

Attachment 1: Product information for AusPAR - Xembify – Human Normal Immunoglobulin - Grifols Australia Pty Ltd PM-2020-06238-1-2 Final 23 January 2023. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-one>>

Xembify® Product Information

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

AUSTRALIAN PRODUCT INFORMATION

XEMBIFY®

NORMAL IMMUNOGLOBULIN (HUMAN) 20% SOLUTION FOR SUBCUTANEOUS INJECTION

1. NAME OF THE MEDICINE

Normal Immunoglobulin (Human) 20% solution for subcutaneous injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Normal immunoglobulin

One ml contains:

Normal immunoglobulin 200 mg
(purity of at least 98% human immunoglobulin G (IgG))

Produced from the plasma of human donors.

For the full list of excipients, see [section 6.1](#).

3. PHARMACEUTICAL FORM

Dosage form: Injection

Solution for injection, for subcutaneous use.

The solution is clear to slightly opalescent, and colourless or pale yellow or light brown.

Xembify® has an approximate osmolality range of 280 to 404 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications for subcutaneous administration (SCIg)

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

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

4.2 Dose and method of administration

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

Dosage

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. 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 (approximately once per week) to reach a cumulative monthly dose of the order of 0.4 to 0.8 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.

Dosing for Patients Switching from Other Subcutaneous or Intravenous Immunoglobulin Treatments

	Xembify® Dosing Frequency		
	Weekly	Biweekly (every 2 weeks)	Frequent (2 to 7 times per week)
For patients switching from Normal Immunoglobulin (Human) Subcutaneous treatment (SCIg)	The weekly dose of Xembify® (in grams) is recommended to be the same as the weekly dose of prior SCIg treatment (in grams) ^a	Multiply the calculated weekly dose by 2	Divide the calculated weekly dose by the desired number of times per week
For patients switching from Normal Immunoglobulin (Human) Intravenous treatment (IVIg) ^b	To calculate the initial weekly dose, divide the previous IVIg dose in grams by the number of weeks between intravenous doses ^{a,b}		

^a To convert the dose (in grams) to millilitres (ml), multiply the calculated dose (in grams) by 5.

^b Begin treatment with Xembify® one week after the patient's last IVIg.

If a dose is missed or therapy is interrupted, administration of Xembify® should re-commence as soon as feasible with appropriate monitoring of IgG trough level if clinically indicated.

Dose guidance

Refer to the dose adjustment table below for suggested dose changes (in ml) to achieve a desired IgG trough level change (increase or decrease), once Xembify® treatment has been initiated.

For dose adjustments, calculate the difference (in mg/dl) of the patient's serum IgG trough level from the target IgG trough level, then find this difference below. Locate the corresponding amount (in ml) by which to increase or decrease the weekly dose based on the patient's body weight. For example, if a patient with a body weight of 70 kg has an actual IgG trough level of 900 mg/dl and the target level is 1,000 mg/dl, this results in a difference of 100 mg/dl. Therefore, increase the weekly dose of subcutaneous dose by 5 ml.

The patient's clinical response should be the primary consideration in dose adjustment. If a patient on Xembify® does not maintain an adequate clinical response or a serum IgG trough level equivalent to that of a previous treatment, adjust the dose accordingly.

Calculate the difference between the patients' 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 dose based on the patient's body weight. However, the patient's clinical response should be the primary consideration which guides dosing.

