PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

XEMBIFY™

Subcutaneous Immunoglobulin (Human)

20% Solution for subcutaneous use

Passive Immunizing Agent

Manufactured by:

Grifols Therapeutics LLC
8368 U.S. 70 Bus. Hwy West
Clayton, North Carolina
27520
U.S.A.

Imported and Distributed by:

Grifols Canada Ltd.
5060 Spectrum Way
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Mississauga, Ontario
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RECENT MAJOR LABEL CHANGES

Not Applicable - New Product

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

XEMBIFY (Subcutaneous Immunoglobulin [Human]) is indicated for:

- The treatment of patients 2 years of age and older with Primary Immune Deficiency (PID) and Secondary Immune Deficiency (SID) who require immunoglobulin replacement therapy.

1.1 Pediatrics

Pediatrics (2-16 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of XEMBIFY in pediatric patients aged 2 to 16 years has been established.

1.2 Geriatrics

Geriatrics (> 65 years of age): Use caution when administering XEMBIFY to patients age 65 and over who are at increased risk for thrombosis (see Warnings and Precautions).

2 CONTRAINDICATIONS

XEMBIFY (Subcutaneous Immunoglobulin [Human]) is contraindicated in:

- Patients who have had an anaphylactic or severe systemic reaction to the administration of human immunoglobulin, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- Patients with severe, selective IgA deficiency with antibodies against IgA and history of hypersensitivity.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

There is clinical evidence of an association between the administration of all immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. Therefore, caution should be exercised when prescribing and administering immunoglobulins. Thrombosis may occur even in the absence of known risk factors.

Risk factors for thromboembolic events include: obesity, advanced age, hypertension, diabetes mellitus, history of vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severely hypovolemic patients, diseases which increase blood viscosity, hypercoagulable conditions, use of estrogens, indwelling central venous catheters, and cardiovascular risk factors (see Warnings and Precautions - Thromboembolic Events subsection).

The drug product should be administered at the minimum rate of infusion practicable. Patients should be adequately hydrated before administration. Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and have blood viscosity assessed.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Administer XEMBIFY (Subcutaneous Immunoglobulin [Human]) at regular intervals from daily up to every two weeks (biweekly).
- Monitor serum IgG trough levels regularly to guide subsequent dose adjustments and dosing intervals as needed, see Dose Adjustment (Table 1).

4.2 Recommended Dose and Dosage Adjustment

- Administer XEMBIFY at regular intervals from daily up to every two weeks (biweekly).
- Individualize the dose based on the patient's pharmacokinetic and clinical response. Weekly maintenance doses typically range from 0.1 g/kg to 0.2 g/kg.
- Monitor serum IgG trough levels regularly to guide subsequent dose adjustments and dosing intervals as needed, see Table 1.
- To convert the XEMBIFY dose (in grams) to milliliters (mL), multiply the calculated Initial subcutaneous dose (in grams) by 5.
- Doses divided over the course of a week, or once weekly, or biweekly, achieve similar exposure when administered regularly at steady-state.
- To determine the dose for alternative dosing intervals:
    - Frequent dosing (2-7 times per week): Divide the calculated weekly dose by the desired number of times per week.
    - Biweekly dosing: Multiply the calculated weekly dose by 2.
- To guide dose adjustments, see section Dose Adjustment (Table 1).

Over time, the dose may need to be adjusted to achieve the desired clinical response and serum IgG trough level. To determine if a dose adjustment may be considered, measure the patient's serum IgG trough level as early as 5 weeks after initiating XEMBIFY treatment. To determine if further dose adjustments are necessary, monitor the patient's IgG trough level every 2 to 3 months.

To adjust the dose based on trough levels, calculate the difference (in mg/dL) of the patient's serum IgG trough level from the target IgG trough level. Then find this difference in Table 1 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 in dose adjustment.

Table 1: 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)*												
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

* 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).

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.

For patients switching from immunoglobulin intravenous (human) treatment (IVIG)

- Begin treatment with XEMBIFY one week after the patient's last IVIG infusion.
- Establish the initial weekly subcutaneous dose by converting the monthly IVIG dose into an equivalent weekly dose and increasing it using a dose adjustment factor (1.37), as follows:

$$\text{Initial weekly dose (grams)} = \frac{\text{Prior IVIG dose (in grams)}}{\text{Number of weeks between IVIG doses}} \times 1.37$$

For patients switching from another immunoglobulin subcutaneous (human) treatment (IGSC):

- Administer the same total weekly dose of XEMBIFY (as daily to bi-weekly dose in grams) as the weekly dose of prior IGSC treatment (in grams).

For patients naïve to immunoglobulin treatment:

- As a loading dose during the first week of treatment, administer the planned weekly maintenance dose of XEMBIFY on five consecutive days (one planned weekly dose administered every day during 5 days).

Alternatively:

- Administer an initial dose of IVIG as a loading dose, followed by the planned dose of XEMBIFY after 48 – 72 hours.

4.3 Administration

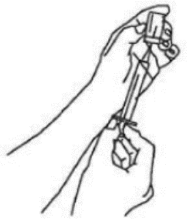
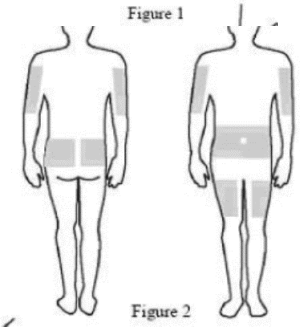
XEMBIFY is for subcutaneous infusion only.

