PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

WARNING: THROMBOEMBOLISM

See 4.4 Special warnings and precautions for use

• Thromboembolism may occur with immune globulin products, including CUVITRU. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors.

• For patients at risk of thromboembolism, administer CUVITRU at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thromboembolism and assess blood viscosity in patients at risk of hyperviscosity.

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CUVITRU 1 (solution for subcutaneous injection)

CUVITRU 2 (solution for subcutaneous injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 200 mg Human normal immunoglobulin (SCIg) (Purity of at least 98 % IgG)

Each vial of 5 ml contains: 1 g of human normal immunoglobulin

Each vial of 10 ml contains: 2 g of human normal immunoglobulin

Distribution of IgG subclasses (approx. values):

IgG1 ≥56,9 %

IgG2 ≥26,6 %

IgG3 ≥3,4 %

IgG4 ≥1,7 %

The maximum IgA content is 280 micrograms/ml. Produced from the plasma of human donors.

For the full list of excipients, see 6.1. List of excipients

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear and colourless or pale yellow or light-brown. pH of 4,6 to 5,1 (measured by dilution at 1 % in saline).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Indications for subcutaneous administration (SCIg)

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

- Primary immunodeficiency syndromes with impaired antibody production (see 4.4 Special warnings and precautions for use).
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4g/l.

(*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines).

4.2 Posology and method of administration

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

Posology

The dose and dose regimen are dependent on the indication.

Replacement therapy

The product should be administered via the subcutaneous route.

In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. Dose based on body weight may require adjustment in underweight or overweight patients. The following dose regimens are given as a guideline.

Solution for subcutaneous injection

Replacement therapy in primary immunodeficiency syndromes (as defined in section 4.1)

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l and aim to be within the reference interval of serum IgG for age. A loading dose of at least 0,2 to 0,5 g/kg (1 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 (see section 5.2 Pharmacokinetic properties for details). Each single dose may need to be injected at different anatomic sites.

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

Replacement therapy in secondary immunodeficiencies (as defined in section 4.1)

The recommended dose administered at repeated intervals is to reach a cumulative monthly dose to the order of 0,2-0,4 g/kg. Each single dose may need to be injected at different anatomic sites.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection-free.

Paediatric population

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

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

Method of administration

For subcutaneous use 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.

The infusion must be started immediately upon transfer of Cuvitru into the syringe. The administration is foreseen to take up to two hours. Should an administration shorter than two hours not be possible due to required dose or administration rate of Cuvitru, the required dose is to be portioned and administered at different infusion sites. If Cuvitru remains in siliconized syringes for more than two hours, visible particles may form. See 4.4 Special warnings and precautions for use for further details.

Cuvitru must not be diluted.

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.

<u>Infusion rate</u>

Cuvitru can be infused using:

- an infusion device, or
- by manual administration using a syringe.

The recommended initial infusion rate depends on the individual patient's needs. An increase in the infusion rate of successive infusions may be considered at the discretion of the patient and based on the healthcare professionals' judgement.

Device-assisted infusion:

It is recommended to use an initial administration speed of 10 ml/h/infusion site. If well tolerated (see section 4.4 Special warnings and precautions for use), 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. For further infusions, the infusion rate may be increased as tolerated.

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.

Manual administration infusion:

Cuvitru may be administered using a syringe at a single infusion site. If administration at additional sites is required, a new sterile injection needle should be used. The proposed maximum infusion rate is approximately 1-2 ml per minute. The rate of administration should be adjusted for each patient's local tolerance which may depend on the site of each subcutaneous infusion and the amount of the individual patient's subcutaneous tissue at that site. The amount of product infused into a particular site varies. In infants and children, infusion site may be changed every 5-15 ml. In adults doses over 30 ml may be divided according to patient preference.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in 6.1 List of excipients (see section 4.4 Special warnings and precautions for use).

Severe IgA deficiency and a history of hypersensitivity to human immunoglobulin treatment.

Cuvitru must not be given intravascularly or intramuscularly.

4.4. Special warnings and precautions for use

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

The recommended infusion rate and administration instructions given in section 4.2 Posology and method of administration must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. If the product remains in a siliconized syringe for more than two hours, visible particles may form.

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 Posology and method of 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.

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 Cuvitru only under close medical supervision. Cuvitru contains trace amounts of IgA (not more than 280 micrograms/ml). 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 immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity).

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

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 paraproteinemia.

