Immunoglobulins

CONSIDERATIONS FOR THE CLINICAL PRACTICE



GRIFOLS

Immunoglobulins

CONSIDERATIONS FOR THE CLINICAL PRACTICE[1,2]

As more immunoglobulin (IG) products become available, it becomes increasingly difficult to choose which attributes should guide treatment decisions.

Considerations as to route of administration as well as indications further help inform the decision, but do not always determine the best choice for individual patients, since idiosyncratic and personal differences in tolerability to a particular product exist.

Therefore, when selecting a specific product, it is important to consider that manufacturing processes, final formulations, and product compositions differ widely among IG products. Multiple product features, which may affect tolerability, should be taken into account when selecting a specific brand:

- Increased sodium concentrations may be associated with a higher incidence of cardiovascular adverse events and thromboembolic complications
- Sugar content has been associated with adverse events, especially renal failure and insufficiency. Products that contain sugar may also disrupt glucose control or glucose readings in diabetic patients
- Osmolality is an important concern as hyperosmotic solutions have been implicated in thrombotic complications

How the differences in products affect outcomes is not well-defined. Unfortunately, very few comparative studies exist, and choices are often based on product attributes alone.

TABLE 1 ■ PRODUCT PROPERTIES CONSIDERATIONS[2-7]

	Product	Company	Indications	Gamma Globulin Content (%)	Monomers (%)	Half-life (days)	IgA Content (µg/mL)	IgM Content	pH	Sodium Content	Stabilizer	Osmolality/Osmolarity (mOsm/kg)
INTRAVENOUS	**Flebogamma 5% DIF**	Grifols	PIDD	≥99	>99.96	32±5 (4-week dosing)	<3.1	Trace	5.6±0.1	Trace (<3.2 mEq/L)	5% sorbitol (polyol)	325±4.8
	Flebogamma 10% DIF	Grifols	ITP, PIDD	≥99	>99.87	37±13 (4-week dosing)	<3.1	Trace	5.5±0.1	Trace (<3.2 mEq/L)	5% sorbitol (polyol)	343±6.4
	GAMUNEX-C 10%	Grifols	CIDP, ITP, PIDD	100	100 monomers + dimers	35	46	Trace	4.0-4.5	Trace (<7 mEq/L)	Glycine	258
	Privigen 10%	CSL Behring	CIDP, ITP, PIDD	≥98	≥98 monomers + dimers	36.6	≤25	3 mg/L	4.6-5.0	Trace	Proline	240-440
	Gammagard Liquid 10%	Takeda	MMN, PIDD	≥98	≥95 monomers + dimers	35	37	Trace	4.9-5.2	No sodium added	Glycine	240-300
	Gammagard S/D 5%	Takeda	CLL, ITP, KD, PIDD	≥90	96.4	37.7±15	<1	Trace	6.4-7.2	146 mEq/mL	2% glucose, glycine	636 mOsm/L (5%); 1250 mOsm/L (10%)
	Octagam 5%	Octapharma	PIDD	≥96	≥90 monomers + dimers	40	<200	≤0.1 mg/mL	5.1-6.0	≤30 mmol/L	10% Maltose	310-380
	Octagam 10%	Octapharma	ITP	≥96	≥94 monomers + dimers	36-40	106	<106 µg/mL	4.5-5.0	≤30 mmol/L	Maltose (90 mg/mL)	310-380
	Gammaked 10%	Kedrion (manufactured by Grifols)	CIDP, ITP, PIDD	100	100 monomers + dimers	35	46	Trace	4.0-4.5	Trace (<7 mEq/L)	Glycine	258
	Gammaplex 5%	BPL	ITP, PIDD	>99	≥99 monomers + dimers	41±14 (4-week dosing)	<10	<0.1 mg/mL	4.8-5.1	30-50 mM	Sorbitol and glycine, Polysorbate 80	420-500, but not <240
	Gammaplex 10%	BPL	ITP, PIDD	>99	99.7-100 monomers + dimers	34.8 (4-week dosing)	<20	<0.1 mg/mL	4.9-5.2	≤5 mM	Glycine, Polysorbate 80	280-288, but not <240
	Panzyga 10%	Octapharma	ITP, PIDD	≥96	≥90 monomers + dimers	NA	100	Trace	4.5-5.0	Trace	Glycine	240-310

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TABLE 1 ■ PRODUCT PROPERTIES CONSIDERATIONS[2-7]

(continued)

SUBCUTANEOUS

Product	Company	Indications	Gamma Globulin Content (%)	Monomers (%)	Half-life (days)	IgA Content (µg/mL)	IgM Content	pH	Sodium Content	Stabilizer	Osmolality/Osmolarity (mOsm/kg)
GAMUNEX-C 10%	Grifols	CIDP, ITP, PIDD*	100	100 monomers + dimers	35	46	Trace	4.0-4.5	Trace (<7 mEq/L)	Glycine	258
Hizentra 20%	CSL Behring	PIDD (SC only) CIDP	≥98	≥90 monomers + dimers	NA	≤50	Trace	4.6-5.2	Trace	Proline	380
Cuvitru 20%	Takeda	PIDD (SC only)	≥98	≥90 monomers + dimers	NA	80 (average)	NA	4.6-5.1	No sodium added	Glycine	280-292
Gammagard Liquid 10%	Takeda	MMN, PIDD*	≥98	≥95 monomers + dimers	35	37	Trace	4.9-5.2	No sodium added	Glycine	240-300
HyQvia 10% (IgG 10% + HY 5%)	Takeda	PIDD (SC only)	≥98	≥95 monomers + dimers	35	37	Trace	4.6-5.1	No sodium added	Glycine	240-300
Gammaked 10%	Kedrion (manufactured by Grifols)	CIDP, ITP, PIDD*	100	100 monomers + dimers	35	46	Trace	4.0-4.5	Trace (<7 mEq/L)	Glycine	258
XEMBIFY 20%	Grifols	PIDD	100	99±1 momoners + dimers	NA	≤0.07 mg/mL	<0.004 mg/mL	4.1-4.8	Trace	Glycine and polysorbate 80	280-404
Cutaquig 16.5%	Octapharma	PIDD	99.5±0.4	≥94 monomers + dimers	NA	≤0.6 mg/mL	0.005± 0.003 mg/mL	5.0-5.5	≤30 mmol/L	Maltose and polysorbate 80	310-380

*Subcutaneous administration approved for PIDD indication only.

Please see Important Safety Information for Flebogamma® 5% DIF (immune globulin intravenous [human]), Flebogamma® 10% DIF (immune globulin intravenous [human]), XEMBIFY® (immune globulin subcutaneous human–klhw) 20%, and GAMUNEX®-C (immune globulin injection [human], 10% caprylate/chromatography purified) on pages 11-14, and refer to accompanying full Prescribing Information.