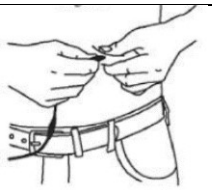
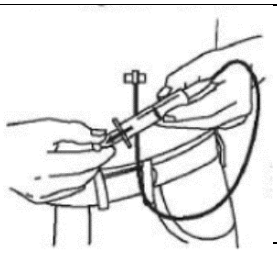
XEMBIFY is clear to slightly opalescent and colorless or pale yellow or light brown solution.

- Do not use if the solution is cloudy.
- Visually inspect XEMBIFY for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid.
- Do not freeze. Do not use solutions that have been frozen.
- Allow the solution to reach ambient room temperature prior to administration.
- Do not shake.
- Do not dilute.
- The XEMBIFY vial is for single use only. XEMBIFY contains no preservative. Use any vial that has been entered promptly. Discard partially used vials. Do not store after entry into bottle.
- Administer within 8 hours after beginning infusion preparation (i.e. once XEMBIFY is transferred from the vial into a syringe).
- Do not mix XEMBIFY with other medications.
- Do not use after expiration date.

Infuse XEMBIFY in the abdomen, thigh, upper arm, sides, back and/or lateral hip.

1. Use aseptic technique when preparing and administering XEMBIFY for injection.
2. Inspect the vials: inspect for clarity, color, and expiration date(s).
3. Prepare for infusion:
    - Gather supplies: XEMBIFY vial(s), ancillary supplies, sharps container, patient's treatment diary/logbook, and the infusion pump, if applicable.
    - Prepare a clean work area.
    - Wash hands.
4. Prepare XEMBIFY:
    - Remove the protective cap from the vial to expose the central portion of the stopper. If the packaging shows any sign of tampering, do not use the product and notify Grifols Canada Ltd. immediately by calling 1-866-482-5226.
5. Wipe the stopper with alcohol and allow to dry.

6. Using a sterile syringe and needle, prepare to withdraw XEMBIFY by first injecting air into the vial that is equivalent to the amount of XEMBIFY to be withdrawn. Then withdraw the desired volume of XEMBIFY. If multiple vials are required to achieve the desired dose, repeat this step. (Figure 1)	 Figure 1
7. If using a pump, follow the manufacturer's instructions for preparing the pump, administration tubing and Y-site connection tubing, if needed. Be sure to prime the administration tubing to ensure that no air is left in the tubing or needle by filling the	 Figure 2

tubing/needle with XEMBIFY. 8. Select the number and location of injection sites. (Figure 2)	
9. Cleanse the injection site(s) with antiseptic solution using a circular motion working from the center of the site and moving to the outside. Sites should be clean, dry, and at least 5cm apart. (Figure 3)	 Figure 3
10. Grasp the skin between 2 fingers (pinch at least 2.5cm of skin) and insert the needle at a 90-degree angle into the subcutaneous tissue. (Figure 4)	 Figure 4
11. After inserting each needle, make sure that a blood vessel has not been accidentally entered. Attach a sterile syringe to the end of the primed administration tubing, pull back on the plunger, and if you see blood, remove and discard the needle and administration tubing. (Figure 5)	 Figure 5

12. Repeat priming and needle insertion steps using a new needle, administration tubing and a new infusion site. Secure the needle in place by applying sterile gauze or transparent dressing over the site.
13. If using multiple, simultaneous injection sites, use Y-site connection tubing and secure to the administration tubing.
14. If a pump is being used, infuse XEMBIFY following the manufacturer's instructions for the pump.

Infuse XEMBIFY at a maximum rate of 25 mL per hour per infusion site and with up to 8 infusion sites (most patients used 4 infusion sites). Ensure that the infusion sites are at least 5 cm apart for patients of all ages.

Self-Administration

If self-administration is deemed to be appropriate by the physician, clear instructions and training on subcutaneous infusion should be given to the patient/caregiver. The information provided to the patient/caregiver should include, but not be limited to, the Patient Medication Information provided in the present Product Monograph.

4.4 Missed Dose

A missed dose should be administered as soon as possible.

5 OVERDOSAGE

Consequences of an overdose are not known with XEMBIFY.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous infusion	20% Solution of Human Immunoglobulin G	Glycine, Polysorbate 80

XEMBIFY is supplied in single-use vials containing the labeled amount of functionally active IgG. XEMBIFY is clear to slightly opalescent, and colourless or pale yellow or light brown. XEMBIFY is not made with natural rubber latex. XEMBIFY is supplied in the following sizes:

Table 3- Formats of XEMBIFY

Size	Gram Protein
5 ml vial	1
10 ml vial	2
20 ml vial	4
50 ml vial	10

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

XEMBIFY is purified from human plasma obtained from healthy donors. When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by: (1) epidemiological controls on the donor population and selection of individual donors by a medical interview; (2) screening of individual donations and plasma pools for viral infection markers; and (3) manufacturing procedures with demonstrated capacity to inactivate/remove pathogens.

ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Canada Ltd. [1-866-482-5226].

The physician should discuss the risks and benefits of this product with the patient, before

prescribing or administering to the patient.