Adjustment (±ml) of the Weekly Subcutaneous Dose Based on the Difference (±mg/dl) From the Target Serum IgG Trough Level

Difference From Target IgG Trough Level (mg/dl)	Body Weight (kg)												
	10	15	20	30	40	50	60	70	80	90	100	110	120
	Dose Adjustment (ml per Week) ^a												
50	0	1	1	1	2	2	2	3	3	3	4	4	5
100	1	1	2	2	3	4	5	5	6	7	8	8	9
150	1	2	2	3	5	6	7	8	9	10	11	13	14
200	2	2	3	5	6	8	9	11	12	14	15	17	18
250	2	3	4	6	8	9	11	13	15	17	19	21	23
300	2	3	5	7	9	11	14	16	18	20	23	25	27
350	3	4	5	8	11	13	16	19	21	24	27	29	32
400	3	5	6	9	12	15	18	21	24	27	30	33	36
450	3	5	7	10	14	17	20	24	27	31	34	38	41
500	4	6	8	11	15	19	23	27	30	34	38	42	45

^a Dose adjustment in ml is based on the slope of the serum IgG trough level response to subcutaneous administration of Xembify® dose increments (about 6.6 mg/dl per increment of 1 mg/kg per week).

Paediatric population

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

Xembify® was evaluated in 43 paediatric subjects with PID aged 2 to 16 years (inclusive), which included 28 subjects 12 years of age or younger. No paediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

No clinical trials have been conducted with Xembify® in children of age 0 to < 2 years. However, experience with immunoglobulins suggests a safety profile similar to that for children of age 2-18 years and adults with Xembify® is to be expected.

Method of administration

For subcutaneous use only.

Subcutaneous infusion for home treatment should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. Infusion pumps appropriate for subcutaneous administration of immunoglobulins can be used. The patient must be instructed in the use of an infusion pump, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

Xembify® may be injected into sites such as abdomen, thigh, upper arm, and lateral hip. The recommended initial infusion rate depends on the individual needs of the patient and should not exceed an administration speed of 25 ml/h/site.

If well tolerated (see [section 4.4](#)) for two infusions, the infusion speed can gradually be increased to 35 ml/h/site.

More than one pump can be used simultaneously. The amount of product infused into a particular site varies. In infants and children infusion sites may be changed every 5 ml to 15 ml. In adults doses over 30 ml may be divided according to patient preference. There is no limit to the number of infusion sites. Infusion sites should be at least 5 cm apart.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see [section 4.4](#)).

Xembify® must not be given intravascularly or intramuscularly.

Patients who have had an anaphylactic or severe systemic reaction to the administration of normal immunoglobulin.

IgA deficient patients with antibodies against IgA and history of hypersensitivity to normal immunoglobulin treatment.

4.4 Special warnings and precautions for use

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

The recommended infusion rate given under section 4.2 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently in patients who receive normal immunoglobulin for the first time or, in rare cases, when the normal immunoglobulin product is switched or when there has been a long interval since the previous infusion. Common adverse reaction reported during initial infusions were: local infusion site reactions (erythema, pruritus, nodule, pain, swelling/induration, bruising, mass, rash, urticaria, scab, haemorrhage, extravasation), headache, arthralgia, back pain, diarrhoea, rhinitis, pyrexia, nausea, pruritus, and papule.

Potential complications can often be avoided by:

- initially injecting the product slowly ([see section 4.2](#));
- ensuring that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to 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. 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 Xembify® only under close medical supervision.

Rarely, normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with normal immunoglobulin.

Thromboembolism

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with preexisting risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity).

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

Renal Failure/Renal Impairment

Severe renal adverse reactions have been reported in patients receiving normal immunoglobulin treatment, particularly those products containing sucrose (Xembify® 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.

In patients at risk of developing renal dysfunction, monitor renal function and consider lower, more frequent Xembify® dosing. Ensure that patients are not volume depleted prior to administration of Xembify®.

Aseptic Meningitis Syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with subcutaneous immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following treatment. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.

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

Haemolysis/Haemolytic Anemia

Normal immunoglobulin products, including Xembify® can contain 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 normal immunoglobulin therapy due to enhanced RBC sequestration, and acute haemolysis consistent with intravascular haemolysis has been reported. If signs and/or symptoms of hemolysis are present after Xembify® infusion, perform appropriate confirmatory laboratory testing.