TABLE 2 ■ MANUFACTURING PROCESS CONSIDERATIONS[2-4]

	Product	Company	Plasma Source	Manufacturing Process	Specific Pathogen Inactivation/Removal Steps
INTRAVENOUS	**Flebogamma 5% DIF**	Grifols	US source IQPP-certified plasma from FDA-registered sites	Cohn-Oncley, ion-exchange chromatography, acid pH treatment, PEG precipitation, SD, pasteurization, dual nanofiltration (35 + 20 nm)	Pasteurization (60ºC, 10 h), SD, 20 nm nanofiltration, fraction I precipitation, fraction II+III incubation, PEG precipitation, acid treatment, TSE removal
	Flebogamma 10% DIF	Grifols	US source IQPP-certified plasma from FDA-registered sites	Cohn-Oncley, ion-exchange chromatography, acid pH treatment, PEG precipitation, SD, pasteurization, dual nanofiltration (35 + 20 nm)	Pasteurization (60ºC, 10 h), SD, 20 nm nanofiltration, fraction I precipitation, fraction II+III incubation, PEG precipitation, acid treatment, TSE removal
	GAMUNEX-C 10%	Grifols	US source IQPP-certified plasma from FDA-registered sites	Cold ethanol fractionation, anion-exchange chromatography, caprylate chromatography purified, low pH incubation	Caprylate precipitation/depth filtration, caprylate incubation, depth filtration, column chromatography, low pH incubation, TSE removal
	Privigen 10%	CSL Behring	Plasmapheresis, US donors (≥60,000)	Cold ethanol fractionation, octanoic acid fractionation, anion-exchange chromatography, pH 4.0 incubation, depth filtration, nanofiltration (20 nm)	pH 4.0 incubation, 20 nm virus filtration, depth filtration, TSE removal
	Gammagard Liquid 10%	Takeda	Plasma from FDA-registered sites	Cohn-Oncley, anion-exchange chromatography, SD, nanofiltration, ultrafiltration, low pH incubation	SD, low pH, nanofiltration
	Gammagard S/D 5%	Takeda	Plasmapheresis, 10,000 donors from FDA-registered sites	Cohn-Oncley, ultrafiltration, anion-exchange chromatography, SD	SD
	Octagam 5%	Octapharma	US source and recovered plasma from FDA-registered sites	Cold ethanol fractionation, ultrafiltration, chromatography, SD, pH 4.0 incubation	Cold ethanol, pH 4.0 incubation, SD
	Octagam 10%	Octapharma	US source and recovered plasma from FDA-registered sites	Cold ethanol fractionation, ultrafiltration, chromatography, SD, pH 4.0 incubation	Cold ethanol, pH 4.0 incubation, SD
	Gammaked 10%	Kedrion (manufactured by Grifols)	US source IQPP-certified plasma from FDA-registered sites	Cold ethanol fractionation, anion-exchange chromatography, caprylate chromatography purified, low pH incubation	Caprylate precipitation/depth filtration, caprylate incubation, depth filtration, column chromatography, low pH incubation, TSE removal
	Gammaplex 5%	BPL	US source plasma from FDA-registered sites	Cold ethanol fractionation, ion-exchange chromatography, SD, nanofiltration (20 nm), ultrafiltration/diafiltration, terminal low pH incubation	SD, nanofiltration, terminal low pH incubation
	Gammaplex 10%	BPL	US source plasma from FDA-registered sites	Cold ethanol fractionation, ion-exchange chromatography, SD, nanofiltration (20 nm), ultrafiltration/diafiltration, terminal low pH incubation	SD, nanofiltration, terminal low pH incubation
	Panzyga 10%	Octapharma	US source and recovered plasma from FDA-registered sites	Cold ethanol fractionation, nanofiltration (20 nm), ion-exchange chromatography, SD	Nanofiltration (20 nm), ion-exchange chromatography

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TABLE 2 ■ MANUFACTURING PROCESS CONSIDERATIONS[2-4]

(continued)

	Product	Company	Plasma Source	Manufacturing Process	Specific Pathogen Inactivation/Removal Steps
SUBCUTANEOUS	**GAMUNEX-C 10%**	Grifols	US source IQPP-certified plasma from FDA-registered sites	Cold ethanol fractionation, anion-exchange chromatography, caprylate chromatography purified, low pH incubation	Caprylate precipitation/depth filtration, caprylate incubation, depth filtration, column chromatography, low pH incubation, TSE removal
	Hizentra 20%	CSL Behring	Plasmapheresis, US donors	Cold ethanol fractionation, anion-exchange chromatography, octanoic acid fractionation, pH 4.0 incubation, depth filtration, nanofiltration (20 nm)	pH 4.0 incubation, depth filtration, virus filtration, TSE reduction
	Cuvitru 20%	Takeda	Plasma from FDA-registered sites	Cohn-Oncley, anion-exchange chromatography, SD, nanofiltration, ultrafiltration, low pH incubation	SD, low pH, nanofiltration
	Gammagard Liquid 10%	Takeda	Plasma from FDA-registered sites	Cohn-Oncley, anion-exchange chromatography, SD, nanofiltration, ultrafiltration, low pH incubation	SD, low pH, nanofiltration
	HyQvia 10% (IgG 10% + HY 5%)	Takeda	Plasma from FDA-registered sites	Cohn-Oncley, anion-exchange chromatography, SD, nanofiltration, ultrafiltration, low pH incubation	SD, low pH, nanofiltration
	Gammaked 10%	Kedrion (manufactured by Grifols)	US source IQPP-certified plasma from FDA-registered sites	Cold ethanol fractionation, anion-exchange chromatography, caprylate chromatography purified, low pH incubation	Caprylate precipitation/depth filtration, caprylate incubation, depth filtration, column chromatography, low pH incubation, TSE removal, nanofiltration
	XEMBIFY 20%	Grifols	US source IQPP-certified plasma from FDA-registered sites	Cold ethanol fractionation, caprylate precipitation and filtration, anion-exchange chromatography	Caprylate precipitation/depth filtration, caprylate incubation, column chromatography, nanofiltration low pH incubation, TSE removal
	Cutaquig 16.5%	Octapharma	US source and recovered plasma from FDA-registered sites	Cold ethanol fractionation, ultrafiltration, chromatography, SD, pH 4.0 incubation	Cold ethanol, pH 4.0 incubation, SD

Please see Important Safety Information for Flebogamma® 5% DIF (immune globulin intravenous [human]), Flebogamma® 10% DIF (immune globulin intravenous [human]), XEMBIFY® (immune globulin subcutaneous human–klhw) 20%, and GAMUNEX®-C (immune globulin injection [human], 10% caprylate/chromatography purified) on pages 11-14, and refer to accompanying full Prescribing Information.

TABLE 3 ■ FORMULATION, STORAGE, AND INFUSION CONSIDERATIONS[2-4,6]