Hypersensitivity
Severe hypersensitivity reactions may occur with human immunoglobulin products, including XEMBIFY. In case of hypersensitivity, discontinue XEMBIFY infusion immediately and institute appropriate treatment. Have medications such as epinephrine available for immediate treatment of an acute hypersensitivity reaction.

XEMBIFY contains IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. XEMBIFY is contraindicated in severely IgA deficient patients with antibodies against IgA and history of hypersensitivity reaction. (see Contraindications)

Thromboembolic Events
There is clinical evidence of an association between the administration of all immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis.

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

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

Risk factors for thromboembolic adverse events include: obesity, advanced age, hypertension, diabetes mellitus, history of vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilisation, severely hypovolemic patients, diseases which increase blood viscosity, hypercoagulable conditions, use of estrogens, indwelling central vascular catheters, and cardiovascular risk factors.

Aseptic Meningitis Syndrome (AMS)
AMS may occur infrequently with human immunoglobulin treatment, including XEMBIFY. Discontinuation of immunoglobulin treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to two days following immunoglobulin treatment. AMS is characterized by the following symptoms and signs: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such symptoms and signs including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of immunoglobulin products.

Renal Dysfunction/Failure
Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis and death has been know to occur upon use of intravenous human immunoglobulin products, especially those containing sucrose. XEMBIFY does not contain sucrose. The risk of

acute renal dysfunction/failure associated with subcutaneous administration of human immunoglobulin is unknown. Ensure that patients are not volume depleted prior to the initiation of the infusion of XEMBIFY.

Hemolysis
XEMBIFY may contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and hemolysis. Delayed hemolytic anemia has been known to develop subsequent to intravenous human immunoglobulin therapy due to enhanced RBC sequestration, and acute hemolysis consistent with intravascular hemolysis has been reported. Risk factors which may be related to the development of hemolysis include high doses (e.g., ≥ 2 g/kg, single administration or divided over several days) and non-O blood group. Underlying inflammatory state in an individual patient may increase the risk of hemolysis, but its role is uncertain. The risk of hemolysis associated with subcutaneous administration of human immunoglobulin is unknown.

Monitor patients receiving XEMBIFY for clinical signs and symptoms of hemolysis. 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 intravenous human immunoglobulin 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. The risk of TRALI associated with subcutaneous administration of human immunoglobulin is unknown.

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.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data with XEMBIFY use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with XEMBIFY. It is not known whether XEMBIFY can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. XEMBIFY should be given to a pregnant woman only if clearly needed.

7.1.2 Breast-feeding

There is no information regarding the presence of XEMBIFY in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XEMBIFY and any potential adverse effects on the breastfed infant from XEMBIFY or from the underlying maternal condition.

7.1.3 Pediatrics

Pediatrics (2-16 years of age): XEMBIFY was evaluated in 14 pediatric subjects with PID in the pivotal multicenter clinical trial. (see Clinical Studies) The safety and efficacy profiles were similar to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Pediatrics (0-2 years of age): The safety and effectiveness of XEMBIFY have not been established in pediatric patients below the age of 2 years.

7.1.4 Geriatrics

Use caution when administering XEMBIFY to patients age 65 and over who are at increased risk for thrombosis. Clinical studies of XEMBIFY did not include sufficient numbers of subjects over age 65 years to determine whether they respond differently from younger subjects. However among 3 subjects who received XEMBIFY in this age group, no differences in safety, pharmacokinetics (PK) or efficacy were observed for this group relative to the results for the overall trial.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions observed in 2 or more subjects receiving XEMBIFY treatment in the clinical trial were infusion site nodule, infusion site bruising, infusion site pain, infusion site rash, infusion site scab, asthma, arthralgia, papule, pruritus, and rash. Adverse reactions were defined as events that were either potentially related to treatment, occurred during an infusion, or occurred within 72 hours after an infusion (excluding infections).

8.2 Clinical Trial Adverse Reactions

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

XEMBIFY was administered subcutaneously in one prospective, open-label, multi-center trial to evaluate efficacy, safety, tolerability, and pharmacokinetics in subjects with primary immunodeficiency (PID). In this clinical trial 42 of 49 subjects treated with XEMBIFY completed the trial including 12 of 14 subjects aged 2 to ≤ 16 years old.

A total of 1053 XEMBIFY infusions were administered during the clinical trial. There were a total of 80 adverse reactions (defined as adverse events that are either potentially related or occurring during or within 72 hours of an infusion [excluding infections]), which occurred at a rate per infusion of 0.076. Among these 80 adverse reactions, 78 were mild or moderate. The two severe adverse reactions (2/80; 2.5%) were intervertebral disc degeneration requiring hospitalization for orthopedic surgery and non-serious polymyalgia rheumatica. The intervertebral disc degeneration was an unrelated serious adverse reaction (1/80; 1.3%) that occurred within 72 hours of XEMBIFY infusion . Adverse reactions occurring in 2 or more subjects receiving XEMBIFY are shown in Table 4.