Transfusion-related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following treatment with human immune globulin products. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically occur within 1 to 6 hours after treatment. Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

Important information about some of the ingredients of Xembify®

The medicinal product is essentially sodium free.

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 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 (HCV) virus, and for the non-enveloped hepatitis A virus (HAV). The measures taken may be of limited value against non-enveloped viruses such as 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 Xembify® 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 hepatic impairment

There are no known specific considerations with regard to patients with hepatic impairment.

Use in the elderly

Use caution when administering Xembify® to patients age 65 and over who are at increased risk for thrombosis. While older individuals may have decreased renal, hepatic, or cardiac reserve, there are no specific considerations for subcutaneous administration based on age alone apart from aforementioned thromboembolism risk. No dose adjustments are specifically necessary in this age group and choice of dose level is dependent on best medical judgement for each individual patient. Do not exceed the recommended dose of Xembify® and employ a conservative infusion rate if indicated. Assure adequate hydration before Xembify® administration. Among drugs commonly used in the elderly population there are no anticipated drug-drug interactions based on metabolic or elimination pathways.

Paediatric use

The listed warnings and precautions apply to both adults and children. Paediatric patients <2 years of age were not included in studies and subsequently there is lack of data specific to this population.

Effects on laboratory tests

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

4.5 Interactions with other medicines and other forms of interactions

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this medicinal product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Use in pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Immunoglobulin products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

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

The ability to drive and operate machines may be impaired by some adverse reactions associated with Xembify®. 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 normal immunoglobulin 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.

For safety information with respect to transmissible agents, see [section 4.4](#).

Clinical trials experience

The safety of Xembify® administered subcutaneously was evaluated in two prospective, open-label, phase 3, non-controlled multicentre studies in 110 subjects with primary immune deficiency (PID).

Across both studies eight subjects discontinued Xembify® due to adverse reactions, all were mild or moderate in severity except for aortic valve incompetence due to congenital anomaly.

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

Frequencies have been evaluated according to the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

The table below provides a display of all adverse events during Xembify® treatment, regardless of relationship to Xembify® or timeframe relative to infusion excluding infections.

Frequency of Adverse Events with Xembify® in 1% or more of Subjects

MedDRA System Organ Class (SOC)	Adverse Event	Frequency per subject^a (N=110 subjects)	Frequency per infusion^b (N=4098 infusions)
Infections and infestations	Rhinitis	4 (3.6%) common	7 (0.0017) uncommon
Blood and lymphatic system disorders	Lymphadenopathy	2 (1.8%) common	2 (0.0005) rare
	Thrombocytopenia	2 (1.8%) common	2 (0.0005) rare
Immune system disorders	Seasonal allergy	3 (2.7%) common	3 (0.0007) rare
Psychiatric disorders	Anxiety	2 (1.8%) common	2 (0.0005) rare
Nervous system disorders	Headache	8 (7.3%) common	22 (0.0054) uncommon
	Migraine	3 (2.7%) common	3 (0.0007) rare
Respiratory, thoracic and mediastinal disorders	Cough	10 (9.1%) common	12 (0.0029) uncommon
	Oropharyngeal pain	3 (2.7%) common	4 (0.0010) uncommon
	Rhinorrhoea	3 (2.7%) common	4 (0.0010) uncommon
	Asthma	3 (2.7%) common	3 (0.0007) rare
	Epistaxis	2 (1.8%) common	5 (0.0012) uncommon
Gastrointestinal disorders	Diarrhoea	9 (8.2%) common	10 (0.0024) uncommon
	Vomiting	5 (4.5%) common	7 (0.0017) uncommon
	Nausea	4 (3.6%) common	6 (0.0015) uncommon
	Abdominal pain upper	2 (1.8%) common	3 (0.0007) rare
Skin and subcutaneous tissue disorders	Rash	4 (3.6%) common	4 (0.0010) uncommon
	Dermatitis contact	3 (2.7%) common	3 (0.0007) rare
	Papule	2 (1.8%) common	2 (0.0005) rare
	Pruritus	2 (1.8%) common	2 (0.0005) rare
Musculoskeletal and connective tissue disorders	Arthralgia	7 (6.4%) common	8 (0.0020) uncommon
	Back pain	5 (4.5%) common	6 (0.0015) uncommon
	Neck pain	2 (1.8%) common	3 (0.0007) rare

