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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XEMBIFY safely and effectively. See full prescribing information for XEMBIFY.

XEMBIFY (immune globulin subcutaneous, human – klhw)  
20% solution

Initial U.S. Approval: 2019

### WARNING: THROMBOSIS

See full prescribing information for complete boxed warning.

- Thrombosis may occur with immune globulin products, including XEMBIFY. 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. Thrombosis may occur in the absence of known risk factors.
- For patients at risk of thrombosis, administer XEMBIFY at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

### INDICATIONS AND USAGE

XEMBIFY (immune globulin subcutaneous, human- klhw) is a 20% immune globulin solution for subcutaneous injection indicated for treatment of Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older. (1)

### DOSAGE AND ADMINISTRATION

For subcutaneous infusion only.

Before switching to XEMBIFY, obtain the patient's serum IgG trough level to guide subsequent dose adjustments.

#### Dose (2.1)

- Switching from immune globulin intravenous (human), 10% (IVIG) to XEMBIFY: calculate the dose by using a dose adjustment factor (1.37)
- Weekly: Begin XEMBIFY one week after last IVIG infusion.
- Establish initial weekly dose by converting the monthly (or every 3 weeks) IVIG dose into an equivalent weekly dose and increasing it using a dose adjustment factor (1.37).

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

- Frequent dosing (2-7 times per week): Divide the calculated weekly dose by the desired number of times per week.
- Switching from immune globulin subcutaneous (human) treatment (IGSC): Weekly dose (grams) should be the same as the weekly dose of prior IGSC treatment (grams).

#### Administration (2.3)

Infusion sites: up to 6 infusion sites simultaneously, with at least 2 inches (5 cm) between sites avoiding bony prominences. Rotate sites for each administration.

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### DOSAGE FORMS AND STRENGTHS

XEMBIFY is a solution containing 0.2 g/mL (200 mg/mL; 20%) protein solution for subcutaneous infusion. (3)

### CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin or inactive ingredients of XEMBIFY such as polysorbate 80. (4)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4)

### WARNINGS AND PRECAUTIONS

- Hypersensitivity and anaphylactic reactions may occur. IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity or anaphylactic reactions. (5.1)
- Aseptic Meningitis Syndrome (AMS) may occur within two days of treatment. (5.3)
- Monitor for renal function in patients at risk for renal failure. (5.4)
- Hemolysis can develop. Risk factors include high doses and non-O blood group. Closely monitor for hemolysis and hemolytic anemia. (5.5)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]). (5.6)
- XEMBIFY is made from human plasma and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.7)
- Passive transfer of antibodies may confound serologic testing. (5.8)

### ADVERSE REACTIONS

The most common adverse reactions in  $\geq 5\%$  of subjects in the clinical trial were local adverse reactions including infusion site erythema (redness), infusion site pain, infusion site swelling (puffiness), infusion site bruising, infusion site nodule, infusion site pruritus (itching), infusion site induration (firmness), infusion site scab, infusion site edema, and systemic reactions including cough and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics at 1-800-520-2807 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

The passive transfer of antibodies may transiently interfere with the response to live virus vaccines, such as measles, mumps, rubella, and varicella. (7.2)

### USE IN SPECIFIC POPULATIONS

Geriatric: In patients over 65 years, do not exceed the recommended dose and infuse XEMBIFY at the minimum rate practicable. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2019

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: THROMBOSIS**

- 3 • **Thrombosis may occur with immune globulin products, including XEMBIFY. Risk**  
4 **factors may include: advanced age, prolonged immobilization, hypercoagulable**  
5 **conditions, history of venous or arterial thrombosis, use of estrogens, indwelling**  
6 **central vascular catheters, hyperviscosity, and cardiovascular risk factors.**  
7 **Thrombosis may occur in the absence of known risk factors. [see *Warnings and***  
8 ***Precautions (5.2), Patient Counseling Information (17)*]**
- 9 • **For patients at risk of thrombosis, administer XEMBIFY at the minimum dose and**  
10 **infusion rate practicable. Ensure adequate hydration in patients before**  
11 **administration. Monitor for signs and symptoms of thrombosis and assess blood**  
12 **viscosity in patients at risk for hyperviscosity. [see *Warnings and Precautions (5.2)*]**

13  
14 **1 INDICATIONS AND USAGE**

15 XEMBIFY (immune globulin subcutaneous, human – klhw) is a 20% immune globulin  
16 solution for subcutaneous injection indicated for treatment of primary humoral  
17 immunodeficiency (PI) in patients 2 years of age and older. This includes, but is not limited  
18 to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked  
19 agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined  
20 immunodeficiencies.<sup>1-4</sup>

21 **2 DOSAGE AND ADMINISTRATION**

22 **For subcutaneous infusion only.**

23 Before switching to XEMBIFY, obtain the patient's serum IgG trough level to guide  
24 subsequent dose adjustments.

25 **2.1 Dose**

26 Individualize the dose based on the patient's pharmacokinetic and clinical response.

27 Measure the patient's serum IgG trough level as early as 5 weeks after initiating XEMBIFY  
28 treatment to determine if a dose adjustment is needed.

29 Monitor the patient's IgG trough level every 2 to 3 months to determine subsequent dose  
30 adjustments and dosing intervals as needed (Table 1).

31 Doses divided over the course of a week or once weekly achieve similar exposure when  
32 administered regularly at steady-state.

33  
34 For frequent dosing (2-7 times per week), divide the calculated weekly dose by the desired  
35 number of times per week.

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

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

**Table 1: Adjustment ( $\pm$ mL) of the Weekly Subcutaneous Dose Based on the Difference ( $\pm$ 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).

45  
 46 Switching to XEMBIFY from IVIG

47 Begin treatment with XEMBIFY one week after the patient's last IVIG infusion.  
 48 Calculate the initial weekly dose of XEMBIFY. Divide the previous monthly (or every 3  
 49 weeks) IVIG dose in grams by the number of weeks between IVIG infusions, then multiply  
 50 this dose by the dose adjustment factor of 1.37.

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

51

52 To convert the XEMBIFY dose (in grams) to milliliters (mL), multiply the calculated Initial  
53 SC dose (in grams) by 5.

54

55 Provided the total weekly dose is maintained, any dosing interval from daily up to weekly  
56 will achieve similar systemic IgG exposure when administered regularly at steady-state.

57

58 Switching to XEMBIFY from subcutaneous immune globulin (IGSC)

59 Administer the same weekly dose of XEMBIFY (in grams) as the weekly dose of prior IGSC  
60 treatment (in grams).

61

## 62 **2.2 Preparation and Handling**

63 XEMBIFY is a clear to slightly opalescent, and colorless or pale yellow solution.

64

65 Visually inspect XEMBIFY for particulate matter and discoloration prior to administration,  
66 whenever solution and container permit.

67

68 Do not use if the solution is cloudy or turbid.

69

70 Do not shake.

71

72 Do not dilute.

73

74 The XEMBIFY vial is for single use only.

75

76 Do not store any vial that has been entered by a needle during preparation for infusion,  
77 punctured, partially used, or opened.

78

79 Administer within 8 hours after beginning infusion preparation (i.e., once XEMBIFY is  
80 transferred from the vial into a syringe).

81

82 Administer XEMBIFY separately from other drugs or medications that the patient may be  
83 receiving.

84

85 Do not mix XEMBIFY with other medications including immune globulins from other  
86 manufacturers.

87

88 Do not use after expiration date.

89

90 Discard unused portion.

91

## 92 **2.3 Administration**

### 93 **For subcutaneous infusion only.**

94 Prior to use, allow the solution to reach ambient room temperature.

95 Do not shake.

96 Follow the steps below and use aseptic technique to administer XEMBIFY.

97

98 1. Inspect the vials: inspect for clarity, color, and expiration date (s).