Table 4 Adverse Reactions in 2 or more Subjects Associated with Infusions of XEMBIFY

Adverse Reaction*	By Subject n (%)† (N=49 subjects)	By Infusion n (rate)‡ (N=1053 infusions)
Infusion site nodule	6 (12.2%)	9 (0.009)
Infusion site bruising	3 (6.1%)	3 (0.003)
Infusion site pain	3 (6.1%)	3 (0.003)
Infusion site rash	2 (4.1%)	5 (0.005)
Infusion site scab	2 (4.1%)	5 (0.005)
Asthma	2 (4.1%)	2 (0.002)
Arthralgia	2 (4.1%)	2 (0.002)
Papule	2 (4.1%)	2 (0.002)
Pruritus	2 (4.1%)	2 (0.002)
Rash	2 (4.1%)	2 (0.002)

* Excluding infections.
† Number and percentage of subjects with the adverse reaction.
‡ Rate per infusion is calculated as the total number of adverse reactions divided by the total number Of infusions

The overall rate of local infusion site reactions (ISRs) considered as adverse reactions was 0.039 per infusion of XEMBIFY. Local ISRs that were not considered as adverse reactions were not impactful to the patient in terms of requiring (a) concomitant medication, (b) infusion interruption or discontinuation, or (c) affecting the patient's general condition in the Investigator's opinion, occurred at a rate of 0.331 per infusion of XEMBIFY. There were no severe or serious adverse reactions that were local ISRs.

8.3 Post-Market Adverse Reactions

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.

Postmarketing Experience of Immunoglobulin Products

The following adverse reactions have been identified and reported during the postmarketing use of immunoglobulin products administered subcutaneously:

- Immune system disorders: Anaphylactic reaction
- Cardiac disorders: Tachycardia
- Nervous system disorders: Tremor and paresthesia
- Respiratory, thoracic and mediastinal disorders: Dyspnea and laryngospasm
- General disorders and administration site conditions: Injection site reaction (such as induration and warmth) and chest discomfort

9 DRUG INTERACTIONS

9.1 Overview

Administer XEMBIFY separately from other drugs or medications which the patient may be receiving. Do not mix XEMBIFY with immunoglobulin from other manufacturers.

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella. Inform the immunizing physician of recent therapy with XEMBIFY so that appropriate measures may be taken.

9.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs) test.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

XEMBIFY supplies a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against bacterial, viral, parasitic, and mycoplasmal agents, and their toxins. XEMBIFY also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system. The role of these antibodies and the mechanism of action of IgG in XEMBIFY in PID has not been fully elucidated.

10.2 Pharmacodynamics

Human normal immunoglobulin contains mainly (IgG) with a broad spectrum of antibodies against infectious agents. Human normal immunoglobulin contains the IgG antibodies present in the normal population. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of XEMBIFY may restore abnormally low IgG levels to the normal range.

10.3 Pharmacokinetics

Pharmacokinetic (PK) parameters of subcutaneously administered XEMBIFY were evaluated in

subjects with primary immunodeficiency (PID) during a clinical trial. Subjects were treated intravenously with a comparator product [GAMUNEX®, immunoglobulin injection (human), 10% caprylate/chromatography purified] during a 3-4 months Run-in period prior to IV PK profiling in 50 subjects, and then 49 subjects switched to weekly subcutaneous infusions of XEMBIFY for 24 weeks at 137% of the intravenous dose with PK profiling at SC Week #13-14. A comparison of the area under the curve (AUC) for subcutaneous versus intravenous infusion was performed.

At this dose adjustment, the geometric least-squares means ratio of the AUC for subcutaneous XEMBIFY versus IV administration of GAMUNEX® was 104% (90% CI: 100%-107%). The peak IgG level occurred at a mean of 76 hours after subcutaneous XEMBIFY administration. The average mean IgG trough level at steady state was higher with XEMBIFY (1245 mg/dL) compared with IV GAMUNEX® (957 mg/dL) (average mean trough ratio SC/IV of 1.333). PK parameters of XEMBIFY are summarized in Table 5. PK parameters did not significantly differ between age groups (see Table 6).

Table 5: PK Parameters of Total IgG at Steady-State in IV and SC Phases (PK Population)

Phase	Statistics	$AUC_{(0\text{-}7\ days)}$ (h*mg/dL)*	C_{max} (mg/dL)	t_{max} (hour)
IV	n	49	49	49
	Mean±SD	212150.5±41832.11	2153.7±436.90	5.814±8.0194
	CV%	20	20	137.93
	Min, Max	106091, 308405	1430, 3170	0.75, 48.93
	Geometric Mean	207921.5	2112.3	
	90% CI for Geometric Mean	197865.8, 218488.2	2014.7, 2214.6	
SC	n	39	41	41
	Mean±SD	218315.6±48121.25	1395.2±312.32	76.089±35.7163
	CV%	22	22	46.94
	Min, Max	102650, 367496	636, 2320	0.00, 167.72 †
	Geometric Mean	213141.4	1360.7	
	90% CI for Geometric Mean	200568.6, 226502.3	1280.7, 1445.8	

* $AUC_{(0\text{-}7\ days)}$ in the IV Phase is calculated as $AUC_{(0\text{-}21\ days)}/3$ for subjects on an every-3-week IV dosing schedule, and as $AUC_{(0\text{-}28\ days)}/4$ for subjects on an every-4-week IV dosing schedule.

† The apparent variability in t_{max} in the SC Phase can be attributed to the low fluctuation in IgG concentrations and is unlikely to be of any clinical relevance.