MedDRA System Organ Class (SOC)	Adverse Event	Frequency per subject ^a (N=110 subjects)	Frequency per infusion ^b (N=4098 infusions)
	Pain in extremity	2 (1.8%) common	2 (0.0005) rare
General disorders and administration site conditions	Infusion site erythema	11 (10.0%) very common	27 (0.0066) uncommon
	Infusion site pruritus	9 (8.2%) common	20 (0.0049) uncommon
	Infusion site nodule	8 (7.3%) common	11 (0.0027) uncommon
	Infusion site pain	8 (7.3%) common	8 (0.0020) uncommon
	Pyrexia	6 (5.5%) common	8 (0.0020) uncommon
	Infusion site swelling	5 (4.5%) common	13 (0.0032) uncommon
	Infusion site induration	3 (2.7%) common	6 (0.0015) uncommon
	Fatigue	3 (2.7%) common	3 (0.0007) rare
	Infusion site bruising	3 (2.7%) common	3 (0.0007) rare
	Infusion site mass	3 (2.7%) common	3 (0.0007) rare
	Malaise	3 (2.7%) common	3 (0.0007) rare
	Infusion site rash	2 (1.8%) common	5 (0.0012) uncommon
	Infusion site scab	2 (1.8%) common	5 (0.0012) uncommon
	Infusion site urticaria	2 (1.8%) common	5 (0.0012) uncommon
	Infusion site haemorrhage	2 (1.8%) common	3 (0.0007) rare
Infusion site extravasation	2 (1.8%) common	2 (0.0005) rare	
Investigations	Blood immunoglobulin G decreased	2 (1.8%) common	2 (0.0005) rare
	Protein urine present	2 (1.8%) common	2 (0.0005) rare
Injury, poisoning and procedural complications	Skin abrasion	2 (1.8%) common	3 (0.0007) rare

^a The frequency per subject is calculated using the number of subjects with adverse events excluding infections divided by the total number of subjects.

^b The frequency per infusion is calculated using the number of infusions associated with adverse events excluding infections divided by the total number of infusions.

The table below displays the adverse reactions from the 2 clinical studies.

Frequency of Adverse Reactions (ADRs) with Xembify® in 1% or more of Subjects

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency per subject ^a (N=110 subjects)	Frequency per infusion ^b (N=4098 infusions)
Infections and infestations	Rhinitis	3 (2.7%) common	4 (0.0010) uncommon
Nervous system disorders	Headache	4 (3.6%) common	4 (0.0010) uncommon
Gastrointestinal disorders	Diarrhoea	3 (2.7%) common	3 (0.0007) rare
	Nausea	2 (1.8%) common	2 (0.0005) rare
Skin and subcutaneous tissue disorders	Papule	2 (1.8%) common	2 (0.0005) rare
	Pruritus	2 (1.8%) common	2 (0.0005) rare
Musculoskeletal and connective tissue disorders	Arthralgia	3 (2.7%) common	3 (0.0007) rare
	Back pain	3 (2.7%) common	3 (0.0007) rare
General disorders and administration site conditions	Infusion site erythema	11 (10.0%) very common	27 (0.0066) uncommon
	Infusion site pruritus	9 (8.2%) common	20 (0.0049) uncommon
	Infusion site nodule	7 (6.4%) common	10 (0.0024) uncommon
	Infusion site pain	7 (6.4%) common	7 (0.0017) uncommon
	Infusion site swelling	5 (4.5%) common	13 (0.0032) uncommon
	Infusion site induration	3 (2.7%) common	6 (0.0015) uncommon
	Infusion site bruising	3 (2.7%) common	3 (0.0007) rare
Infusion site mass	3 (2.7%) common	3 (0.0007) rare	