99

100 2. Prepare for infusion:

101

102 Gather supplies: XEMBIFY vial(s), ancillary supplies, sharps container, patient's  
103 treatment diary/logbook, and the infusion pump.

104

105 Prepare a clean work area.

106

107 Wash hands.

108

109 3. Remove the protective cap from the vial to expose the central portion of the stopper.


110 *If the packaging shows any sign of tampering, do not use the product and notify Grifols*

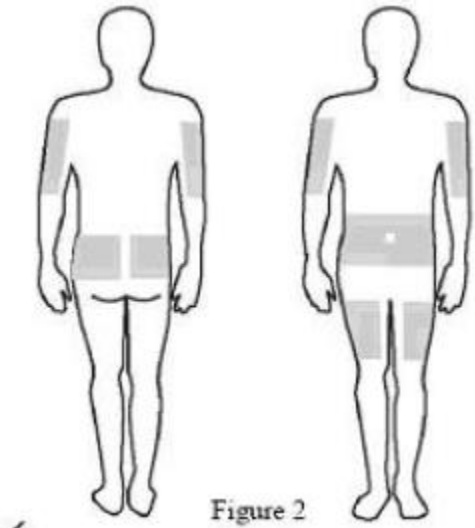


111 *Therapeutics LLC immediately [1-800-520-2807].*

112

113 4. Wipe the stopper with alcohol and allow to dry.

114

<p>5. 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)</p> <p>6. Use XEMBIFY as soon as practicable, within 2 hours to avoid the potential formation of particles caused by siliconized syringes.</p>	 <p>Figure 1</p>
<p>7. Follow the manufacturer's instructions for preparing the pump and administration tubing.</p>	

<p>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.</p>	 <p>Figure 2</p>
<p>8. Select the number and location of injection sites. Rotate sites for each administration. (Figure 2)</p> <p>Infuse XEMBIFY in the abdomen, thigh, upper arm, sides, back and/or lateral hip.</p> <p>Avoid bony areas, scars, areas of inflammation, superficial infection or blood vessels.</p>	
<p>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 2 inches (5cm) apart. (Figure 3)</p>	 <p>Figure 3</p>
<p>10. Grasp the skin between 2 fingers (pinch at least one inch (2.5cm) of skin) and insert the needle at a 90-degree angle into the subcutaneous tissue. (Figure 4)</p>	 <p>Figure 4</p>

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)

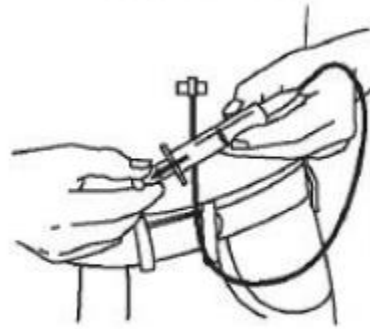


Figure 5

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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. Infuse XEMBIFY at a maximum rate of 25 mL per hour per infusion site using up to 6 infusion sites (most patients used 4 infusion sites). Ensure that the infusion sites are at least 2 inches (5 cm) apart for patients of all ages. The number of infusion sites is at healthcare provider discretion. Children will require less total volume for a specific XEMBIFY dose (mg/kg body weight) than adults. The healthcare provider may choose a smaller volume/site for children and/or fewer infusion sites to achieve the target total dose, depending on the needs of the child. The total dose volume of XEMBIFY is divided by the desired volume (mL/site) to obtain number of infusion sites to be used.

<u>Volume to be infused SC</u>	<u>Rate</u>	<u>Number of Sites (most frequent is 4)</u>	<u>Site Distance Apart</u>
25 mL per site	≤ 25 mL/hr/infusion site	≤ 6	≥ 2 inches (5 cm)

- 130  
131  
132  
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136  
137  
138  
139
- Record information about the infusion (e.g., lot number, expiration date, dose, date, time, infusion site location(s), side effects) in a patient treatment record or infusion log.
14. Discard the needle(s) and infusion line(s) in an appropriate container. Follow the manufacturer's instructions for storage of the infusion pump.
15. Discard partially used vial(s).

### 140 3 DOSAGE FORMS AND STRENGTHS

141 XEMBIFY is a protein solution containing 20% IgG (200 mg/ml; 0.2 g/ml) for subcutaneous  
142 infusion.



143 **4 CONTRAINDICATIONS**

144 XEMBIFY is contraindicated in:

145

146 Patients who have had an anaphylactic or severe systemic reaction to the administration of  
147 human immune globulin.

148

149 IgA deficient patients with antibodies against IgA and history of hypersensitivity to human  
150 immune globulin treatment.

151

152 **5 WARNINGS AND PRECAUTIONS**

153 **5.1 Hypersensitivity**

154 Severe hypersensitivity reactions may occur with human immune globulin products,  
155 including XEMBIFY. If a hypersensitivity reaction occurs, discontinue the XEMBIFY  
156 infusion immediately and institute appropriate treatment.

157 XEMBIFY contains IgA. Patients with known anti-IgA antibodies have a greater risk of  
158 developing potentially severe hypersensitivity and/or anaphylactic reactions. XEMBIFY is  
159 contraindicated in IgA deficient patients with antibodies against IgA and history of  
160 hypersensitivity to human immune globulin treatment. [*see Contraindications (4)*]

161 **5.2 Thrombosis**

162 Thrombosis may occur following treatment with immune globulin products, including  
163 XEMBIFY.<sup>5-7</sup> Risk factors may include: advanced age, prolonged immobilization,  
164 hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens,  
165 indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors.  
166 Thrombosis may occur in the absence of known risk factors.

167 Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity,  
168 including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols  
169 (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer  
170 XEMBIFY at the minimum dose and infusion rate practicable. Ensure adequate hydration in  
171 patients before administration. Monitor for signs and symptoms of thrombosis and assess  
172 blood viscosity in patients at risk for hyperviscosity. [*see Boxed Warning, Dosage and*  
173 *Administration (2.3), Patient Counseling Information (17)*]

174 **5.3 Aseptic Meningitis Syndrome (AMS)**

175 AMS has been reported with the use of human immune globulin administered intravenously  
176 and subcutaneously. It usually begins within several hours to 2 days following immune  
177 globulin treatment. AMS may occur more frequently in females than in males.

178 AMS is characterized by the following signs and symptoms: severe headache, nuchal  
179 rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting.

180 Cerebrospinal fluid (CSF) studies frequently show pleocytosis up to several thousand cells  
181 per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels  
182 up to several hundred mg/dL, but negative culture results. To rule out other causes of  
183 meningitis, conduct a thorough neurological examination on patients exhibiting such  
184 symptoms and signs, including CSF studies. AMS may occur more frequently in association  
185 with high doses ( $\geq 2$  g/kg) and/or rapid infusion of immune globulin products.  
186 Discontinuation of immune globulin treatment has resulted in remission of AMS within  
187 several days without sequelae.

## 188 **5.4 Renal Dysfunction/Failure**

189 Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy,  
190 osmotic nephrosis and death may occur upon use of human immune globulin products,  
191 especially those containing sucrose.<sup>8,9</sup> XEMBIFY does not contain sucrose. Ensure that  
192 patients are not volume depleted prior to administration of XEMBIFY.