	Product	Company	Available Dosing Forms	Form	Vial Sizes (g)	Storage Conditions	Initial Infusion Rate	Maintenance Infusion Rate	Maximum Infusion Rate	Packaging or Labeling Enhancements
INTRAVENOUS	**Flebogamma 5% DIF**	Grifols	IV	Liquid	0.5, 2.5, 5, 10, 20	2ºC-25ºC, 24 mo; do not freeze	0.6 mL/kg/hr	Increase gradually as tolerated to 6 mL/kg/hr	6 mL/kg/hr	Tamper-evident seal with hologram, prior handling recognition, integral suspension band, laser-etched vials with UIN, barcode, peel-off label with product lot number
	Flebogamma 10% DIF	Grifols	IV	Liquid	5, 10, 20	2ºC-25ºC, 24 mo; do not freeze	0.6 mL/kg/hr	Increase gradually as tolerated to 4.8 mL/kg/hr	4.8 mL/kg/hr	Tamper-evident seal with hologram, prior handling recognition, integral suspension band, laser-etched vials with UIN, barcode, peel-off label with product lot number
	GAMUNEX-C 10%	Grifols	IV, SC (SC for PIDD only)	Liquid	1, 2.5, 5, 10, 20, 40	2ºC-8ºC, 36 mo; ≤25ºC, 6 mo; do not freeze	0.6 mL/kg/hr (PIDD, ITP), 1.2 mL/kg/hr (CIDP)	Increase gradually as tolerated to 4.8 mL/kg/hr	4.8 mL/kg/hr	Tamper-evident cap, laser-etched vials with UIN, NDC barcode, integral suspension band on larger vial sizes, peel-off label with product lot number, vial stopper not made with natural rubber latex
	Privigen 10%	CSL Behring	IV	Liquid	5, 10, 20, 40	≤25ºC, 36 mo	0.3 mL/kg/hr (CIDP requires loading dose)	As tolerated, up to maximum recommended rate	2.4 mL/kg/hr (ITP); 4.8 mL/kg/hr (PIDD, CIDP)	Latex-free, single-use vial, tamper-evident seal, RSS barcode, peel-off label with lot number, expiration date
	Gammagard Liquid 10%	Takeda	IV, SC (SC for PIDD only)	Liquid	1, 2.5, 5, 10, 20, 30	2ºC-8ºC, 36 mo; ≤25ºC, 24 mo; do not freeze	0.5 mL/kg/hr for 30 min (PIDD); 0.5 mL/kg/hr (MMN)	Increase every 30 min if tolerated, up to 5 mL/kg/hr (PIDD) Infusion rate may be advanced if tolerated, to 5.4 mL/kg/hr (MMN)	5 mL/kg/hr (PIDD)	Latex-free packaging, tamper-evident cap, RSS barcode, peel-off label with lot number, expiration date
	Gammagard S/D 5%	Takeda	IV	Lyophilized	2.5, 5, 10	≤25ºC, 24 mo; do not freeze	0.5 mL/kg/hr for 30 min	Increase gradually as tolerated to 4 mL/kg/hr	4 mL/kg/hr	Tamper-evident cap, peel-off label with lot number, expiration date
	Panzyga 10%	Octapharma	IV	Liquid	1, 2.5, 5, 10, 20, 30	2ºC-8ºC, 24 mo; do not freeze	0.6 mL/kg/hr	Increase gradually as tolerated every 15-30 mins to 4.8 mL/kg/hr (ITP), 8.4 mL/kg/hr (PIDD)	4.8 mL/kg/hr (new PIDD and ITP patients); 7.2-8.4 mL/kg/hr (experienced PIDD patients)	Tamper-evident, latex-free packaging, peel-off label with lot number, expiration date

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TABLE 3 ■ FORMULATION, STORAGE, AND INFUSION CONSIDERATIONS[2-4,6]

(continued)

	Product	Company	Available Dosing Forms	Form	Vial Sizes (g)	Storage Conditions	Initial Infusion Rate	Maintenance Infusion Rate	Maximum Infusion Rate	Packaging or Labeling Enhancements
INTRAVENOUS	**Octagam 5%**	Octapharma	IV	Liquid	1, 2.5, 5, 10, 25	2ºC-25ºC, 24 mo; do not freeze	0.3 mL/kg/hr for 30 min	0.6 mL/kg/hr for 30 min, then 1.2 mL/kg/hr for 30 min, then 2.4 mL/kg/hr for 30 min, then as tolerated, up to max rate	<4.2 mL/kg/hr	Tamper-evident, latex-free packaging, peel-off label with lot number, expiration date
	Octagam 10%	Octapharma	IV	Liquid	2, 5, 10, 20	2ºC-8ºC, 24 mo; ≤25ºC, 9 mo; after storage at ≤25ºC, product must be used or discarded	0.6 mL/kg/hr for 30 min	Increase gradually as tolerated every 30 min to 7.2 mL/kg/hr	7.2 mL/kg/hr	Tamper-evident, latex-free packaging, peel-off label with lot number, expiration date
	Gammaked 10%	Kedrion (manufactured by Grifols)	IV, SC (SC for PIDD only)	Liquid	1, 2.5, 5, 10, 20	2ºC-8ºC, 36 mo; ≤25ºC, 6 mo; do not freeze	0.6 mL/kg/hr (PIDD, ITP), 1.2 mL/kg/hr (CIDP)	Increase gradually as tolerated to 4.8 mL/kg/hr	4.8 mL/kg/hr	Tamper-evident cap, laser-etched vials with UIN, NDC barcode, integral suspension band on larger vial sizes, peel-off label with product lot number, vial stopper not made with natural rubber latex
	Gammaplex 5%	BPL	IV	Liquid	5, 10, 20	2ºC-25ºC, 36 mo; do not freeze	0.6 mL/kg/hr for 15 min	Increase gradually as tolerated every 15 min to 4.8 mL/kg/hr	4.8 mL/kg/hr	Latex-free, single-use vial, tamper-evident cap, peel-off label with lot number, expiration date
	Gammaplex 10%	BPL	IV	Liquid	5, 10, 20	2ºC-25ºC, 36 mo; do not freeze	0.3 mL/kg/hr for 15 min	Increase gradually as tolerated every 15 min to 4.8 mL/kg/hr	4.8 mL/kg/hr	Latex-free, single-use vial, tamper-evident cap, peel-off label with lot number, expiration date

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TABLE 3 ■ FORMULATION, STORAGE, AND INFUSION CONSIDERATIONS[2-4,6]

(continued)

	Product	Company	Available Dosing Forms	Form	Vial Sizes (g)	Storage Conditions	Initial Infusion Rate	Maintenance Infusion Rate	Maximum Infusion Rate	Packaging or Labeling Enhancements
SUBCUTANEOUS	**GAMUNEX-C 10%**	Grifols	IV, SC (SC for PIDD only)	Liquid	1, 2.5, 5, 10, 20, 40	2ºC-8ºC, 36 mo; ≤25ºC, 6 mo; do not freeze	Adults: 20 mL/hr/site; up to 8 sites simultaneously Children and adolescents weighing ≥25 kg: 15 mL/hr/site; up to 6 sites Children and adolescents weighing <25 kg: 10 mL/hr/site; up to 6 sites	As tolerated, weekly: Adults: 20 mL/hr/site Children and adolescents weighing ≥25 kg: up to 20 mL/hr/site Children and adolescents weighing <25 kg: 10 mL/hr/site	4.8 mL/kg/hr	Tamper-evident cap, laser-etched vials with UIN, NDC barcode, integral suspension band on larger vial sizes, peel-off label with product lot number, vial stopper not made with natural rubber latex
	Hizentra 20%	CSL Behring	SC	Liquid	1, 2, 4, 10	≤25ºC, 30 mo	≤15 mL/hr/site (PIDD), ≤20 mL/hr/site (CIDP); up to 8 sites simultaneously*	Increased to 25 mL/hr/site (PIDD), 50 mL/hr/site (CIDP) as tolerated*	50 mL/hr/site*	Latex-free packaging, single-use tamper-evident vials, peel-off label with lot number, expiration date
	Cuvitru 20%	Takeda	SC	Liquid	1, 2, 4, 8, 10	2ºC-8ºC, 36 mo; ≤25ºC, 24 mo; do not freeze	10-20 mL/hr/site	≤60 mL/hr/site	≤60 mL/hr/site	Latex-free packaging, tamper-evident cap, RSS barcode, peel-off label with lot number, expiration date
	Gammagard Liquid 10%	Takeda	IV, SC (SC for PIDD only)	Liquid	1, 2.5, 5, 10, 20, 30	2ºC-8ºC, 36 mo; ≤25ºC, 24 mo; do not freeze	40 kg BW and greater: 30 mL/site at 20 mL/hr/site Under 40 kg BW: 20 mL/site at 15 mL/hr/site	40 kg BW and greater: 30 mL/site at 20 to 30 mL/hr/site Under 40 kg BW: 20 mL/site at 15 to 20 mL/hr/site	5 mL/kg/hr (PIDD)	Latex-free packaging, tamper-evident cap, RSS barcode, peel-off label with lot number, expiration date
	HyQvia 10% (IgG 10% + HY 5%)	Takeda	SC	Liquid	2.5, 5, 10, 20, 30	2ºC-8ºC, 36 mo; do not freeze	1 to 2 mL per minute, or as tolerated†	As tolerated, ramp up as per recommended rates (weight-dependent)†	As tolerated, ramp up as per recommended rates (weight-dependent)†	Latex-free packaging, tamper-evident cap, RSS barcode, peel-off label with lot number, expiration date

*Source: Hizentra Prescribing Information. CSL Behring.
†Source: HyQvia Prescribing Information. Takeda.