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency per subject ^a (N=110 subjects)	Frequency per infusion ^b (N=4098 infusions)
	Infusion site rash	2 (1.8%) common	5 (0.0012) uncommon
	Infusion site scab	2 (1.8%) common	5 (0.0012) uncommon
	Infusion site urticaria	2 (1.8%) common	5 (0.0012) uncommon
	Pyrexia	2 (1.8%) common	4 (0.0010) uncommon
	Infusion site haemorrhage	2 (1.8%) common	3 (0.0007) rare
	Infusion site extravasation	2 (1.8%) common	2 (0.0005) rare
Investigations	Blood immunoglobulin G decreased	2 (1.8%) common	2 (0.0005) rare

^a The frequency per subject is calculated using the number of subjects with ADRs excluding infections for which there was at least a possibility of causal relationship with Xembify[®] divided by the total number of subjects.

^b The frequency per infusion is calculated using the number of infusions associated with ADRs excluding infections for which there was at least a possibility of causal relationship with Xembify[®] divided by the total number of infusions.

Postmarketing

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The following adverse reactions have been identified and reported during the postmarketing use of Xembify[®] administered subcutaneously.

- Nervous system disorders: Headache
- Gastrointestinal disorders: Nausea
- General disorders and administration site conditions: infusion or injection site erythema, infusion site inflammation or injection site swelling.

Paediatric population

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

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.

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, for extravascular administration, ATC code: J06BA01

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

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.

Mechanism of action

Xembify® supplies a broad spectrum of opsonising and neutralising immunoglobulin G (IgG) antibodies against bacteria and their toxins. The role of these antibodies and the mechanism of action of IgG in Xembify® in PID has not been fully elucidated.

Clinical efficacy in PID

In the European study, a total of 61 subjects with primary immunodeficiency syndromes aged between 2 years and 69 years were treated with Xembify® for up to 52 weeks. The mean dose administered each week was 125.5 mg/kg body weight (bw). Sustained IgG trough levels with mean concentration of 947.64 mg/dl were thereby achieved during the treatment period. Subjects received a total of 3045 weekly Xembify® infusions. The annual rate of serious bacterial infections (SBIs) was 0.017 per subject-year (1-sided 99% upper confidence limit 0.036), which reflected one subject with pneumonia treated with oral antibiotics as an outpatient with resolution in 4 days.

In the North American study, a total of 49 subjects with primary immunodeficiency syndromes aged between 2 years and 72 years were treated with Xembify® for up to 24 weeks. The mean dose administered each week was 178.9 mg/kg body weight. Sustained IgG trough levels with a mean concentration of 1244.84 mg/dl were thereby achieved during the treatment period. Subjects received in total 1053 weekly Xembify® infusions. The annual rate of SBIs during Xembify® treatment was 0.049 per subject-year (1-sided 99% upper confidence limit 0.110), which reflected one subject with sepsis due to cat bite.

Paediatric population

The safety and effectiveness of Xembify® have been established in paediatric subjects. Xembify® was evaluated in 28 paediatric subjects with PID aged 2 years to 12 years of age (inclusive) and in 15 paediatric subjects aged older than 12 years to less than 17 years. There were no differences in the pharmacokinetics, safety and efficacy profiles as compared with adult subjects. No paediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. No differences were seen in the pharmacodynamic properties between adult and paediatric study patients with PID. Paediatric patients <2 years of age were not included in studies and subsequently there is lack of data specific to this population.

5.2 Pharmacokinetic properties

Following subcutaneous administration of Xembify®, peak serum levels are achieved after approximately three days.

In a clinical trial with Xembify® (n = 61) in Europe, the subjects achieved sustained IgG trough levels (median 909.10 mg/dl) over a period of 52 weeks when receiving median weekly doses of 113.0 mg/kg. Data from the clinical trial of Xembify® show that serum IgG trough levels can be maintained by dosing regimens of 400 to 848 mg/kg body weight/4 weeks.