193 In patients at risk of developing renal dysfunction, including patients with any degree of  
194 preexisting renal insufficiency or predisposition to acute renal failure (such as diabetes  
195 mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or patients  
196 receiving known nephrotoxic drugs), monitor renal function and consider lower, more  
197 frequent dosing. [*see Dosage and Administration (2.3)*]

198 Periodic monitoring of renal function and urine output is particularly important in patients  
199 judged to have a potential increased risk for developing acute renal failure. Assess renal  
200 function, including measurement of blood urea nitrogen (BUN)/serum creatinine, prior to the  
201 initial infusion of XEMBIFY and again at appropriate intervals thereafter. If renal function  
202 deteriorates, consider discontinuation of XEMBIFY. [*see Patient Counseling Information*  
203 *(17)*]

## 204 **5.5 Hemolysis**

205 IgG products, including XEMBIFY can contain blood group antibodies that may act as  
206 hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin,  
207 causing a positive direct antiglobulin (Coombs') test result and hemolysis.<sup>10-13</sup> Delayed  
208 hemolytic anemia can develop subsequent to human immune globulin therapy due to  
209 enhanced RBC sequestration, and acute hemolysis consistent with intravascular hemolysis  
210 has been reported. [*see Adverse Reactions (6)*]

211 Monitor XEMBIFY recipients for clinical signs and symptoms of hemolysis, particularly  
212 patients with risk factors such as non-O blood group, or patients receiving high IgG doses ( $\geq$   
213 2 grams/kg).<sup>14</sup> Underlying inflammatory state in an individual patient may increase the risk  
214 of hemolysis, but its role is uncertain.<sup>15</sup>

215 If signs and/or symptoms of hemolysis are present after XEMBIFY infusion, perform  
216 appropriate confirmatory laboratory testing.

## 217 **5.6 Transfusion-related Acute Lung Injury (TRALI)**

218 Noncardiogenic pulmonary edema may occur in patients following treatment with human  
219 immune globulin products.<sup>16</sup> TRALI is characterized by severe respiratory distress,  
220 pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms  
221 typically occur within 1 to 6 hours after treatment.

222 Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform  
223 appropriate tests for the presence of anti-neutrophil and anti-HLA antibodies in both the  
224 product and patient serum. TRALI may be managed using oxygen therapy with adequate  
225 ventilatory support.

## 226 **5.7 Transmissible Infectious Agents**

227 Because XEMBIFY is made from human blood, it may carry a risk of transmitting infectious  
228 agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically,  
229 the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging  
230 viruses and other pathogens. No cases of transmission of viral diseases or CJD have been  
231 associated with the use of XEMBIFY. ALL infections suspected by a physician to have  
232 possibly been transmitted by XEMBIFY should be reported by the physician or other  
233 healthcare provider to Grifols Therapeutics LLC [1-800-520-2807].

## 234 **5.8 Interference with Laboratory Tests**

235 After infusion with XEMBIFY, the transitory rise of various passively transferred antibodies  
236 in the patient's blood may yield false-positive serological testing results, with the potential  
237 for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g.,  
238 A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

## 239 **6 ADVERSE REACTIONS**

240 The most common adverse reactions in  $\geq 5\%$  of subjects in the clinical trial were local  
241 adverse reactions including infusion site erythema (redness), infusion site pain, infusion site  
242 swelling (puffiness), infusion site bruising, infusion site nodule, infusion site pruritus  
243 (itching), infusion site induration (firmness), infusion site scab, infusion site edema, and  
244 systemic reactions including cough and diarrhea.

### 245 **6.1 Clinical Trials Experience**

246 Because clinical studies are conducted under widely varying conditions, adverse reaction  
247 rates observed in the clinical trials of one drug cannot be directly compared to rates in other  
248 clinical trials of another drug and may not reflect the rates observed in clinical practice.

249 Clinical safety data are based on an open-label, single-arm prospective multi-center study of  
250 49 subjects with primary immunodeficiency (PI) who received subcutaneous XEMBIFY for  
251 at least 6 months.

252 A total of 49 subjects received 1053 XEMBIFY infusions, including 14 subjects between 2 to  
 253 16 years of age during the clinical trial. The average number of infusions per subject was  
 254 21.5 infusions, median 24 infusions (range 1-26 infusions). There were a total of 390 local  
 255 infusion site reactions which occurred at a rate per infusion of 0.370 (about 1 in 2.7  
 256 infusions). Of these, the most common was infusion site erythema which had a median  
 257 duration of 24.9 hours. Infusion site swelling, and infusion site pain had median durations of  
 258 24.5 and 22.8 hours, respectively. Local infusion site reactions of all kinds by site of infusion  
 259 (where site of infusion was recorded) occurred in 50.0% and 52.6% of patients during  
 260 infusions in the abdomen versus thigh, respectively, and across 773 abdominal infusions and  
 261 279 thigh infusions rates were 0.184 and 0.735 per infusion, respectively; this corresponds to  
 262 1 in 5.4 infusions (for abdomen) and 1 in 1.4 infusions (for thigh). No local infusion site  
 263 reactions were severe or serious.

264 The adverse reactions occurring in  $\geq 5\%$  of subjects on XEMBIFY in the clinical trial for the  
 265 duration of the subcutaneous (SC) phase are depicted in the table below which includes all  
 266 treatment-emergent adverse reactions except infections.

267  
 268

**Table 2: Adverse Reactions in  $\geq 5\%$  of Subjects During Infusions of XEMBIFY**

<b>Adverse Reaction*</b>	<b>By Subject n (%)<sup>†</sup> (N=49 subjects)</b>	<b>By Infusion n (rate)<sup>‡</sup> (N=1053 infusions)</b>
Infusion site erythema	19 (39%)	123 (0.117)
Infusion site pain	9 (18%)	32 (0.030)
Infusion site swelling	8 (16%)	124 (0.118)
Infusion site bruising	8 (16%)	26 (0.025)
Infusion site nodule	8 (16%)	13 (0.012)
Infusion site pruritus	5 (10%)	28 (0.027)
Infusion site induration	4 (8%)	6 (0.006)
Infusion site scab	3 (6%)	6 (0.006)
Infusion site edema	3 (6%)	5 (0.005)
Cough	3 (6%)	4 (0.004)
Diarrhea	3 (6%)	3 (0.003)

\* Including all adverse reactions that occurred after the first dose of XEMBIFY regardless of causality, excluding infections.

<sup>†</sup> Number and percentage of subjects with the adverse reaction.

<sup>‡</sup> Rate per infusion is calculated as the total number of adverse reactions divided by the total number of infusions.

269 Four subjects discontinued XEMBIFY due to adverse reactions which were infusion site  
 270 nodules, infusion site discomfort, skin papules/plaques, and arthralgia/myalgia.

271

272 **6.2 Postmarketing Experience**

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

276 The following adverse reactions have been identified and reported during the postmarketing  
277 use of immune globulin products administered subcutaneously:

278 Cardiac disorders: Tachycardia

279 Nervous system disorders: Tremor and paresthesia

280 Respiratory, thoracic and mediastinal disorders: Dyspnea and laryngospasm

281

282 **7 DRUG INTERACTIONS**

283 **7.1 Serological Testing**

284 Various passively transferred antibodies in immunoglobulin preparations, including  
285 XEMBIFY, can confound the results of serological testing.

286 **7.2 Live Attenuated Virus Vaccines**

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

291 **8 USE IN SPECIFIC POPULATIONS**

292 **8.1 Pregnancy**

293 **Risk Summary**

294 No human data are available to indicate the presence or absence of drug associated risk.  
295 Animal reproduction studies have not been conducted with XEMBIFY. It is not known  
296 whether XEMBIFY can cause fetal harm when administered to a pregnant woman or can  
297 affect reproduction capacity. Immune globulins cross the placenta from maternal circulation  
298 increasingly after 30 weeks of gestation. In the U.S. general population, the estimated  
299 background risk of major birth defect and miscarriage in clinically recognized pregnancies is  
300 2-4% and 15-20%, respectively.

