject) in three domains: Treatment Interference, Therapy-related Problems and Therapy Settings. The TSQM-9 was assessed in subjects aged 2 to 12 years (observer: parent) and 13 years and older (observer: subject) in 3 domains: Effectiveness, Convenience and Global Satisfaction. Differences between scores during the intravenous study part and subcutaneous 20% study part were calculated for selected domains of the instruments, see Table 8.

Scale	Difference	p-value
SF-36 Physical Component Score	0.89	0.067
SF-36 Mental Component Score	1.31	0.976
Total Score (PedsQL)	1.09	0.449
Treatment Interference (LQI)	1.50	0.008
Convenience (TSQM-9)	11.11	<0.001

5.2 PHARMACOKINETIC PROPERTIES

Following subcutaneous administration of CUVITRU, peak serum levels are achieved after approximately 3 days.

In a clinical trial 170903 with CUVITRU (n = 48), the subjects achieved sustained IgG trough levels (median 8.26 g/L) over a period of 52 weeks when receiving median weekly doses of 0.125 g/kg.

Data from the clinical trial 170903 of CUVITRU show that serum IgG trough levels can be maintained by dosing regimens of 0.3 to 1.0 g/kg body weight per 4 weeks.

The pharmacokinetics of CUVITRU were evaluated in the phase 3 efficacy and safety study in 31 patients with primary immunodeficiency (PID) aged 12 years and older. The pharmacokinetic results are presented in table 9 below.

Parameter	CUVITRU Median (95% CI), n=31
AUC [g*days/L]	62.52 (57.16 to 68.86)
AUC / (Dose/Weight) [(g*days/L)/(g/kg)]	589.49 (448.40 to 638.81)
Apparent clearance [mL/kg/day]	1.70 (1.57 to 2.23)
C _{max} [g/L]	9.80 (9.31 to 10.62)
C _{min} [g/L]	8.04 (7.30 to 8.99)
T _{max} [hours]	73.92 (69.82 to 120.08)
IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.	

Once Weekly, Biweekly or more Frequent Dosing (2-7 times per week)

Pharmacokinetic (PK) characterisation of biweekly or more frequent dosing of CUVITRU was undertaken using population PK-based modelling and simulation. Serum IgG concentration data consisted of 724 samples from 32 unique paediatric and adult subjects with PID. Compared with weekly administration, PK modelling and simulation predicted that administration of CUVITRU on a biweekly basis at double the weekly dose results in overlapping IgG exposure across an entire 2-week interval. In addition, PK modelling and simulation predicted that for the same total weekly dose, CUVITRU infusions given 2-7 times per week (frequent dosing) results also in overlapping IgG exposure across an entire 2-week interval.

Paediatric population

There are no theoretical or observed differences in the pharmacokinetics of immunoglobulins in children compared to adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

CUVITRU contains a human plasma derived native protein, which is not anticipated to possess genotoxic potential.

Carcinogenicity

CUVITRU contains a human plasma derived native protein, which is not anticipated to possess carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

CUVITRU contains the excipients listed in Table 10.

Table 10: Composition of the CUVITRU 20 % (w/v) [Immunoglobulin G (IgG) 200 mg/mL]					
Name of the components	Nominal values per vial expressed as protein with at least 98% IgG content				
	5 mL	10 mL	20 mL	40 mL	50 mL
Stabilising agent: Glycine	0.095 g	0.19 g	0.38 g	0.76 g	0.95 g
pH*	4.6 to 5.1	4.6 to 5.1	4.6 to 5.1	4.6 to 5.1	4.6 to 5.1
Water for Inject. qs	5 mL	10 mL	20 mL	40 mL	50 mL

Note*: pH is measured after the solution is diluted to 1% protein with saline. The pH range of 4.6 to 5.1 corresponds to a range of 4.4 to 4.9 when the solution is measured undiluted.

6.2 INCOMPATIBILITIES

Administration of CUVITRU with other medicinal products is not recommended.

6.3 SHELF LIFE

In Australia, information on the shelf-life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Keep the vial in the outer carton in order to protect from light.

Do not use after the expiry date printed on the carton and the label.

6.5 NATURE AND CONTENTS OF CONTAINER

CUVITRU is presented as a 20% (20 g/100 mL) solution for subcutaneous administration. The solution is dispensed into a glass vial and closed with a rubber stopper and aluminium crimp cap, with a plastic flip off disc providing a tamper evident seal.