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Please see Important Safety Information for Flebogamma® 5% DIF (immune globulin intravenous [human]), Flebogamma® 10% DIF (immune globulin intravenous [human]), XEMBIFY® (immune globulin subcutaneous human–klhw) 20%, and GAMUNEX®-C (immune globulin injection [human], 10% caprylate/chromatography purified) on pages 11-14, and refer to accompanying full Prescribing Information.

TABLE 3 ■ FORMULATION, STORAGE, AND INFUSION CONSIDERATIONS[2-4,6]

(continued)

	Product	Company	Available Dosing Forms	Form	Vial Sizes (g)	Storage Conditions	Initial Infusion Rate	Maintenance Infusion Rate	Maximum Infusion Rate	Packaging or Labeling Enhancements
SUBCUTANEOUS	**Gammaked 10%**	Kedrion (manufactured by Grifols)	IV, SC (SC for PIDD only)	Liquid	1, 2.5, 5, 10, 20	2ºC-8ºC, 36 mo; ≤25ºC, 6 mo; do not freeze	Adults: 20 mL/hr/site; up to 8 sites simultaneously Children and adolescents weighing ≥25 kg: 15 mL/hr/site; up to 6 sites Children and adolescents weighing <25 kg: 10 mL/hr/site; up to 6 sites	As tolerated, weekly: Adults: 20 mL/hr/site Children and adolescents weighing ≥25 kg: up to 20 mL/hr/site Children and adolescents weighing <25 kg: 10 mL/hr/site	4.8 mL/kg/hr	Tamper-evident cap, laser-etched vials with UIN, NDC barcode, integral suspension band on larger vial sizes, peel-off label with product lot number, vial stopper not made with natural rubber latex
	XEMBIFY 20%	Grifols	SC	Liquid	1, 2, 4, 10	2ºC-8ºC, 36 mo; ≤25ºC, 6 mo; do not freeze	Adults: Maximum rate of 25 mL/hr/site; up to 6 sites	Adults: Maximum rate of 25 mL/hr/site; up to 6 sites	≤25mL/hr/site	Tamper-evident cap, laser-etched vials with UIN, NDC barcode, integral suspension band on larger vial sizes, peel-off label with product lot number, vial stopper not made with natural rubber latex
	Cutaquig 16.5%	Octapharma	SC	Liquid	1, 1.65, 2, 3.3, 4, 8	2ºC-8ºC, 24 mo; do not freeze	First 6 infusions: maximum rate of 15 to 20 mL/hr/site	Maximum rate of 25 mL/hr/site	25mL/hr/site	Tamper-evident, latex-free packaging, peel-off label with lot number, expiration date

Please see Important Safety Information for Flebogamma® 5% DIF (immune globulin intravenous [human]), Flebogamma® 10% DIF (immune globulin intravenous [human]), XEMBIFY® (immune globulin subcutaneous human–klhw) 20%, and GAMUNEX®-C (immune globulin injection [human], 10% caprylate/chromatography purified) on pages 11-14, and refer to accompanying full Prescribing Information.

KEY

BW	body weight	**KD**	Kawasaki disease
CIDP	chronic inflammatory demyelinating polyneuropathy	**MMN**	multifocal motor neuropathy
CLL	chronic lymphocytic leukemia	**NA**	Information Not Available
FDA	Food and Drug Administration	**NDC**	National Drug Code
HY	hyaluronidase	**NS**	normal saline
IgA	immunoglobulin A	**PEG**	polyethylene glycol
IgG	immunoglobulin G	**PIDD**	primary immunodeficiency disease
IgM	immunoglobulin M	**RSS**	reduced space symbology
IQPP	International Quality Plasma Program	**SC**	subcutaneous
ITP	idiopathic thrombocytopenic purpura	**SD**	solvent detergent
IV	intravenous	**TSE**	transmissible spongiform encephalopathies
IVIG	intravenous immunoglobulin	**UIN**	Unique Identifier Number

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Flebogamma® 5% DIF (immune globulin intravenous [human])
Important Safety Information

Flebogamma® 5% DIF is an immune globulin intravenous (human) solution indicated in adults and pediatric patients 2 years of age and older for the treatment of primary immunodeficiency (PIDD), including the humoral immune defects in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome.

Thrombosis may occur with immune globulin products, including Flebogamma 5% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. For patients at risk of thrombosis, administer Flebogamma 5% DIF 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.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death have been related to intravenous immune globulin (IVIG) products. Patients predisposed to acute renal failure include patients with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Administer Flebogamma 5% DIF at the minimum rate of infusion practicable in patients at risk for renal dysfunction or failure. Reports of renal dysfunction and acute renal failure occur more commonly in patients receiving IVIG products containing sucrose as a stabilizer. They account for a disproportionate share of the total number of reported cases of renal dysfunction and acute renal failure. Flebogamma 5% DIF does not contain sucrose.

Flebogamma 5% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of human immune globulin and in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

Severe hypersensitivity reactions may occur with IVIG products, including Flebogamma 5% DIF. In case of hypersensitivity, discontinue Flebogamma 5% DIF infusion immediately and institute appropriate treatment.

Monitor renal function, including blood urea nitrogen (BUN), serum creatinine, and urine output in patients at risk of developing acute renal failure.

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Flebogamma 5% DIF therapy.

Aseptic meningitis syndrome (AMS) has been reported to occur following IVIG treatment. AMS may occur more frequently following high dose (eg, > 1.0 g/kg body weight) and/or rapid infusion of IVIG.

Hemolysis, either intravascular or due to enhanced red blood cell sequestration, can develop subsequent to Flebogamma 5% DIF treatments. Risk factors include high doses and non-O blood group. Monitor patients for hemolysis and hemolytic anemia.

Noncardiogenic pulmonary edema (transfusion-related acute lung injury [TRALI]) has been reported in patients following IVIG treatment. If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient serum.

Individuals receiving Flebogamma 5% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for the development of fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events.

Because Flebogamma 5% DIF is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. No cases of transmission of viral diseases or CJD have been associated with the use of Flebogamma 5% DIF.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of Flebogamma 5% DIF and at appropriate intervals thereafter.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potentially increased risk of thrombosis.

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.

Flebogamma 5% DIF contains sorbitol. The presence of sorbitol presents a risk to those with hereditary fructose intolerance (HFI). Flebogamma 5% DIF must not be administered to subjects with HFI.

The most common adverse reactions (reported in at least 5% of clinical trial adult subjects) were headache, pyrexia/fever, pain, infusion site reactions, diarrhea, rigors or chills, urticaria, and infusion site inflammation.