301 **8.2 Lactation**

302 **Risk Summary**

303

304 No human data are available to indicate the presence or absence of drug associated risk. The  
305 developmental and health benefits of breastfeeding should be considered along with the

306 mother's clinical need for XEMBIFY and any potential adverse effects on the breastfed  
307 infant from XEMBIFY or from the underlying maternal condition.

#### 308 **8.4 Pediatric Use**

309 XEMBIFY was evaluated in 14 pediatric subjects with PI (2-16 years of age) in a multi-  
310 center clinical trial. The safety and efficacy profiles were similar to adult subjects. No  
311 pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

312 Safety and effectiveness of XEMBIFY in pediatric patients below 2 years of age have not  
313 been established.

#### 314 **8.5 Geriatric Use**

315 Clinical studies of XEMBIFY did not include sufficient numbers of subjects over age 65  
316 years to determine whether they respond differently from younger subjects. Three study  
317 subjects enrolled in the clinical trial were 65 years and older. In general, dose selection for  
318 an elderly patient should be cautious, usually starting at the low end of the dosing range,  
319 reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of  
320 concomitant disease or other drug therapy.

### 321 **11 DESCRIPTION**

322 XEMBIFY, immune globulin subcutaneous, human-klhw, is a 20% ready-to-use sterile, non-  
323 pyrogenic solution of human immune globulin protein for subcutaneous administration. The  
324 purity is  $\geq 98\%$  IgG with a sub-class distribution similar to that found in normal serum.

325 XEMBIFY consists of 18% to 22% protein in 0.16 M to 0.26 M glycine and 10 to 40 mcg/  
326 mL polysorbate 80 at a pH of 4.1 to 4.8. The solution is clear to slightly opalescent, and  
327 colorless or pale yellow. The osmolality range is 280 to 404 mOsmol/kg. XEMBIFY  
328 contains no preservative and is not made with natural rubber latex.

329 XEMBIFY is made from large pools of human plasma by a combination of cold ethanol  
330 fractionation, caprylate precipitation and filtration, and anion-exchange chromatography.  
331 Isotonicity is achieved by the addition of glycine. XEMBIFY is incubated in the final  
332 container (at the low pH of 4.1 to 4.8).

333 The capacity of the manufacturing process to remove and/or inactivate enveloped and non-  
334 enveloped viruses has been validated by laboratory spiking studies on a scaled down process  
335 model, using the following enveloped and non-enveloped viruses: human immunodeficiency  
336 virus, type I (HIV-1) as the relevant virus for HIV-1 and HIV-2; bovine viral diarrhea virus  
337 (BVDV) as a model for hepatitis C virus; pseudorabies virus (PRV) as a model for large  
338 enveloped DNA viruses (e.g. herpes viruses); West Nile Virus (WNV) as a relevant virus;  
339 Reovirus type 3 (Reo) as a model for non-enveloped viruses and for its resistance to physical  
340 and chemical inactivation; hepatitis A virus (HAV) as relevant non-enveloped virus, and  
341 porcine parvovirus (PPV) as a model for human parvovirus B19.

342 Overall virus clearance capacity was calculated only from steps that were mechanistically  
 343 independent from each other and truly additive. In addition, each step was verified to provide  
 344 robust virus reduction across the production range for key parameters.

**Table 3: Summary of Virus Clearance Capacity (Log<sub>10</sub>)**

Process Step	Enveloped Virus				Non-Enveloped Virus		
	HIV-1	BVDV	PRV	WNV	Reo3	HAV	PPV
Caprylate Precipitation/Depth Filtration	C/I*	2.7	C/I*	C/I*	≥3.5	≥3.6	4.0
Caprylate Incubation†	≥4.5	≥4.5	≥4.6	≥5.1	NA‡	NA‡	NA‡
Column Chromatography	≥3.0	4.0	≥3.3	ND§	≥4.0	≥1.4	4.2
Nanofiltration	≥3.7	≥4.1	ND§	ND§	≥1.8	ND§	0.5
Low pH Final Container Incubation	≥5.3	4.9	≥5.1	≥5.3	NA‡	NA‡	NA‡
<b>Overall Clearance Capacity</b>	<b>≥16.5</b>	<b>≥20.2</b>	<b>≥13.0</b>	<b>≥10.4</b>	<b>≥9.3</b>	<b>≥5.0</b>	<b>8.2</b>

\* C/I: Interference by caprylate precluded determination of virus clearance capacity for this step.

† DHBV and SINV were also evaluated for the caprylate incubation step. The log<sub>10</sub> clearance capacities were ≥3.6 and ≥6.0, respectively.

‡ NA = Not applicable: This step is not applicable to non-enveloped viruses.

§ Due to interfering effects of the process intermediate matrix the virus clearance capacity could not be determined.

345 Additionally, the manufacturing process was investigated for its capacity to decrease the  
 346 infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE),  
 347 considered as a model for the variant Creutzfeldt-Jakob disease (vCJD), and Creutzfeldt-  
 348 Jakob disease (CJD) agents.

349 Several of the individual production steps of the manufacturing process have been shown to  
 350 decrease TSE infectivity of an experimental model agent. TSE reduction steps include depth  
 351 filtrations (a total of ≥ 6.6 log<sub>10</sub>). These studies provide reasonable assurance that low levels  
 352 of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

## 353 12 CLINICAL PHARMACOLOGY

### 354 12.1 Mechanism of Action

355 XEMBIFY supplies a broad spectrum of opsonizing and neutralizing immunoglobulin G  
 356 (IgG) antibodies against bacterial, viral, parasitic, and mycoplasmal agents and their toxins.  
 357 XEMBIFY also contains a spectrum of antibodies capable of interacting with and altering the  
 358 activity of cells of the immune system. The role of these antibodies and the mechanism of  
 359 action of XEMBIFY are not fully understood.

### 360 12.2 Pharmacodynamics

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

363 present in the normal population. XEMBIFY has a distribution of IgG subclasses closely  
 364 proportional to that in native human plasma. Adequate doses of XEMBIFY may restore  
 365 abnormally low IgG levels to the normal range.

### 366 12.3 Pharmacokinetics

367 Pharmacokinetic (PK) parameters of subcutaneously administered XEMBIFY were evaluated  
 368 in subjects with primary immunodeficiency (PI) during a clinical trial. [see *Clinical Studies*  
 369 (14)] Subjects were treated intravenously with a comparator product [GAMUNEX-C,  
 370 immune globulin injection (human), 10% caprylate/chromatography purified] during a 3-4  
 371 months run-in period prior to IV PK profiling in 50 subjects, and then 49 subjects switched to  
 372 weekly subcutaneous infusions of XEMBIFY for 24 weeks at 137% of the intravenous dose  
 373 with PK profiling at SC Week #13-14. A comparison of the area under the curve (AUC) for  
 374 subcutaneous versus intravenous infusion was performed.

375 At this dose adjustment, the geometric least-squares means ratio of the AUC for  
 376 subcutaneous XEMBIFY versus IV administration of GAMUNEX-C was 104% (90% CI:  
 377 100%-107%). The peak IgG level occurred at a mean of 76 hours after subcutaneous  
 378 XEMBIFY administration. The average mean IgG trough level at steady state was higher  
 379 with XEMBIFY (1245 mg/dL) compared with IV GAMUNEX-C (957 mg/dL) (average  
 380 mean trough ratio SC/IV of 1.3). PK parameters of XEMBIFY are summarized in Table 4.  
 381 PK parameters did not significantly differ between age groups (Table 5).