Table 6: Steady-State PK Parameters for XEMBIFY by Age

Age Group (years) Statistics	$AUC_{(0\text{-}7\ days)}$ (h*mg/dL)*	C_{max} (mg/dL)	Mean Trough (mg/dL)	t_{max} (hour)†
All Subjects (N)	39	41	44	41
Mean±SD	218315.6±48121.25	1395.2±312.32	1244.84±272.151	76.089 ±35.7163
CV%	22	22	21.9	46.94
Min, Max	102650, 367496	636, 2320	651.5, 2047.5	0.00, 167.72
2 -5 (n)	1	1	1	1
Mean±SD	183864.0±NC‡	1130.0±NC‡	1077.50± NC‡	72.030±NC‡
CV%	NC‡	NC‡	NC‡	NC‡
Min, Max	183864, 183864	1130, 1130	1077.5, 1077.5	72.03, 72.03
>5 -12 (n)	5	5	6	5
Mean±SD	215557.6±27604.33	1372.0±182.54	1193.63±182.887	70.988 ±26.3771
CV%	13	13	15.3	37.16
Min, Max	187838, 245614	1200, 1580	993.0, 1510.0	28.17, 100.78
>12 -16 (n)	4	5	5	5
Mean±SD	240008.8±40578.07	1548.0±281.28	1378.50±209.199	72.672 ±49.7365
CV%	17	18	15.2	68.44
Min, Max	205646, 298678	1290, 2000	1095.0, 1665.0	23.65, 143.10
>16 (n)	29	30	32	30
Mean±SD	216987.0±52388.87	1382.5±335.15	1238.79±295.575	77.644 ±36.2324
CV%	24	24	23.9	46.66
Min, Max	102650, 367496	636, 2320	651.5, 2047.5	0.00, 167.72

* $AUC_{(0\text{-}7\ days)}$ was calculable for 39 of 41 subjects in the SC phase PK population due to discrepancies in actual collection time for the last sample and the resulting percentage of AUC due to extrapolation exceeded 40% for 2 subjects.

† The apparent variability in t_{max} can be attributed to the low fluctuation in IgG concentrations and is unlikely to be of any clinical relevance.

‡ NC = Not calculated.

11 STORAGE, STABILITY AND DISPOSAL

- Store XEMBIFY at 2–8°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.
- Do not use after expiration date printed on the packaging.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Immunoglobulin Subcutaneous (Human), 20%

Chemical name: Human Immunoglobulin G

Molecular mass: Glycoprotein of approximately 150 kD

Structural formula: The active principle in XEMBIFY, immunoglobulin (IgG), is a glycoprotein 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 three resulting domains of the protein are arranged in the shape of a "Y".

Physicochemical properties: The carboxyl terminal portions of the heavy chains are 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 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: IgG_1, IgG_2, IgG_3 and IgG_4.

Product Characteristics
XEMBIFY is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. Isotonicity is achieved by the addition of glycine. XEMBIFY is incubated in the final container (at the low pH of 4.1 to 4.8). XEMBIFY consists of 18%–22% protein in 0.16–0.26 M glycine and 10 to 40 mcg/mL polysorbate 80. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin. The product is intended for subcutaneous administration.

XEMBIFY contains no preservative and is not made with natural rubber latex.

Pathogen Safety Measures
When medicinal biological products are administered, the possibility of infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by epidemiological surveillance of the donor population and selection of individual donors by medical interview; testing of individual donations and plasma pools; and the presence in the manufacturing processes of steps with demonstrated capacity to inactivate/remove pathogens.

In the manufacturing process of XEMBIFY, there are several steps with the capacity for virus inactivation or removal. The main steps of the manufacturing process that contribute to the virus clearance capacity are as follows:

- Caprylate precipitation/depth filtration

- Caprylate incubation
- Column chromatography
- Nanofiltration
- Low pH final container incubation

To provide additional assurance of the pathogen safety of the final product, the capacity of the XEMBIFY manufacturing process to remove and/or inactivate viruses has been demonstrated by laboratory spiking studies on a scaled down process model using a wide range of viruses with diverse physicochemical properties.

The combination of all of the above mentioned measures provides the final product with a high margin of safety from the potential risk of transmission of infectious viruses.

The caprylate/chromatography manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the variant Creutzfeldt-Jakob disease (vCJD), and Creutzfeldt-Jakob disease (CJD) agents. These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed by the caprylate/chromatography manufacturing process.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 7 - Summary of patient demographics for clinical trials in Primary Immune Deficiency

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
GTI 1502	prospective, open-label, multi-center safety and PK study	1.37 x IV dose; subcutaneous administration for 6 months	53 (safety population)	36.8 years (range 2 to 72 years)	50.9% M 49.1% F

The study included a 3 or 4 month Run-In Phase (required for subjects who were not receiving IGIV-C 10% prior to enrolment), an IV Phase (involving administration of two IGIV 10% infusions), and a SC Phase (involving 24 weekly doses of IGSC 20% study treatment).

The safety population consisted of all 53 subjects who were infused with any amount of study drug. Two pediatric subjects aged ≥2 to ≤5 years of age, 7 pediatric subjects aged >5 to ≤12 years of age, and 6 adolescent subjects aged >12 to 16 years of age participated in the study. The remaining 38 subjects were >16 years of age. The majority (90.6%, 48/53) of subjects were Caucasian.