The most common adverse reactions (reported in at least 5% of clinical trial pediatric subjects) were headache, pyrexia, hypotension, tachycardia, diastolic hypotension, nausea, abdominal pain, diarrhea, pain, and vomiting.

Please see accompanying full Prescribing Information for Flebogamma 5% DIF.

Flebogamma® 10% DIF (immune globulin intravenous [human])
Important Safety Information

Flebogamma® 10% DIF is an immune globulin intravenous (human) 10% preparation that is indicated for the treatment of primary immunodeficiency disease (PIDD), including the humoral immune defect in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome. Flebogamma 10% DIF is also indicated for the treatment of chronic primary immune thrombocytopenia (ITP) in patients 2 years of age and older.

Thrombosis may occur with immune globulin products, including Flebogamma 10% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. For patients at risk of thrombosis, administer Flebogamma 10% DIF 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.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death have been related to intravenous immune globulin (IVIG) products. Patients predisposed to acute renal failure include patients with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Administer Flebogamma 10% DIF at the minimum rate of infusion practicable in patients at risk for renal dysfunction or failure. Reports of renal dysfunction and acute renal failure occur more commonly in patients receiving IVIG products containing sucrose as a stabilizer. They account for a disproportionate share of the total number of reported cases of renal dysfunction and acute renal failure. Flebogamma 10% DIF does not contain sucrose.

Flebogamma 10% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of human immune globulin and in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

Severe hypersensitivity reactions may occur with IVIG products, including Flebogamma 10% DIF. In case of hypersensitivity, discontinue Flebogamma 10% DIF infusion immediately and institute appropriate treatment.

Monitor renal function, including blood urea nitrogen (BUN), serum creatinine, and urine output in patients at risk of developing acute renal failure.

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Flebogamma 10% DIF therapy.

Aseptic meningitis syndrome (AMS) has been reported to occur following IVIG treatment. AMS may occur more frequently following high doses (2 g/kg) and/or rapid infusion of IVIG.

Hemolytic anemia can develop subsequent to IVIG therapy, including Flebogamma 10% DIF. Flebogamma 10% DIF may contain blood group antibodies that may act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test and hemolysis. If signs and/or symptoms of hemolysis are present after an infusion of Flebogamma 10% DIF, perform appropriate laboratory testing for confirmation.

Noncardiogenic pulmonary edema (transfusion-related acute lung injury [TRALI]) has been reported in patients following IVIG treatment. If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

Individuals receiving Flebogamma 10% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for the development of fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events.

Because Flebogamma 10% DIF is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. No cases of transmission of viral diseases or CJD have been associated with the use of Flebogamma 10% DIF.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of Flebogamma 10% DIF and at appropriate intervals thereafter.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potential for increased risk of thrombosis.

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.

Flebogamma 10% DIF contains sorbitol. The presence of sorbitol presents a risk to those with hereditary fructose intolerance (HFI). HFI is typically suspected based on dietary history, especially in young children who become symptomatic after breast-feeding. Flebogamma 10% DIF must not be administered to subjects with HFI.

In clinical studies, the most common adverse reactions observed with Flebogamma 10% DIF were headache, fever/pyrexia, shaking, tachycardia, hypotension, back pain, myalgia, hypertension, chest pain, pain, nausea, infusion-site reactions, and pain in extremities (in PIDD) and headache, pyrexia, nausea, chills, vomiting, body temperature increase, dizziness, back pain, hypotension, hypertension, heart rate increase, and diarrhea (in ITP).

The most serious adverse reactions observed with Flebogamma 10% DIF were back pain, chest pain, headache, and chills/tachycardia (2 patients) and bacterial pneumonia, subcutaneous abscess, and cellulitis (1 patient) (in PIDD) and soft tissue inflammation (1 patient) unrelated to the study drug and headache (2 patients) possibly related to the study drug (in ITP).

Please see accompanying full Prescribing Information for Flebogamma 10% DIF.

XEMBIFY® (immune globulin subcutaneous human–klhw) 20%

Indication

XEMBIFY® (immune globulin subcutaneous human–klhw) is a 20% immune globulin indicated for treatment of primary humoral immunodeficiency disease (PIDD) in patients 2 years of age and older. XEMBIFY is for subcutaneous administration only.

Important Safety Information

WARNING: THROMBOSIS

- **Thrombosis may occur with immune globulin products, including XEMBIFY. Risk factors may include: advanced age, prolonged immobilization, 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 of hyperviscosity**

Contraindications

XEMBIFY is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. It is contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity.

Warnings and Precautions

Hypersensitivity. Severe hypersensitivity reactions may occur with immune globulin products, including XEMBIFY. In case of hypersensitivity, discontinue infusion immediately and institute appropriate treatment. XEMBIFY contains IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions.

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

Aseptic meningitis syndrome (AMS). AMS may occur with human immune globulin treatment, including XEMBIFY. Conduct a thorough neurological exam on patients exhibiting signs and symptoms to rule out other causes of meningitis. Discontinuation of treatment has resulted in remission within several days without sequelae.

Renal dysfunction/failure. Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, and death may occur with use of human immune globulin products, especially those containing sucrose. XEMBIFY does not contain sucrose. Ensure patients are not volume-depleted prior to starting infusion. In patients at risk due to preexisting renal insufficiency or predisposition to acute renal failure, assess renal function prior to the initial infusion of XEMBIFY and again at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation.

Hemolysis. XEMBIFY may contain blood group antibodies that may cause a positive direct antiglobulin reaction and hemolysis. Monitor patients for clinical signs and symptoms of hemolysis. If signs and symptoms are present after infusion, perform confirmatory lab testing.

Transfusion-related acute lung injury (TRALI). Noncardiogenic pulmonary edema may occur in patients following treatment with immune globulin products, including XEMBIFY. Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of antineutrophil and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

Transmissible infectious agents. Because XEMBIFY is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases, vCJD, or CJD have ever been associated with the use of XEMBIFY.

Interference with lab tests. After infusion of XEMBIFY, passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.

Adverse Reactions

The most common adverse reactions in ≥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.

Drug Interactions

Passive transfer of antibodies may transiently interfere with the immune responses to live attenuated virus vaccines (eg, measles, mumps, rubella, and varicella).

Please see accompanying full Prescribing Information for XEMBIFY.

GAMUNEX®-C (immune globulin injection [human], 10% caprylate/chromatography purified) Important Safety Information

GAMUNEX®-C (immune globulin injection [human], 10% caprylate/chromatography purified) is indicated for the treatment of primary humoral immunodeficiency disease (PIDD) in patients 2 years of age and older, idiopathic thrombocytopenic purpura (ITP) in adults and children, and chronic inflammatory demyelinating polyneuropathy (CIDP) in adults.

Thrombosis may occur with immune globulin products, including GAMUNEX-C. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. For patients at risk of thrombosis, administer GAMUNEX-C 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.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IVIG) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIG products containing sucrose. GAMUNEX-C does not contain sucrose. For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable.

GAMUNEX-C is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. It is contraindicated in IgA-deficient patients with antibodies against IgA and history of hypersensitivity.

Severe hypersensitivity reactions may occur with IVIG products, including GAMUNEX-C. In case of hypersensitivity, discontinue GAMUNEX-C infusion immediately and institute appropriate treatment.

Monitor renal function, including blood urea nitrogen (BUN), serum creatinine, and urine output in patients at risk of developing acute renal failure.

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IVIG treatment, including GAMUNEX-C.

There have been reports of aseptic meningitis, hemolytic anemia, and noncardiogenic pulmonary edema (transfusion-related acute lung injury [TRALI]) in patients administered with IVIG, including GAMUNEX-C.