382 **Table 4: PK Parameters of Total IgG at Steady-State in IV and SC Phases (PK**  
 383 **Population) in children and adults**

Phase	Statistics	AUC <sub>(0-7 days)</sub> (h*mg/mL)*	C <sub>max</sub> (mg/mL)	t <sub>max</sub> (hour)
IV	n	49	49	49
	Mean±SD	2122±418	22±4	5.814
	CV%	20	20	
SC	n	39	41	41
	Mean±SD	2183±481	14±3	76±36
	CV%	22	22	47
	Min, Max	1027, 3675	6, 23	0, 168†

\* AUC<sub>(0-7 days)</sub> in the IV Phase is calculated as AUC<sub>(0-21 days)</sub>/3 for subjects on an every-3-week IV dosing schedule (n=6), and as AUC<sub>(0-28 days)</sub>/4 for subjects on an every-4-week IV dosing schedule (n=43).

† The apparent variability in t<sub>max</sub> in the SC Phase can be attributed to the low fluctuation in IgG concentrations and is unlikely to be of any clinical relevance.

384



**Table 5: Steady-State PK Parameters for XEMBIFY by Age**

Age Group (years)	Statistics	AUC <sub>(0-7 days)</sub> (h*mg/mL)	C <sub>max</sub> (mg/mL)	Mean Trough (mg/mL)	t <sub>max</sub> (hour)
2-5 (n)		1	1	1	1
	Mean±SD	1839±NC*	11±NC*	11± NC*	72±NC*
>5-12 (n)		5	5	6	5
	Mean±SD	2156±276	14±2	12±2	71 ±26
	CV%	13	13	15.3	37.16
	Min, Max	1878, 2456	12, 16	10, 15	28.2, 100.8
>12-16 (n)		4	5	5	5
	Mean±SD	2400±406	15±3	14±2	73 ±50
	CV%	17	18	15.2	68.44
	Min, Max	2056, 2987	13, 20	11, 17	23.7, 143.1
>16 (n)		29	30	32	30
	Mean±SD	2170±524	14±3	12±3	78 ±36
	CV%	24	24	23.9	46.66
	Min, Max	1027, 3675	6, 23	7, 20	0.00, 167.7

\* NC = Not calculated

## 385 13 NONCLINICAL TOXICOLOGY

### 386 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

### 389 13.2 Animal Toxicology and/or Pharmacology

390 Single and repeated dose toxicology studies were conducted in male New Zealand White  
391 rabbits. In a single-dose toxicity study, no adverse effects were observed with subcutaneous  
392 dose levels of 500, 1000 and 1500 mg/kg. In a repeated-dose toxicity study, the systemic  
393 safety and toxicity profiles of XEMBIFY and comparator GAMUNEX-C were similar  
394 following 5 consecutive daily subcutaneous doses at levels of 500, 1000 and 1500  
395 mg/kg/day. Transient local injection site swelling was observed in XEMBIFY but not in the  
396 GAMUNEX-C groups.

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

## 402 14 CLINICAL STUDIES

403 Study 1 was a prospective, open-label single-arm, multi-center clinical trial designed to  
404 evaluate pharmacokinetics and safety of XEMBIFY as compared to GAMUNEX-C. Efficacy  
405 was based on annualized serious bacterial infection (SBI) rate during the 6 months on

406 XEMBIFY. The GAMUNEX-C run-in phase prior to XEMBIFY (subcutaneous phase)  
 407 lasted 3 or 4 months to achieve steady state prior to pharmacokinetic profiling. The definition  
 408 of SBI was either bacteremia/sepsis, bacterial meningitis, bacterial pneumonia,  
 409 osteomyelitis/septic arthritis, or visceral abscess.

410 This clinical trial determined the safety and pharmacokinetics of XEMBIFY in 53 adult and  
 411 pediatric subjects with PI (9.4% Hispanic or Latino; 90.6% White, 3.8% Black or African  
 412 American, 5.7% American Indian or Alaskan Native). During the run-in and IV  
 413 GAMUNEX-C phases 4 subjects discontinued (1 lost to follow-up, 2 withdrawal by subject,  
 414 1 adverse event). XEMBIFY was administered to a total of 49 subjects (14 children aged 2 to  
 415 ≤ 16 years and 35 adults) with a mean ± SD dose of 179 ± 45 mg/kg/week for a median  
 416 treatment duration of 24 weeks and mean ± SD of 21.6 ± 6.5 weeks. The median dose was  
 417 171 mg/kg/week and the range of doses was 71 mg/kg/week to 276 mg/kg/week. The total  
 418 exposure of XEMBIFY was 20.28 subject-years and 1053 infusions.

419 Study 2 is an ongoing study in which XEMBIFY is being administered for 1 year and is  
 420 being conducted in the European Union and Australia. A total of 61 subjects including 29  
 421 children were enrolled. The interim safety data in adult and pediatric study subjects appear  
 422 consistent with the safety results of the clinical trial in Study 1.

423 The rate of serious bacterial infections (SBIs) which was an exploratory endpoint in Study 1,  
 424 was 0.05 events per subject-year (1 event in 20 subject-years) (upper 99% confidence limit:  
 425 0.11) during XEMBIFY treatment. This annual rate was lower than 1.0 SBI/subject-year, the  
 426 threshold specified as effective.

427 The summary of infections and associated events for subjects during subcutaneous treatment  
 428 with XEMBIFY is summarized in Table 6.  
 429

**Table 6: Summary of Infections and Associated Events on XEMBIFY in Study 1**

<b>Parameters</b>	<b>Results</b>
Number of Subjects (efficacy period)	49
Total number of subject days on treatment	7,407
Total number of subject-years on treatment	20.28
<u>Infections</u>	
Annual rate of SBIs* (per subject-year)	0.05 (95% CI: 0.02 - 0.10)
Annual rate of infections of any kind (per subject-year)	2.4 (95% CI: 1.6 - 3.3)
Days on antibiotics (prophylactic) (rate per subject-year)	27.7 (95% CI: 13.6 - 49.0)
Days on antibiotics (therapeutic) (rate per subject-year)	28.9 (95% CI: 17.3 - 44.8)

Days missed work/school/unable to perform normal daily activities due to infections (rate per subject-year)	2.3 (95% CI: 1.1 - 4.2)
Hospitalizations due to infections (rate per subject-year)	0.05 (95% CI: 0.02 - 0.10)

\* Serious bacterial infections included bacteremia/sepsis, bacterial meningitis, bacterial pneumonia, osteomyelitis/septic arthritis, or visceral abscess.