The mean baseline total IgG concentration was 934.7 mg/dL. At screening, the majority of subjects were maintained on IV immunoglobulin (n=33) on either a 3- or 4- week infusion schedule and 20 subjects (37.7%) received SC immunoglobulin. The majority of the subjects were receiving IgG treatment every 4 weeks (88.7%, 47/53) versus every 3 weeks (11.3%, 6/53) during the Run-In and/or IV phases. Other than age, weight, and height, there were no major

differences in demographic and baseline characteristics across age groups.

13.2 Study Results

Table 8 - Results of study GTI 1502 in Primary Immune Deficiency

Primary Endpoints	Associated values for Study Drug and Control	Statistical significance and Conclusions
Determine XEMBIFY dose to produce steady-state AUC of total IgG that is non-inferior to IV dosing	Mean $AUC_{0\text{-}7\ days}$ Total IgG (h*mg/dL) IV phase[a] (N=49): 212150.5 ± 41832.11 SC phase (N=39): 218315.6 ± 48121.25	ANOVA results indicate that with a dose adjustment factor of 1.37 times the IV dose of SC, the geometric LSM ratio (SC/IV) for steady-state $AUC_{0\text{-}7\ days}$ is 1.04
Determine if XEMBIFY maintained steady-state trough IgG levels comparable to IgG trough of IV dosing	Mean trough concentration IgG (mg/dL) IV phase (N=49): 957 SC phase (N-39): 1245	Average mean trough ratio (SC:IV) of 1.333, indicates 33% higher trough concentrations for SC vs. IV dosing.
Assess safety and tolerability of XEMBIFY as IgG replacement therapy in patients with primary immune deficiency	Subjects with ≥1 TEAE: Run-in + IV: 62.3% SC phase: 83.7% *All mild/moderate except for 1 subject in IV phase and 3 subjects in SC phase* Subjects with any infection: Run-in + IV: 50.9% SC phase: 53.1%	Overall, XEMBIFY is both well tolerated and has safety profile similar to IGIV-C 10%

[a] $AUC_{0\text{-}7}$ days in the IV Phase is calculated as $AUC_{0\text{-}21}$ days/3 for subjects on an every-3-week IV dosing schedule, and as $AUC_{0\text{-}28}$ days/4 for subjects on an every-4-week IV dosing schedule.

14 NON-CLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No nonclinical studies were conducted to evaluate the carcinogenic or mutagenic effects of XEMBIFY or its effects on fertility.

14.2 Animal Toxicology and/or Pharmacology

Single and repeated dose toxicology studies were conducted in male New Zealand White rabbits. In a single-dose toxicity study, no adverse effects were observed with subcutaneous dose levels of 500, 1000 and 1500 mg/kg. In a repeated-dose toxicity study, the systemic safety and toxicity profiles of XEMBIFY and comparator GAMUNEX were similar following 5 consecutive daily subcutaneous doses at levels of 500, 1000 and 1500 mg/kg/day. Transient

local injection site swelling was observed in XEMBIFY but not in the GAMUNEX groups.

In improper delivery route studies, XEMBIFY administered as a single intravenous, intra-arterial or perivascular dose of 100 mg/kg caused injection site irritation in New Zealand White rabbits. The findings were of higher incidence following perivascular administration of either XEMBIFY or GAMUNEX, and were within the norms of this route of administration in this species.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

XEMBIFY™
Immunoglobulin Subcutaneous (Human), 20%

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

Serious Warnings and Precautions

- Immunoglobulin Intravenous (Human) products have been reported to be associated with heart and blood circulation problems such as heart attack, stroke and blood clots (thrombosis). You should talk to your doctor if you have risk factors for these kinds of conditions. Some of these risk factors include obesity, old age, high blood pressure, diabetes, or a history of heart disease. Thrombosis may occur even in the absence of known risk factor.

What is XEMBIFY used for?

- **XEMBIFY** can help prevent infections in patients who have poorly functioning immune systems

How does XEMBIFY work?

XEMBIFY is made of highly purified antibodies (also called immunoglobulins) taken from blood donors with healthy immune systems. These antibodies are part of the immune system that defend the body against infections such as viruses and bacteria. Routine infusions of **XEMBIFY** can replace antibodies that are missing in patients with poorly functioning immune systems, and help lower the number and severity of infections.

What are the ingredients in XEMBIFY?

Medicinal ingredients: Human Immunoglobulin G
Non-medicinal ingredients: glycine and polysorbate 80

XEMBIFY comes in the following dosage forms:

20% Solution for subcutaneous use

Do not use XEMBIFY if:

- You have ever had a severe reaction to any human immunoglobulin product like XEMBIFY, or to any ingredient included in XEMBIFY or its packaging.
- You have severe deficiency in IgA with antibodies against IgA, and history of reacting to products containing IgA.

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

- Have previously been told that you have Immunoglobulin A (IgA) deficiency
- Have a history or known risk for thromboembolic events such as heart attack, stroke, or blood clots

- Are pregnant or plan to become pregnant

Other warnings you should know about:
XEMBIFY is made from human plasma, and may theoretically carry a risk of transmitting infectious agents, despite steps designed to reduce this risk – i.e. **XEMBIFY** is made using plasma obtained from healthy donors; each plasma donation as well as the manufacturing pools are tested for certain viruses; and the manufacturing process has been shown to have the capacity to remove or inactivate pathogens. You should discuss the benefits and risks of using **XEMBIFY** with your doctor or other healthcare professional.