The high-dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Because GAMUNEX-C is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Do not administer GAMUNEX-C subcutaneously in patients with ITP because of the risk of hematoma formation.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of GAMUNEX-C and at appropriate intervals thereafter.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potentially increased risk of thrombosis.

If signs and/or symptoms of hemolysis are present after an infusion of GAMUNEX-C, perform appropriate laboratory testing for confirmation.

If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient's serum.

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.

In clinical studies, the most common adverse reactions with GAMUNEX-C were headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia (in CIDP); cough, rhinitis, pharyngitis, headache, asthma, nausea, fever, diarrhea, and sinusitis with intravenous use (in PIDD) and local infusion-site reactions, fatigue, headache, upper respiratory tract infection, arthralgia, diarrhea, nausea, sinusitis, bronchitis, depression, allergic dermatitis, migraine, myalgia, viral infection, and pyrexia with subcutaneous use (in PIDD); and headache, ecchymosis, vomiting, fever, nausea, rash, abdominal pain, back pain, and dyspepsia (in ITP).

The most serious adverse reactions in clinical studies were pulmonary embolism (PE) in 1 subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in 1 subject (in PIDD), and myocarditis in 1 subject that occurred 50 days post-study drug infusion and was not considered drug related (in ITP).

Please see accompanying full Prescribing Information for GAMUNEX-C.



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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®-C safely and effectively. See full prescribing information for GAMUNEX-C.

GAMUNEX®-C, [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified]

Initial U.S. Approval: 2003

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE
See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including GAMUNEX-C. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **For patients at risk of thrombosis, administer GAMUNEX-C 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.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX-C does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable. (5.2)**

INDICATIONS AND USAGE

GAMUNEX-C is an immune globulin injection (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older (1.1)
- Idiopathic Thrombocytopenic Purpura (ITP) in adults and children (1.2)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults (1.3)

DOSAGE AND ADMINISTRATION

Intravenous Administration Only: ITP and CIDP

Indication	Dose	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
ITP (2.3)	2 g/kg	1 mg/kg/min	8 mg/kg/min
CIDP (2.4)	loading dose 2 g/kg maintenance dose 1 g/kg	2 mg/kg/min	8 mg/kg/min Every 3 weeks

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue GAMUNEX-C if renal function deteriorates. (5.2)
- For patients at risk of renal dysfunction or thrombosis, administer GAMUNEX-C at the minimum infusion rate practicable. (5.2, 5.4)

Intravenous or Subcutaneous Administration: PI (2.2)

DO NOT ADMINISTER SUBCUTANEOUSLY FOR ITP PATIENTS (5.10)

Route of Administration	Dose*	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
Intravenous (IV)	300-600 mg/kg	1 mg/kg/min	8 mg/kg/min Every 3 to 4 weeks
Subcutaneous (SC)	1.37 x current IV dose in grams/IV dose interval in weeks	Adult:† 20 mL/hr/site Pediatric:† 10 mL/hr/site (< 25 kg) 15 mL/hr/site (≥ 25 kg)	Adult:† 20 mL/hr/site Pediatric:† 10 mL/hr/site (< 25 kg) 20 mL/hr/site (≥ 25 kg) Weekly

*See section 2.2.

† Adults: use up to 8 infusion sites simultaneously; pediatric: use up to 6 infusion sites simultaneously; for all ages, ensure infusion sites are at least 2 inches (5 cm) apart. (2.5)

DOSAGE FORMS AND STRENGTHS

GAMUNEX-C is a sterile solution for injection supplied in 1 g (10 mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), 20 g (200 mL), or 40 g (400 mL) single use vials. (3)

CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin (4.1)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4.2)

WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions. (5.1)
- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may occur in patients receiving IGIV therapy. (5.3)
- Aseptic Meningitis Syndrome (AMS) may occur, especially with high doses or rapid infusion. (5.5)
- Hemolysis, either intravascular or due to enhanced RBC sequestration, can develop subsequent to GAMUNEX-C treatments. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia, especially in patients with pre-existing anemia and/or cardiovascular or pulmonary compromise. (5.6)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]). (5.7)
- Volume overload. (5.8)
- GAMUNEX-C 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. (5.9)
- GAMUNEX-C is not approved for subcutaneous use in ITP patients. Due to a potential risk of hematoma formation, do not administer GAMUNEX-C subcutaneously in patients with ITP. (5.10)
- Passive transfer of antibodies may confound serologic testing. (5.12)

ADVERSE REACTIONS

The most common adverse reactions observed in ≥ 5% patients were: (6.1)

PI: Intravenous: Cough increased, rhinitis, pharyngitis, headache, asthma, nausea, fever, diarrhea, and sinusitis.

Subcutaneous: Local infusion site reactions, fatigue, headache, upper respiratory tract infection, arthralgia, diarrhea, nausea, sinusitis, bronchitis, depression, allergic dermatitis, erythema, migraine, myalgia, viral infection, and pyrexia.

ITP: Headache, ecchymosis, vomiting, fever, nausea, rash, abdominal pain, back pain, and dyspepsia.

CIDP: Headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics LLC at 1-800-520-2807 or FDA at 1-800-FDA-1088 or 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 and rubella. (7)

USE IN SPECIFIC POPULATIONS

- Geriatric: In patients over 65 years of age do not exceed the recommended dose, and infuse GAMUNEX-C at the minimum infusion rate practicable. (8.5)

See 17 for PATIENT COUNSELING INFORMATION. **Revised: 1/2020**

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION, and ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including GAMUNEX-C. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. *[see Warnings and Precautions (5.4), Patient Counseling Information (17)]***
- **For patients at risk of thrombosis, administer GAMUNEX-C 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. *[see Dosage and Administration (2.5), Warnings and Precautions (5.4)]***
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX-C does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable. *[see Warnings and Precautions (5.2)]***

1 INDICATIONS AND USAGE

GAMUNEX-C is an immune globulin injection (human) 10% liquid that is indicated for the treatment of:

1.1 Primary Humoral Immunodeficiency (PI)

GAMUNEX-C is indicated for treatment of primary humoral immunodeficiency in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[1-4]

1.2 Idiopathic Thrombocytopenic Purpura (ITP)

GAMUNEX-C is indicated for the treatment of adults and children with Idiopathic Thrombocytopenic Purpura to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery.[5,6]

1.3 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

GAMUNEX-C is indicated for the treatment of CIDP in adults to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation and Handling

- Visually inspect GAMUNEX-C 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.
- Prior to use, allow the solution to reach ambient room temperature.
- If the packaging shows any signs of tampering, do not use the product and notify Grifols Therapeutics LLC immediately [1-800-520-2807].
- The GAMUNEX-C vial is for single use only. GAMUNEX-C contains no preservative. Use any vial that has been entered promptly. Discard partially used vials. Do not store after entry into vial.
- Infuse GAMUNEX-C using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The GAMUNEX-C infusion line can be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.
- If dilution is required, GAMUNEX-C may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline.
- Content of vials may be pooled under aseptic conditions into sterile infusion bags and infused within 8 hours after pooling.
- Avoid simultaneous administration of GAMUNEX-C and Heparin through a single lumen delivery device due to GAMUNEX-C, Heparin incompatibilities. Flush Heparin Lock (Hep-Lock) through which GAMUNEX-C was administered with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection, and do not flush with Heparin. See table below.