Pack size

The product is supplied in the following pack sizes:

- 1 g in a 5 mL solution
- 2 g in a 10 mL solution
- 4 g in a 20 mL solution
- 8 g in a 40 mL solution
- 10 g in a 50 mL solution.

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

CUVITRU has a purity $\geq 98\%$ IgG and a pH of 4.6 to 5.1. The osmolality is 280-292 milliosmoles per kilogram. CUVITRU contains 200 mg/mL protein. The average immunoglobulin A (IgA) concentration is 0.08 mg/mL. CUVITRU contains a broad spectrum of IgG antibodies against bacterial and viral agents, glycine (which acts as a stabilising and buffering agent), and does not contain preservatives.

Chemical name

Normal Immunoglobulin (human).

Chemical structure

The active ingredient in CUVITRU is a human polyvalent IgG. Immunoglobulins are made up of four polypeptide chains, comprising two identical light chains of a molecular weight of approximately 25 kD and two identical heavy chain of a molecular weight of approximately 50 kD. The four chains form a three-dimensional Y-shaped structure as shown by X-ray crystallography. Carbohydrate groups are attached covalently at a distinct position of the heavy chains. The overall molecular weight of IgG is approximately 150 kD.

Immunoglobulin G antibodies are the most common immunoglobulin class, with a level of 9 - 12 grams per litre of plasma, accounting for about 75 % of the total immunoglobulins in plasma of healthy individuals. Immunoglobulin G is further divided into subclasses with different heavy chain isotypes: IgG₁, IgG₂, IgG₃, and IgG₄.

CAS number

Normal Immunoglobulin 20% (Human): not available.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 39
225 George Street
Sydney NSW 2000
Australia
Telephone: 1800 012 612
www.takeda.com/en-au

9 DATE OF FIRST APPROVAL

5 October 2017

10 DATE OF REVISION

03 November 2022

Summary table of changes

Section Changed	Summary of new information
2, 6.1, 6.5	Addition of new pack size 10 g/50mL
ALL	Typographical updates

CUVITRU[®] is a trademark of Baxalta Incorporated.



TAKEDA[®] and the TAKEDA Logo[®] are registered trademarks of Takeda Pharmaceutical Company Limited.


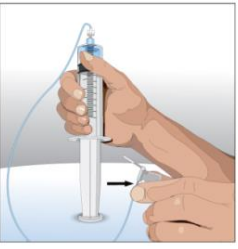
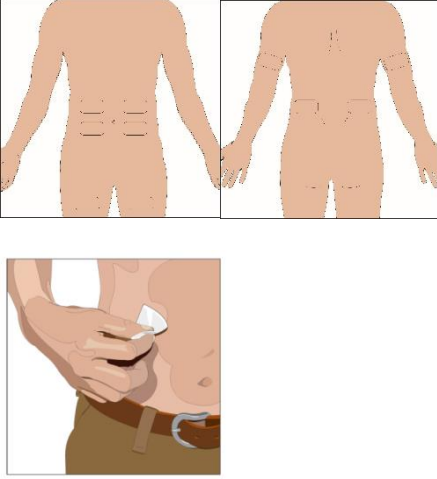
Detailed Instructions for Administration for Patients

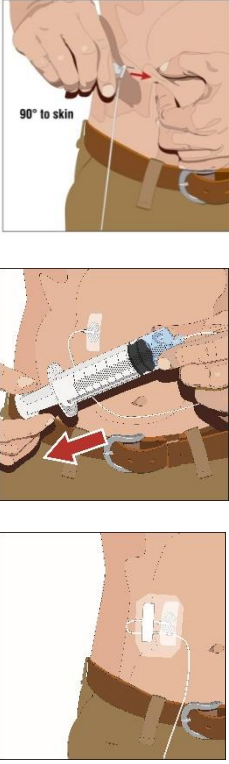
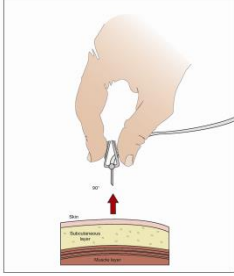
Do not use CUVITRU at home until you get instructions and training from your healthcare professional.