## 430 15 REFERENCES

- 431 1. Buckley RH, Schiff RI. The use of intravenous immune globulin in immunodeficiency  
432 diseases. *N Engl J Med* 1991;325(2):110-7.
- 433 2. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and  
434 immunological features of 248 patients. *Clin Immunol* 1999;92(1):34-48.
- 435 3. Pruzanski W, Sussman G, Dorian W, et al. Relationship of the dose of intravenous  
436 gammaglobulin to the prevention of infections in adults with common variable  
437 immunodeficiency. *Inflammation* 1996;20(4):353-9.
- 438 4. Stephan JL, Vlekova V, Le Deist F, et al. Severe combined immunodeficiency: a  
439 retrospective single-center study of clinical presentation and outcome in 117 patients. *J*  
440 *Pediatr* 1993;123(4):564-72.
- 441 5. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of  
442 precipitating thromboembolic events. *Neurology* 1994;44:223-6.
- 443 6. Woodruff RK, Grigg AP, Firkin FC, et al. Fatal thrombotic events during treatment of  
444 autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients.  
445 *Lancet* 1986;2:217-8.
- 446 7. Wolberg AS, Kon RH, Monroe DM, et al. Coagulation factor XI is a contaminant in  
447 intravenous immunoglobulin preparations. *Am J Hematol* 2000;65:30-4.
- 448 8. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune  
449 globulin therapy: a report of two cases and an analysis of the literature. *J Am Soc*  
450 *Nephrol* 1997;8(11):1788-94.
- 451 9. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Trans*  
452 *Med Rev* 2003;17:241-51.
- 453 10. Copelan EA, Strohm PL, Kennedy MS, et al. Hemolysis following intravenous immune  
454 globulin therapy. *Transfusion* 1986;26:410-2.
- 455 11. Thomas MJ, Misbah SA, Chapel HM, et al. Hemolysis after high-dose intravenous Ig.  
456 *Blood* 1993;15:3789.

457 12. Wilson JR, Bhoopalam N, Fisher M. Hemolytic anemia associated with intravenous  
458 immunoglobulin. *Muscle & Nerve* 1997;20:1142-5.

459 13. Kessary-Shoham H, Levy Y, Shoenfeld Y, et al. In vivo administration of intravenous  
460 immunoglobulin (IVIg) can lead to enhanced erythrocyte sequestration. *J Autoimmun*  
461 1999;13:129-35.

462 14. Kahwaji J, Barker E, Pepkowitz S, et al. Acute hemolysis after high-dose intravenous  
463 immunoglobulin therapy in highly HLA sensitized patients. *Clin J Am Soc Nephrol*  
464 2009;4:1993-7.

465 15. Daw Z, Padmore R, Neurath D, et al. Hemolytic transfusion reactions after administration  
466 of intravenous immune (gamma) globulin: A case series analysis. *Transfusion*  
467 2008;48:1598-601.

468 16. Rizk A, Gorson KC, Kenney L, et al. Transfusion-related acute lung injury after the  
469 infusion of IVIG. *Transfusion* 2001;41:264-8.

470 **16 HOW SUPPLIED/STORAGE AND HANDLING**

471 XEMBIFY is supplied in 1, 2, 4, and 10 gram single use vials.

<b>Package NDC Number</b>	<b>Container NDC Number</b>	<b>Size</b>	<b>Gram Protein</b>
13533-810-05	13533-810-06	5 ml	1
13533-810-10	13533-810-11	10 ml	2
13533-810-20	13533-810-21	20 ml	4
13533-810-50	13533-810-51	50 ml	10

472  
473 Components used in the packaging are not made with natural rubber latex and contains no  
474 preservative.

475  
476 Store XEMBIFY at 2–8°C (36–46°F).  
477 Note: XEMBIFY may be stored at temperatures not to exceed 25°C (77°F) for up to 6  
478 months any time prior to the expiration date. Following 25°C (77°F) storage, use the  
479 product immediately or discard.

480  
481 Do not freeze.

482  
483 Do not use solutions that have been frozen.

484  
485 Do not use after expiration date.

486  
487 Discard unused portion.

488

489 **17 PATIENT COUNSELING INFORMATION**

490 Advise the patient to read the FDA-approved patient labeling (Information for Patients).

491 Ask about a history of IgA deficiency, and hypersensitivity reactions to immune globulin  
492 treatment. [see *Warnings and Precautions (5.1)*]

493 Inform patients to immediately report the following signs and symptoms to their healthcare  
494 provider: [see *Boxed Warning and Warnings and Precautions*]

495 Hypersensitivity reaction including hives, generalized urticaria, tightness of the chest,  
496 wheezing, low blood pressure, and anaphylaxis. [see *Warnings and Precautions (5.1)*]

497  
498 Symptoms of thrombosis which may include: pain and/or swelling of an arm or leg with  
499 warmth over the affected area, discoloration of an arm or leg, unexplained shortness of  
500 breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse,  
501 numbness or weakness on one side of the body [see *Warnings and Precautions (5.2)*]

502  
503 Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye  
504 movements, nausea, and vomiting [see *Warnings and Precautions (5.3)*]

505  
506 Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath  
507 [see *Warnings and Precautions (5.4)*]

508  
509 Increased heart rate, fatigue, yellowing of the skin or eyes, and dark-colored urine [see  
510 *Warnings and Precautions (5.5)*]

511  
512 Trouble breathing, chest pain, blue lips or extremities, and fever [see *Warnings and*  
513 *Precautions (5.6)*]

514  
515 Inform patients/caregivers that because XEMBIFY is made from human blood, it may carry a  
516 risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease  
517 (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. [see *Warnings*  
518 *and Precautions (5.7)*]

519 Inform patients that XEMBIFY can interfere with their immune response to live virus  
520 vaccines such as measles, mumps, rubella, and varicella. Inform patients to notify their  
521 healthcare provider of this potential interaction when they are receiving vaccinations. [see  
522 *Drug Interactions (7.2)*]

523 **Self-administration**

524 Advise the patient to read the FDA-approved patient labeling (Information for Patients).

525 If self-administration is deemed appropriate by the healthcare provider, provide clear instructions  
526 and training on subcutaneous infusion to the patient/caregiver, and document demonstration of  
527 their ability to independently administer subcutaneous infusions.

528

529 Ensure the patient/caregiver understands the importance of consistent subcutaneous infusions  
530 to maintain appropriate steady IgG levels.

531

532 Tell the patient/caregiver to start the infusion promptly after withdrawing XEMBIFY into the  
533 syringe. Ensure the patient/caregiver understands that administration should be completed  
534 within 2 hours to avoid the potential formation of particles caused by siliconized syringes.

535

536 Instruct patient to rotate infusion sites for subsequent infusions.

537

538 Instruct the patient/caregiver to keep a treatment diary/log book. This diary/log book should  
539 include information about each infusion such as, the time, date, dose, lot number(s), infusion  
540 sites, and any reactions.

541

542 Inform the patient that mild to moderate local infusion site reactions (e.g., pain, redness and  
543 itching) are a common side effect of subcutaneous treatment, but to contact their healthcare  
544 provider if a local reaction increases in severity or persists for more than a few days.

545

546 Instruct patient to return to the healthcare facility for evaluation at regular intervals so IgG  
547 levels can be checked in order to ensure IgG trough levels are adequate.

548

549 **Manufactured by:**

550

551 **GRIFOLS**

552 **Grifols Therapeutics LLC**

553 Research Triangle Park, NC 27709 USA

554 U.S. License No. 1871

555

## INFORMATION FOR PATIENTS

556

### XEMBIFY

557

#### (immune globulin subcutaneous, human-klhw) 20% solution

558

The following summarizes important information about XEMBIFY (zem-ba-fi). Please read  
559 this information carefully before using this medicine. This patient information does not take  
560 the place of talking with your healthcare provider about your medical condition or your  
561 treatment, and it does not include all of the important information about XEMBIFY. If you  
562 have any questions after reading this, contact your healthcare provider.

563

#### **What is XEMBIFY?**

564

XEMBIFY is a ready-to-use, liquid medicine that contains immunoglobulin G (IgG)  
565 antibodies, which protect the body against infection. XEMBIFY is used to treat patients with  
566 primary immunodeficiency disease (PI).

567

There are many forms of PI. The most common types of PI result in an inability to make a  
568 very important type of protein called antibodies, which help the body fight off infections  
569 from bacteria or viruses. XEMBIFY is made from human plasma that is donated by healthy  
570 people. It contains antibodies collected from these healthy people that replace the missing  
571 antibodies in PI patients.