Additional Solutions	Dilution	Line Flush	Delivery Device Flush
5% Dextrose in water	Yes	Yes	Yes
0.9% Sodium Chloride	No	Yes	Yes
Heparin	No	No	No

- Do not mix with immune globulin intravenous (IGIV) products from other manufacturers.
- Do not use after expiration date.

2.2 PI

As there are significant differences in the half-life of IgG among patients with primary humoral immunodeficiencies, the ideal frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response.

Intravenous (IV)

The dose of GAMUNEX-C for patients with PI is 300 mg/kg to 600 mg/kg body weight (3 mL/kg to 6 mL/kg) administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical responses.

The recommended initial infusion rate is 1 mg/kg/min (0.01 mL/kg/min). If the infusion is well-tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min). For patients judged to be at risk for renal dysfunction or thrombosis, administer GAMUNEX-C at the minimum infusion rate practicable. *[see Warnings and Precautions (5.2, 5.4)]*

If a patient routinely receives a dose of less than 400 mg/kg of GAMUNEX-C every 3 to 4 weeks (less than 4 mL/kg), and is at risk of measles exposure (i.e., traveling to a measles endemic area), administer a dose of at least 400 mg/kg (4 mL/kg) just prior to the expected measles exposure. If a patient has been exposed to measles, a dose of 400 mg/kg (4 mL/kg) should be administered as soon as possible after exposure.

Subcutaneous (SC)

The dose should be individualized based on the patient's clinical response to GAMUNEX-C therapy and serum IgG trough levels. Begin treatment with GAMUNEX-C one week after the patient's last IGIV infusion. See below under "Initial Weekly Dose". Prior to switching treatment from IGIV to GAMUNEX-C, obtain the patient's serum IgG trough level to guide subsequent dose adjustments. See below under "Dose Adjustment".

Establish the initial weekly dose of GAMUNEX-C by converting the monthly IGIV dose into a weekly equivalent and increasing it using a dose adjustment factor. The goal is to achieve a systemic serum IgG exposure (Area Under the Concentration-Time Curve [AUC]) not inferior to that of the previous IGIV treatment. If the patient has not been previously treated with IV GAMUNEX-C, convert the monthly IGIV dose (in grams) by multiplying by 1.37, then dividing this dose into weekly doses based on the patient's previous IGIV treatment interval. Monitor the patient's clinical response, and adjust dose accordingly.

Initial Weekly Dose

To calculate the initial weekly dose of subcutaneous administration of GAMUNEX-C, multiply the previous IGIV dose in grams by the dose adjustment factor of 1.37; then divide this by the number of weeks between doses during the patient's IGIV treatment (i.e., 3 or 4).

$$\text{Initial SC dose (in grams)} = \frac{1.37 \times \text{previous IGIV dose (in grams)}}{\text{Number of weeks between IGIV doses}}$$

To convert the GAMUNEX-C dose (in grams) to milliliters (mL), multiply the calculated Initial SC dose (in grams) by 10.

Dose Adjustment

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 on IGIV and as early as 5 weeks after switching from IGIV to subcutaneous. The target serum IgG trough level on weekly SC treatment is projected to be the last IGIV trough level plus 340 mg/dL. 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 (the last IGIV trough level +340 mg/dL). 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	1	1	2	3	3	4	5	6	7	8	8	9	10
100	2	3	3	5	7	8	10	12	13	15	17	18	20
150	3	4	5	8	10	13	15	18	20	23	25	28	30
200	3	5	7	10	13	17	20	23	27	30	33	37	40
250	4	6	8	13	17	21	25	29	33	38	42	46	50
300	5	8	10	15	20	25	30	35	40	45	50	55	60
350	6	9	12	18	23	29	35	41	47	53	58	64	70
400	7	10	13	20	27	33	40	47	53	60	67	73	80
450	8	11	15	23	30	38	45	53	60	68	75	83	90
500	8	13	17	25	33	42	50	58	67	75	83	92	100

* Dose adjustment in mL is based on the slope of the serum IgG trough level response to subcutaneous administration of GAMUNEX-C dose increments (about 6.0 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 12 mL.

Monitor the patient's clinical response, and repeat the dose adjustment as needed.

Dosage requirements for patients switching to GAMUNEX-C from another Immune Globulin Subcutaneous (IGSC) product have not been studied. If a patient on GAMUNEX-C does not maintain an adequate clinical response or a serum IgG trough level equivalent to that of the previous IGSC treatment, adjust the dose accordingly. For such patients, Table 1 also provides guidance for dose adjustment to achieve a desired IGSC trough level.

2.3 ITP

DO NOT ADMINISTER SUBCUTANEOUSLY *[see Warnings and Precautions (5.10)]*

GAMUNEX-C may be administered at a total dose of 2 g/kg, divided in two doses of 1 g/kg (10 mL/kg) given on two consecutive days or into five doses of 0.4 g/kg (4 mL/kg) given on five consecutive days. If after administration of the first of two daily 1 g/kg (10 mL/kg) doses, an adequate increase in the platelet count is observed at 24 hours, the second dose of 1 g/kg (10 mL/kg) body weight may be withheld.

The high dose regimen (1 g/kg × 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern. *[see Warnings and Precautions (5.8), Clinical Studies (14)]*

The recommended initial infusion rate is 1 mg/kg/min (0.01 mL/kg/min). If the infusion is well-tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min). For patients judged to be at risk for renal dysfunction or thrombosis, administer GAMUNEX-C at the minimum infusion rate practicable. *[see Warnings and Precautions (5.2, 5.4)]*

2.4 CIDP

GAMUNEX-C may be initially administered as a total loading dose of 2 g/kg (20 mL/kg) given in divided doses over two to four consecutive days. GAMUNEX-C may be administered as a maintenance infusion of 1 g/kg (10 mL/kg) administered over 1 day or divided into two doses of 0.5 g/kg (5 mL/kg) given on two consecutive days, every 3 weeks. Not all patients may require continued maintenance therapy beyond the initial 6 months of therapy in order to maintain their therapeutic response.

The recommended initial infusion rate is 2 mg/kg/min (0.02 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min). For patients judged to be at risk for renal dysfunction or thrombosis, administer GAMUNEX-C at the minimum infusion rate practicable. *[see Warnings and Precautions (5.2, 5.4)]*

2.5 Administration

Administer intravenously for PI, ITP and CIDP.

GAMUNEX-C may also be administered subcutaneously for the treatment of PI.

- Administer GAMUNEX-C at room temperature.
- Inspect GAMUNEX-C visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.
- Do not use if turbid and/or if discoloration is observed.

Intravenous

- Use only 18 gauge needles to penetrate the stopper for dispensing product from the 10 mL vial.
- Use 16 gauge needles or dispensing pins only with 25 mL vial sizes and larger.
- Insert needles or dispensing pins only once and be within the stopper area delineated by the raised ring.
- Penetrate the stopper perpendicular to the plane of the stopper within the ring.

GAMUNEX®-C vial size	Gauge of needle to penetrate stopper
10 mL	18 gauge
25, 50, 100, 200, 400 mL	16 gauge

- Use promptly any vial that has been opened.
- Discard partially used vials.
- If dilution is required, GAMUNEX-C may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline. Infuse GAMUNEX-C using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The GAMUNEX-C infusion line can be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.

Subcutaneous for PI Only

Instructions for Administration

- Prior to use, allow the solution to reach ambient room temperature.
- DO NOT SHAKE.
- Do not use if the solution is cloudy or has particulates.
- Check the product expiration date on the vial. Do not use beyond the expiration date.