Prepare CUVITRU vial(s):

- Remove CUVITRU from the box. Allow vials to reach room temperature. This may take up to 90 minutes.
- Do not apply heat or place in microwave.
- Do not shake the vial(s).

<p>1. Check the vial(s):</p> <ul style="list-style-type: none"> • Do not use beyond expiration date. • Do not use if the protective cap is missing or broken. • Look at the colour: it should be clear and colourless to pale yellow or light brown. • Do not use if the solution is cloudy or has particles. 	
<p>2. Gather all supplies:</p> <ul style="list-style-type: none"> • Gather all supplies: • Items include: vial(s) of CUVITRU, infusion supplies: subcutaneous needle set, transfer device(s), syringe(s), sterile tip caps, sterile clear bandage, tape, gauze, sharps container, infusion pump, infusion log. • Clean work area. • Program the infusion pump according to prescribed infusion rates and manufacturer’s instructions. • Wash hands thoroughly and allow to dry. • Open supplies as shown by your healthcare professional. 	 

<p>3. Prepare the syringe(s):</p> <ul style="list-style-type: none"> • Remove the cap from the vial. • Wipe each stopper with a sterile alcohol wipe and allow to dry. • Attach a sterile syringe to a vented spike. • Insert the vented spike into the centre of the IG vial. • Turn the vial upside down and pull back on the plunger to pull the IG into the syringe(s). • Repeat these steps, if using multiple vials to achieve the desired dose. • Start the infusion promptly after drawing CUVITRU into the syringe(s). It is suggested to complete the administration within 2 hours. <p>If using a sterile needle: Attach a sterile syringe to the sterile needle and pull back the plunger of syringe to fill with air which should equal the amount of the solution you will be taking from the vial. Insert the needle into the centre of the stopper, and inject air in. Pull back on the plunger to withdraw the desired volume.</p>	
<p>4. Prepare the infusion pump and tubing:</p> <ul style="list-style-type: none"> • Use manufacturer directions for filling the tubing and using the pump. • Attach the syringe filled with CUVITRU to the needle set. • Point the syringe tip up and gently push the plunger of the syringe to remove the air and fill the needle set up to the needle hub. 	
<p>5. Prepare the infusion site(s):</p> <ul style="list-style-type: none"> • Select the number of infusion sites based on the volume of the total dose. • Choose infusion site(s): upper arms, abdomen, thighs, or lower back. • Avoid: bony areas, visible blood vessels, scars and any areas of inflammation (irritation) or infection. • Infuse CUVITRU from 1 to 4 infusion sites at the same time. Select sites at least 4 inches apart. • Rotate sites between future infusions. • Wipe the infusion site(s) with a sterile alcohol wipe beginning at the centre of each infusion site and moving outward in circular motion. Allow the infusion site(s) to dry (at least 30 seconds). 	

<p>6. Insert and secure the subcutaneous needle set:</p> <ul style="list-style-type: none"> • Remove the needle cover. Firmly grasp and pinch at least 1 inch of skin between two fingers. • Insert needle with a rapid motion straight into the skin at a 90 degree angle. Tape needle in place with sterile tape (included on transparent dressing). • If more than one site is used, repeat the steps. • Check for proper needle placement by pulling back on the syringe plunger to check for blood return in the tubing of the needle set. • If blood is seen in the tubing, remove and discard the subcutaneous needle and repeat steps 4, 5 and 6 with a new subcutaneous needle and infusion site. • Secure the needle set in place by applying a sterile protective dressing over the site(s). 	
<p>7. Start the infusion:</p> <ul style="list-style-type: none"> • Follow the manufacturer’s instructions to turn pump on and start the infusion. • Check infusion site(s) occasionally throughout the infusion. 	
<p>8. Remove subcutaneous needle(s) from the infusion site(s):</p> <ul style="list-style-type: none"> • Remove the needle set by loosening the tape on all edges. • Pull the needle wings straight up and out. • Gently press a small piece of gauze over the needle site and cover with a dressing. • Throw away the needle(s) into the sharps container. 	
<p>9. Record the infusion:</p> <ul style="list-style-type: none"> • Remove the peel-off label from the vial(s), which has the product lot number and expiration date, and place the label in your treatment record/infusion log. • Write down the date, time, dose, site(s) of infusion (to assist in rotating sites) and any reactions after each infusion. • Throw away the disposable supplies, vials, and unused product as recommended by your healthcare professional. 	