Aseptic Meningitis Syndrome

Aseptic meningitis syndrome (AMS) has been reported to occur in association with immune globulin treatment, including IGSC 20 % (see section 4.8 Undesirable Effects – Postmarketing). 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 mm3, 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, direct 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.

Interference with serological testing

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

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.

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 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 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.

Sodium Content

Cuvitru is essentially sodium free.

Paediatric population

The listed warnings and precautions apply both to adults and children.

4.5. Interaction with other medicines and other forms of interaction

Live attenuated virus vaccines

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

Health care professionals must balance the potential risk and only prescribe Cuvitru if clearly needed

Pregnancy

The safety of this medicinal 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 and breastfeeding mothers. IG products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Breast-feeding

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

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of the safety profile

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

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

Local reactions at infusion 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 primary immune deficiency (PID).

The majority (98,8 %) of local adverse reactions (ARs) were mild in intensity. One subject discontinued treatment due to a local AR (pain). 112 out of 122 subjects treated with Cuvitru completed a study.

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

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table1: Frequency of Adverse Reactions (ADRs) in clinical studies with Cuvitru

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

NERVOUS SYSTEM DISORDERS… *continued*	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
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS… *continued*	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

[a] The frequency per subject is calculated using the number of subjects associated with all Adverse Effects (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.

The following additional ADRs have been identified and reported during the post-marketing use of another subcutaneous immune globulin product: paraesthesia, tremor, tachycardia, dyspnoea, laryngospasm and chest discomfort.

Table 2: Post-marketing Adverse Reactions (ARs)

Post-Marketing Adverse Reactions (ARs)		
MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency**
Infections and infestations	Meningitis aseptic	Not known

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Additionally, suspected adverse reactions can be reported to AE.SouthafricaSSA@takeda.com or on the 24 hours contact number: 082 525 3040

4.9. Overdose

Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological Class: A. 30.1 Antibodies

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

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.

5.2. Pharmacokinetic properties

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

In a clinical trial 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 of Cuvitru show that serum IgG trough levels can be maintained by dosing regimens of 0,3 to 1,0 g/kg body weight/4 weeks.

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

Pharmacokinetic Parameters of Cuvitru

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) characterization 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

Immune globulins are normal constituents of the human body.

Non-clinical data for immune globulins reveal no special risk for humans based on conventional studies of safety pharmacology and toxicity. Cuvitru was well tolerated locally when infused subcutaneously into animals. Studies of repeated dose toxicity and toxicity to reproduction in animals are impracticable due to induction of and interference by developing antibodies to heterologous proteins.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of Cuvitru or its effect on fertility. An in vitro mutagenicity test was performed for IGI, 10 % and there was no evidence of mutagenicity observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycine

Water for injections

6.2. Incompatibilities

Administration of Cuvitru with other medicinal products is not recommended.

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

Cuvitru must not be diluted.

6.3. Shelf life

2 years.

Once opened, use immediately.

6.4. Special precautions for storage

Store at or below 25 °C

Do not freeze the product.

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

6.5. Nature and contents of container

5 or 10 ml of solution in a vial (Type I glass) with a rubber stopper (bromobutyl) and an aluminium band crimp cap with a polypropylene flip-off disk.

Pack sizes:

1 vial containing 5 ml solution for injection (1 g/5 ml) or:

10 or 20 vials containing 5 ml solution for injection (10 x 1 g/5 ml or 20 x 1 g/5 ml)

1 vial containing 10 ml solution for injection (2 g /10 ml) or:

10 or 30 vials containing 10 ml solution for injection (10 x 2 g/10 ml or 30 x 2 g/10 ml)

Not all pack sizes may be marketed

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

In case the product is stored in a refrigerator, the unopened vials must be placed at room temperature for a minimum of 90 minutes prior to use and kept at room temperature during administration. Do not use heating devices including microwaves.

Solutions that are cloudy or have deposits should not be used.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Takeda (Pty) Ltd

Building A, Monte Circle, 64 Montecasino Boulevard

Fourways 2191, Gauteng, South Africa

Tel: 011 514 3000

8. REGISTRATION NUMBER:

CUVITRU 1: 54/30.1/0790

CUVITRU 2: 54/30.1/0791

9. DATE OF AUTHORISATION / RENEWAL OF THE AUTHORISATION

26 JANUARY 2026

10. DATE OF REVISION OF THE TEXT

20 MAY 2026