572

#### **Who should NOT use XEMBIFY?**

573

Do not use XEMBIFY if you have a known history of severe allergic reaction to immune  
574 globulin (human) or other blood products. If you have such a history, discuss this with your  
575 healthcare provider to determine if XEMBIFY is right for you.

576

Tell your healthcare provider if you have or ever had:

577

- a serious reaction to other medicines that contain immune globulin.

578

- an immunoglobulin A (IgA) deficiency.

579

- a history of heart or blood vessel disease.

580

- blood clots or “thick blood”.

581

- inability to move for some time.

582

#### **How should I take XEMBIFY?**

583

XEMBIFY is given under the skin (subcutaneously). Most of the time, infusions under the  
584 skin are given at home by self-infusion or by infusion with a caregiver’s help. Self-infusion is  
585 different from giving yourself a shot.

586 Instructions for taking XEMBIFY are at the end of this patient information [see "Instructions  
587 for Use"]. Only use XEMBIFY by yourself after you have been instructed by your healthcare  
588 provider.

589 **What should I tell my healthcare provider before using XEMBIFY?**

590 Tell your healthcare provider if you have had a serious reaction to other medicines that  
591 contain immune globulin. Also tell your healthcare provider if you have an immunoglobulin  
592 A (IgA) deficiency.

593 XEMBIFY can make certain types of vaccines (like measles/mumps/rubella or chickenpox)  
594 not work as well for you. Before you get a vaccine, tell the healthcare provider that you are  
595 taking XEMBIFY.

596 Tell your healthcare provider if you are pregnant or plan to become pregnant, or if you are  
597 nursing.

598 **What are possible or reasonably likely side effects of XEMBIFY?**

599 The most common side effects with XEMBIFY are:

600       Infusion site reactions, including but not limited to  
601           infusion site erythema (redness)  
602           infusion site pain  
603           infusion site swelling (puffiness)  
604           infusion site bruising  
605           infusion site nodule  
606           infusion site pruritus (itching)  
607           infusion site induration (firmness)  
608           infusion site scab  
609           infusion site edema

610       Cough  
611       Diarrhea

612  
613 If any of the following problems occur after starting treatment with XEMBIFY, stop the  
614 infusion immediately and contact your healthcare provider or call emergency services. These  
615 could be signs of a serious problem.

616 Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting or  
617 dizziness. These could be signs of a serious allergic reaction.

618  
619 Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light. These could be  
620 signs of irritation of the lining around your brain.

621  
622 Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a  
623 kidney problem.

624



625 Pain, swelling, warmth, redness, or a lump in your legs or arms. These could be signs of a  
626 blood clot.  
627  
628 Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a liver  
629 problem or a blood problem.  
630  
631 Chest pain or trouble breathing, or blue lips or extremities. These could be signs of a serious  
632 heart or lung problem.  
633  
634 Severe headache, stiff neck, fatigue, fever, sensitivity to light, painful eye movements,  
635 nausea and vomiting. These could be signs of a type of brain inflammation called aseptic  
636 meningitis.  
637  
638 Fever over 100°F (37.8°C). This could be a sign of an infection.  
639  
640 Tell your healthcare provider about any side effects that concern you. You can ask your  
641 healthcare provider to give you the full prescribing information available to healthcare  
642 providers. You are encouraged to report side effects to Grifols Therapeutics LLC [1-800-  
643 520-2807].

644 How do I store XEMBIFY?

645 XEMBIFY comes in single use vials.

646       • Keep XEMBIFY refrigerated. Do not freeze.

647       • If needed, you can store XEMBIFY at room temperature for up to 6 months, but  
648       you must use it within that time or you must throw it away.

649       • Do not return XEMBIFY to the refrigerator if it was warmed to room  
650       temperature.

651       • Check the expiration date on the carton and vial label.

652       • Do not use XEMBIFY after the expiration date.

653 What else should I know about XEMBIFY?

654 Do not use XEMBIFY for a medical condition for which it was not prescribed. Do not share  
655 XEMBIFY with other people, even if they have the same diagnosis and symptoms that you  
656 have.

657

658

## INSTRUCTIONS FOR USE

659 Infuse XEMBIFY only after you have been trained by your healthcare provider. Below are  
660 step-by-step instructions to help you remember how to use XEMBIFY. Ask your healthcare  
661 provider about any instructions you do not understand.

### 662 **Before Using XEMBIFY**

663

664 Prior to use, allow the solution to come to room temperature (68-77°F or 20-25°C). This can  
665 take 60 minutes or longer.

666

667 Do not apply heat or place in the microwave.

668

#### 669 Step 1: Assemble supplies

670

671 Gather the XEMBIFY vial(s), ancillary supplies, sharps container, patient's treatment  
672 diary/logbook, and the infusion pump.

673

#### 674 Step 2: Clean surface

675

676 Set up your infusion area on a clean, flat, non-porous surface, such as a kitchen counter.

677

678 Avoid using porous surfaces such as wood. Clean the surface with an alcohol wipe using a  
679 circular motion from the center outward.

680

#### 681 Step 3: Wash hands

682

683 Wash and dry your hands thoroughly before using XEMBIFY.

684

685 Your healthcare provider may recommend that you use antibacterial soap or that you wear  
686 gloves.



687

688

#### 689 Step 4: Check vials

690

691 The liquid in the vial should be clear to slightly opalescent, and colorless or pale yellow.

692

693 Do not use the vial if:

694

- 695
- 696
- the solution is cloudy or discolored. The solution should be clear to slightly opalescent, and colorless or pale yellow.
- 697
- the protective cap is missing, or there is any evidence of tampering. Tell your healthcare provider immediately.
- 698
- the expiration date has passed.
- 699

700

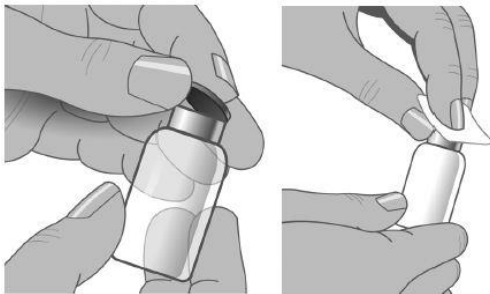
701 Step 5: Remove the protective cap

702 Remove the protective cap from the vial to expose the middle of the stopper.

703

704 Wipe the stopper with alcohol and allow to dry.

705



706

707 Step 6: Transfer XEMBIFY from vial(s) to syringe

708

709 Do not allow your fingers or other objects to touch the inner stem of the plunger, the syringe tip, or other areas that can touch the XEMBIFY solution. Make sure needles are capped until used and that needles and syringes stay on the clean area created in Step 2. This is called

710

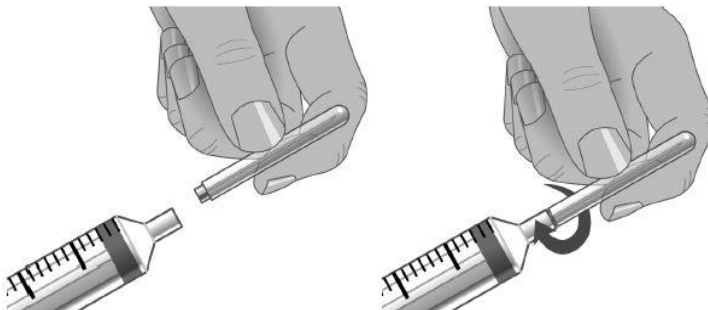
711 “aseptic technique” to prevent germs from getting into the XEMBIFY.