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

How to take XEMBIFY:
XEMBIFY may be infused by a Healthcare Professional, or you or a caregiver may be trained to infuse it yourself. You or a caregiver should only infuse **XEMBIFY** yourselves after you have been trained by a healthcare professional. Below are step-by-step instructions to help you remember how to use **XEMBIFY**. Ask your doctor or healthcare professional about any instructions you do not understand.

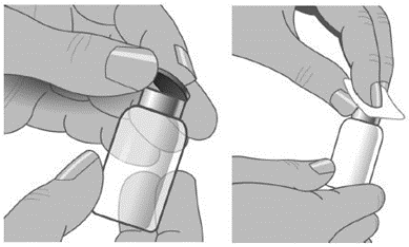
*Before using **XEMBIFY***
- Do not shake the vials.
- Before using, allow the solution to come to room temperature (20-25°C). This can take 60 minutes or longer. Do not microwave or use any kind of direct heat to try and speed up the warming process.
- Do not use the vial if:
    - the solution is cloudy or discolored. The solution should be clear to slightly opalescent, and colorless or pale yellow or light brown.
    - the protective cap is missing, or there is any evidence of tampering. Tell your healthcare provider immediately.
- Gather supplies: **XEMBIFY** vial(s), ancillary supplies, sharps container, your treatment diary/logbook, and the infusion pump (if applicable).
- Sanitize your infusion set-up area by preparing a clean, flat, non-porous surface such as a kitchen counter. Avoid using porous surfaces such as wood. Clean the surface with an alcohol wipe using a circular motion from the center outward.

Step 1:
Wash and dry your hands thoroughly before administering XEMBIFY
- Your healthcare provider may recommend that you use antibacterial soap or that you wear gloves.

Step 2:

Remove the protective cap and sanitize the stopper

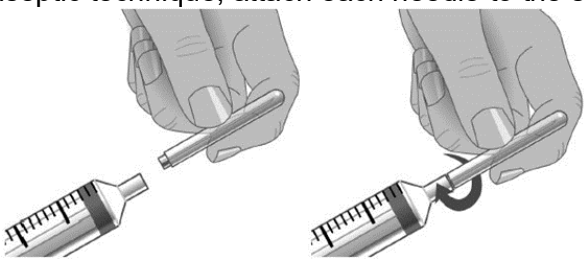
- Remove the protective cap from the vial to expose the central portion of the stopper.
- Wipe the stopper with alcohol and allow to dry.



Step 3:

Use aseptic technique when preparing and administering XEMBIFY

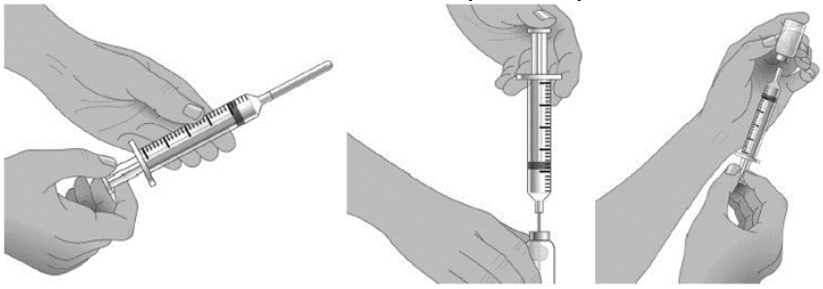
- Do not allow your fingers or other objects to touch the inner stem of the plunger, the syringe tip, or other areas that will come in contact with your **XEMBIFY** solution. This is called aseptic technique and is designed to prevent transmission of germs.
- Using aseptic technique, attach each needle to the syringe tip.



Step 4:

Prepare the syringe and draw XEMBIFY solution into syringe

- Remove cap from needle.
- Pull the syringe plunger back to the level matching the amount of **XEMBIFY** to be withdrawn from the vial.
- Place the **XEMBIFY** bottle on a clean flat surface and insert the needle into the center of the vial stopper.
- Inject air into the vial. The amount of air should match the amount of **XEMBIFY** to be withdrawn.
- Turn the vial upside down and withdraw the correct amount of **XEMBIFY**. If multiple vials are required to achieve the correct dose, repeat Step 4.

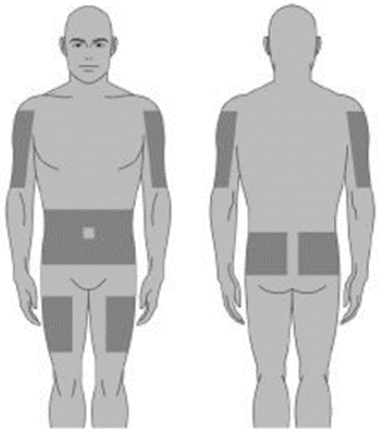


Step 5:
Fill the pump reservoir and prepare the infusion pump (if applicable)

- If using an infusion pump, follow the pump manufacturer's instructions for filling the pump reservoir and preparing the infusion pump, administration tubing and Y-site connection tubing, if needed.
- Be sure to prime the administration tubing to ensure that no air is left in the tubing or needle by filling the tubing/needle with **XEMBIFY**. To prime, hold the syringe in one hand and the administration tubing's capped needle in the other. Gently squeeze on the plunger until you see a drop of **XEMBIFY** exit from the needle.