The pharmacokinetics of Xembify® were evaluated in the phase 3 efficacy and safety study in 27 adult patients with PI. The pharmacokinetic results are presented in the table below.

Pharmacokinetic Parameters of Serum Total IgG for Xembify® (PK Population)

Statistic	Pharmacokinetic Parameters		
	AUC _{0-7 days} (h*mg/dl)	C _{max} (mg/dl)	T _{max} (h)
n	27	27	27
Mean (SD)	177445.7 (31081.89)	1126.6 (190.11)	50.78 (44.596)
CV%	18	17	87.8
Median	172369.0	1080.0	68.80
Min, Max	132728, 250410	828, 1610	0.0, 166.8
Geometric Mean	175002.1	1112.2	
90% CI for Geometric Mean	165652.5, 184879.5	1055.1, 1172.4	

CI = confidence interval; CV = coefficient of variation; SD = standard deviation

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

Once weekly, biweekly or more frequent dosing (2 to 7 times per week)

Pharmacokinetic (PK) characterization of biweekly or more frequent dosing of Xembify® was undertaken using population PK-based modelling and simulation. Serum IgG concentration data consisted of 1841 samples from 95 unique paediatric and adult subjects with PID. Compared with weekly administration, PK modelling and simulation predicted that administration of Xembify® 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, Xembify® infusions given 2-7 times per week (frequent dosing) results also in overlapping IgG exposure across the entire treatment interval.

Paediatric population

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

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Glycine
Polysorbate 80

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

- Store in a refrigerator (2°C to 8°C).
 - Additionally, Xembify® may be stored at temperatures not to exceed 25°C for up to 6 months any time prior to the expiration date.
 - Following 25°C storage, use the product immediately or discard.
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light. Tape over carton ends must be unbroken.
- Administer within 8 hours after beginning infusion preparation (ie, once Xembify® is transferred from the vial into a syringe).
- Do not use if band around vial neck and cap is damaged or missing.

6.5 Nature and contents of container

Container type: Clear glass vial with a chlorobutyl stopper, an aluminum overseal, plastic top and shrink band that guarantee the intactness of packaging.

Xembify® is not made with natural rubber latex.

Product is for single use in one patient only. Discard any residue.

Pack size of 1 vial: 1 g / 5 ml in one carton; 2 g / 10 ml in one carton; 4 g / 20 ml in one carton; and 10 g / 50 ml in one carton

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

Immunoglobulin (IgG) is a glycoprotein of approximately 150 kD consisting of four disulfide-linked polypeptide chains: two light chains of 25 kD and two heavy chains of 55 kD. Disulfide linkage of the amino terminal portions of each pair of light and heavy chain forms an antigen binding site, resulting in two such sites per molecule. The carboxyl terminal portions of the heavy chains are likewise disulfide-linked, forming the carbohydrate-bearing Fc portion of the molecule that can interact with complement, and for which various phagocytes and B lymphocytes bear receptors. The three resulting domains of the protein are arranged in the shape of a "Y". The IgG molecule contains 2.9% carbohydrate by weight and has an isoelectric point of 6.8.

The amino terminal portions of all four chains in IgG contain regions with variable amino acid sequences, responsible for conferring the broad specificity of a population of antibody molecules against diverse antigens. In addition, IgG light and heavy chains contain alternate constant regions which divide the antibody population into four distinct subclasses: IgG1, IgG2, IgG3 and IgG4.

CAS number

227945-81-5

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Grifols Australia Pty Ltd
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Clayton South, Victoria 3169
Australia

For Medical/Technical Enquiries

TOLL FREE: 1800 339 479

9. DATE OF FIRST APPROVAL

Date of first authorisation: 30 June 2022

10. DATE OF REVISION

30 June 2022