712

713

714 Using aseptic technique, attach each needle to the syringe tip.

715



716

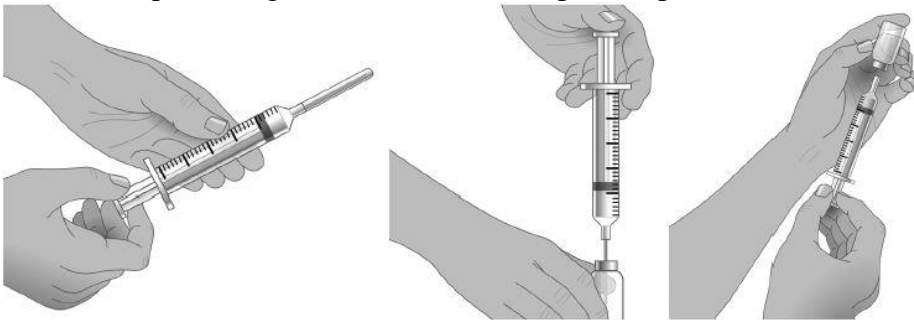
717

718 Step 7: Prepare the syringe and draw XEMBIFY solution into syringe

719 Remove cap from needle.

720

721 Pull the syringe plunger back to the level matching the amount of XEMBIFY to be  
722 withdrawn from the vial.  
723  
724 Place the XEMBIFY vial on a clean flat surface and insert the needle into the center of the  
725 vial stopper.  
726  
727 Inject air into the vial. The amount of air should match the amount of XEMBIFY to be  
728 withdrawn.  
729  
730 Turn the vial upside down and withdraw the correct amount of XEMBIFY. If multiple  
731 vials are required to get the correct dose, repeat Step 4.



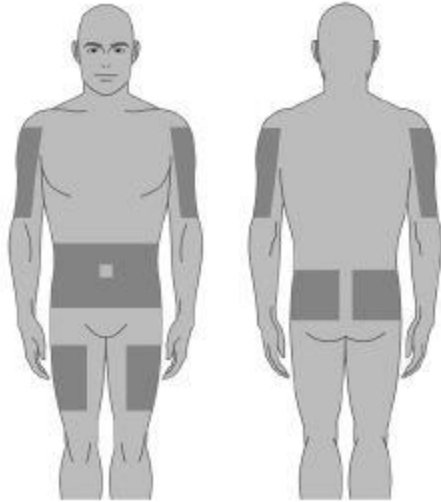
732  
733 Step 8: Fill the pump reservoir and prepare the infusion pump

734 Follow the pump manufacturer's instructions for filling the pump reservoir and preparing the  
735 infusion pump, administration tubing and Y-site connection tubing, if needed.

736  
737 Prime the administration tubing with XEMBIFY to take out any air left in the tubing or  
738 needle. To prime, hold the syringe in one hand and the administration tubing's capped needle  
739 in the other. Gently squeeze on the plunger until you see a drop of XEMBIFY come out of  
740 the needle.

741  
742 Step 9: Select the number and location of infusion sites

743 Select one or more infusion sites as directed by your healthcare provider.  
744 The number and location of injection sites depends on the volume of the total dose.  
745  
746 Avoid: bony areas, visible blood vessels, scars, and any areas of inflammation (irritation) or  
747 infection.  
748  
749 Rotate sites between future infusions.  
750



751  
752

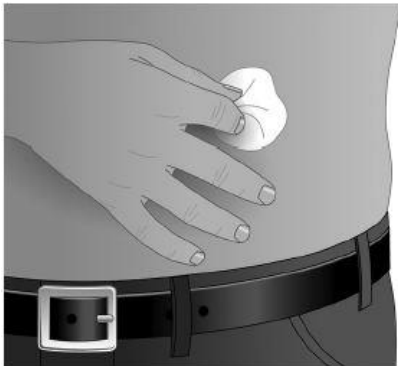
753 Step 10: Prepare the infusion site

754 Wipe the infusion site(s) with a sterile alcohol wipe beginning at the center of each infusion  
755 site and moving outward in circular motion. Allow the infusion site(s) to dry (at least 30  
756 seconds).

757

758 Before infusion, sites should be clean, dry, and at least 2 inches (5cm) apart.

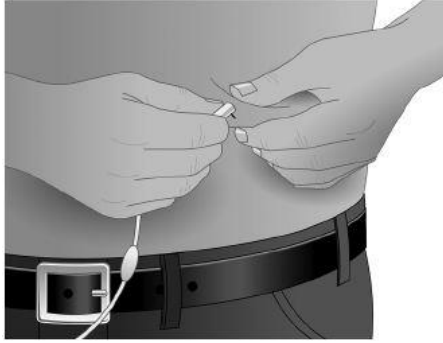
759



760  
761

762 Step 11: Insert the needle

763 Grasp the skin between two fingers (pinch at least 1 inch (2.5 cm) of skin) and insert the  
764 needle at a 90-degree angle into the tissue underneath the skin or subcutaneous tissue.



765  
766

767 Step 12: Make sure the needle is not in a blood vessel

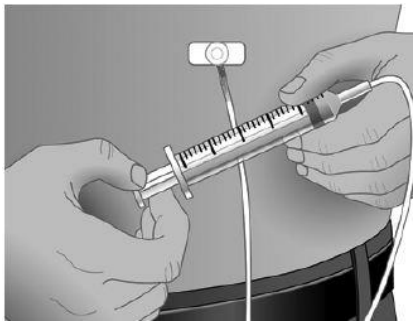
768

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

773

774 If you see any blood, remove and discard the needle and administration tubing.

775



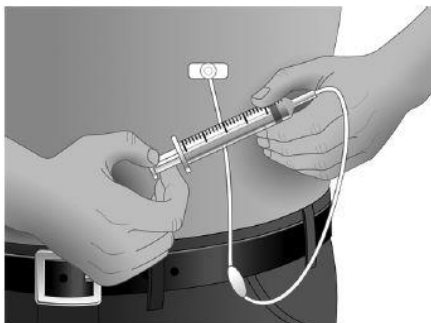
776  
777

778 Repeat priming and needle insertion steps using a new needle, administration tubing and a  
779 new infusion site.

780

781 Secure the needle in place by applying sterile gauze or transparent dressing over the site.

782



783  
784

785 Step 13: Repeat for other sites, as needed

786 Step 14: Infuse XEMBIFY

787

788 Infuse XEMBIFY as soon as possible after it is prepared.

789

790 Follow the pump manufacturer's instructions for filling the tubing and using the infusion  
791 pump.

792

793 Step 15: After infusion

794

795 Follow manufacturer's instructions to turn off pump.

796

797 Undo and discard any dressing or tape.

798

799 Gently remove the inserted needle(s) or catheter(s).

800

801 Discard any unused solution in an appropriate waste container as instructed.

802

803 Discard any used administration equipment in an appropriate waste container.

804

805 Store your supplies in a safe place.

806

807 Follow manufacturer's instructions to care for the infusion pump.

808

809 Step 16: Record each infusion

810 Remove the peel-off label with the product lot number from the XEMBIFY vial and use this  
811 to complete the patient record. Include information about each infusion such as: the time,  
812 date, dose, lot number(s), infusion sites, and any reactions.

813

814 Remember to bring your journal with you when you visit your healthcare provider. Your  
815 healthcare provider may ask to see your treatment diary/logbook.

816

817 Tell your healthcare provider about any problems you have during your infusions. Call your  
818 healthcare provider for medical advice about side effects. You can also report side effects to  
819 FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

820 **Manufactured by:**

821 **GRIFOLS**

822 **Grifols Therapeutics LLC**

823 Research Triangle Park, NC 27709 USA

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