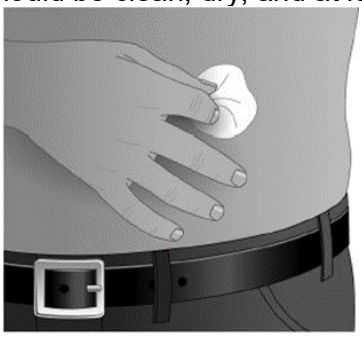
Step 6:
Select the number and location of infusion sites

- Select one or more infusion sites as directed by your healthcare provider.
- The number and location of injection sites depends on the volume of the total dose.



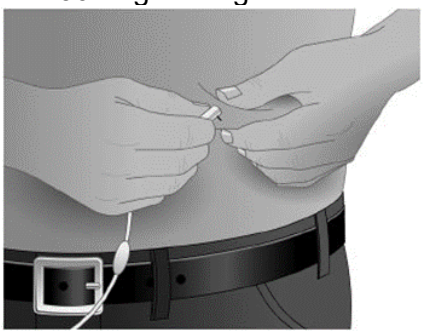
Step 7:
Prepare the infusion site

- Cleanse the infusion site(s) with antiseptic solution using a circular motion working from the center of the site and moving to the outside.
- Sites should be clean, dry, and at least 2 inches (5cm) apart.



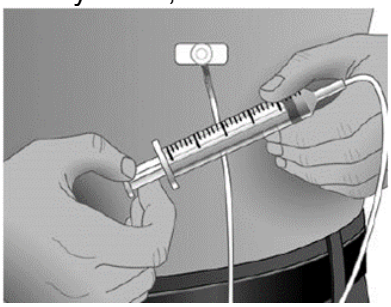
Step 8:
Insert the needle

- Grasp the skin between two fingers (pinch at least1 inch (2.5 cm) of skin) and insert the needle at a 90-degree angle into the subcutaneous tissue.



Step 9:
Do not inject XEMBIFY into a blood vessel

- After inserting each needle into tissue (and before your infusion), make sure that a blood vessel has not been accidentally entered. To do this, attach a sterile syringe to the end of the primed administration tubing. Pull back on the syringe plunger and watch for any blood flowing back into administration tubing.
- If you see any blood, remove and discard the needle and administration tubing.



- Repeat priming and needle insertion steps using a new needle, administration tubing and a new infusion site.
- Secure the needle in place by applying sterile gauze or transparent dressing over the site.

Step 10:
Repeat for other sites, as needed

- If using multiple, simultaneous infusion sites, use Y-site connection tubing and secure to the administration tubing.

Step 11:
Infuse XEMBIFY following the pump manufacturer's instructions for the infusion pump

Step 12:
After infusion, turn off pump (if applicable) and dispose of used supplies

- Follow manufacturer's instructions to turn off pump.

- Undo and discard any dressing or tape.
- Gently remove the inserted needle(s) or catheter(s).
- Discard any unused solution in an appropriate waste container as instructed.
- Discard any used administration equipment in an appropriate waste container.
- Store your supplies in a safe place.
- Follow manufacturer's instructions to care for the infusion pump (if applicable).

Step 13:
Record each infusion

- Remove the peel-off label with the product lot number from the **XEMBIFY** vial and use this to complete the patient record.
- Remember to bring your journal with you when you visit your physician or healthcare provider.

Be sure to tell your doctor about any problems you have doing your infusions. Your doctor may ask to see your treatment diary/logbook, so be sure to take it with you each time you visit the doctor's office.

Usual dose:
Your doctor will tell you how much **XEMBIFY** to inject, and how often.

Overdose:
The effects of taking too much **XEMBIFY** are not known.

If you think you have taken too much **XEMBIFY**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of **XEMBIFY**, take it as soon as possible. Don't just wait for your next scheduled dose.

What are possible side effects from using XEMBIFY?
These are not all the possible side effects you may feel when taking **XEMBIFY**. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects with **XEMBIFY** are as follows. Most of these are related to the injection under the skin, which can cause local irritation:

- Infusion site nodule
- Infusion site bruising
- Infusion site pain
- Infusion site rash
- Infusion site scab
- Asthma
- Arthralgia (pain in the joints)
- Papule (bumps on skin)
- Pruritus (itching)
- Rash

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Potential Symptoms of thrombosis (Blood Clot): Pain/swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body.		√	√
Potential Symptoms of Aseptic Meningitis (brain inflammation): Severe headache, stiff neck, fatigue, fever, sensitivity to light, painful eye movements, nausea and vomiting.	√		√

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

Deviate from HC template – see HC comments on GamaSTAN PM

Reporting Side Effects

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

3 ways to report:

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

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

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

Storage:
Store **XEMBIFY** at 2–8°C.
XEMBIFY may also be stored at room temperature (not to exceed 25°C) for up to 6 months. Once stored at room temperature the product must be used within 6 months or discarded. Do not freeze. Do not use after expiration date printed on the packaging.

Keep out of reach and sight of children.

If you want more information about XEMBIFY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by calling 1-866-482-5226.

This leaflet was prepared by Grifols Therapeutics LLC

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