1. Use aseptic technique when preparing and administering GAMUNEX-C for injection.
2. 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 Therapeutics LLC immediately [1-800-520-2807].
3. Wipe the stopper with alcohol and allow to dry.
4. Using a sterile syringe and needle, prepare to withdraw GAMUNEX-C by first injecting air into the vial that is equivalent to the amount of GAMUNEX-C to be withdrawn. Then withdraw the desired volume of GAMUNEX-C. If multiple vials are required to achieve the desired dose, repeat this step. (Figure 1)
5. Follow the manufacturer's instructions for filling the pump reservoir and 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 tubing/needle with GAMUNEX-C.
6. Select the number and location of injection sites. (Figure 2)
7. 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 two inches apart. (Figure 3)
8. Grasp the skin between two fingers and insert the needle into the subcutaneous tissue. (Figure 4)
9. 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)
10. 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.
11. If using multiple, simultaneous injection sites, use Y-site connection tubing and secure to the administration tubing.
12. Infuse GAMUNEX-C following the manufacturer's instructions for the pump. (Figure 6)

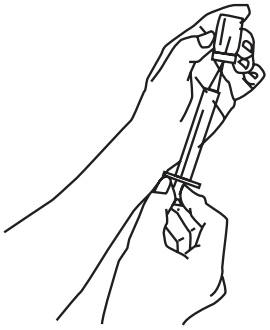


Fig. 1

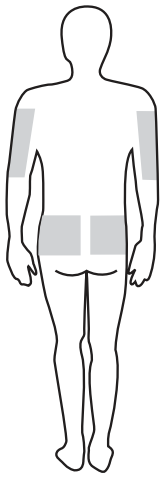


Fig. 2

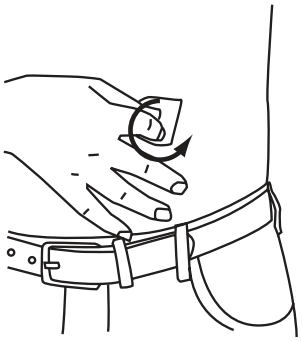


Fig. 3

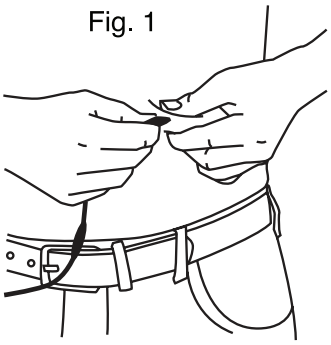


Fig. 4

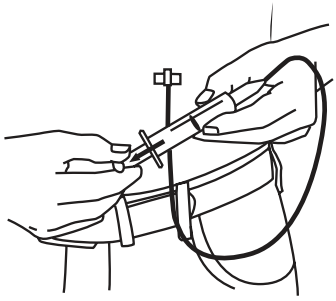


Fig. 5

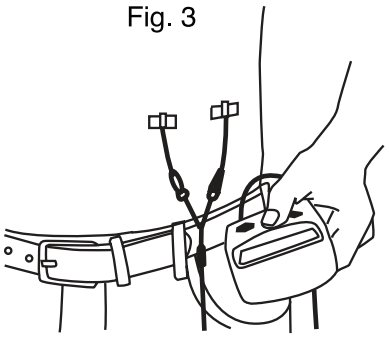


Fig. 6

Rate of Administration

Intravenous

Following initial infusion (see table below), the infusion rate may be gradually increased to a maximum of 0.08 mL/kg per minute (8 mg/kg per minute) as tolerated.

Indication	Initial Infusion Rate (first 30 minutes)	Maximum Infusion Rate (if tolerated)
PI	1 mg/kg/min	8 mg/kg/min
ITP	1 mg/kg/min	8 mg/kg/min
CIDP	2 mg/kg/min	8 mg/kg/min

Monitor patient vital signs throughout the infusion. Slow or stop infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient.

Certain severe adverse drug reactions may be related to the rate of infusion. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients at risk of renal dysfunction or thrombosis, administer GAMUNEX-C at the minimum infusion rate practicable and discontinue GAMUNEX-C if renal function deteriorates.

Subcutaneous for PI Only

For PI, it is recommended that GAMUNEX-C is infused at a rate of 20 mL per hour per infusion site for adults, and up to 8 infusion sites may be used (most patients used 4 infusion sites). Children and adolescents weighing ≥ 25 kg should start out at a slower infusion rate of 15 mL/hour/infusion site and increase their infusion rate up to 20 mL/hour/infusion site. For children and adolescents weighing < 25 kg, a rate of 10 mL/hour/infusion site is recommended. In children up to 6 infusion sites simultaneously may be used. For patients of all ages ensure that the infusion sites are at least 2 inches (5 cm) apart.

3 DOSAGE FORMS AND STRENGTHS

GAMUNEX-C is a sterile solution for injection supplied in 1 g protein (10 mL), 2.5 g protein (25 mL), 5 g protein (50 mL), 10 g protein (100 mL), 20 g protein (200 mL), or 40 g protein (400 mL) single use vials.

4 CONTRAINDICATIONS

4.1 Hypersensitivity Reactions to Immune Globulins

GAMUNEX-C is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.

4.2 IgA Sensitive Patients with History of Hypersensitivity Reaction

GAMUNEX-C is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur with IGIV products, including GAMUNEX-C. In case of hypersensitivity, discontinue GAMUNEX-C infusion immediately and institute appropriate treatment. Have medications such as epinephrine available for immediate treatment of acute hypersensitivity reaction.

GAMUNEX-C contains trace amounts of IgA (average 46 micrograms/mL). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity reaction. *[see Contraindications (4)]*

5.2 Renal Failure

Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis and death may occur upon use of IGIV products, especially those containing sucrose.[7,8] GAMUNEX-C does not contain sucrose. Ensure that patients are not volume depleted prior to the initiation of the infusion of GAMUNEX-C. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, prior to the initial infusion of GAMUNEX-C and again at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of GAMUNEX-C. *[see Patient Counseling Information (17)]* For patients judged to be at risk for developing renal dysfunction, including patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs, administer GAMUNEX-C at the minimum infusion rate practicable [less than 8 mg/kg/min (0.08 mL/kg/min)]. *[see Dosage and Administration (2.5)]*

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV treatment, including GAMUNEX-C. It is clinically critical to distinguish true hyponatremia from a pseudohyponatremia that is associated with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and a possible predisposition to thrombosis.[9]

5.4 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including GAMUNEX-C.[10-12] Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer GAMUNEX-C 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. *[see Boxed Warning, Dosage and Administration (2.5), Patient Counseling Information (17)]*

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently with IGIV treatment, including GAMUNEX-C. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to two days following IGIV 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 cu mm, 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 IGIV.

5.6 Hemolysis

GAMUNEX-C 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.[13-16] Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration, and acute hemolysis consistent with intravascular hemolysis, has been reported. *[see Adverse Reactions (6)]*

The following risk factors may be related to the development of hemolysis: high doses (e.g., ≥2 grams/kg, single administration or divided over several days) and non-O blood group.[17] Underlying inflammatory state in an individual patient may increase the risk of hemolysis, but its role is uncertain.[18]

Closely monitor patients for clinical signs and symptoms of hemolysis *[see Warnings and Precautions (5.11)]*, particularly patients with risk factors noted above and those with pre-existing anemia and/or cardiovascular or pulmonary compromise. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 hours and again 7 to 10 days post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform additional confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following treatment with IGIV products, including GAMUNEX-C.[19] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically occur within 1 to 6 hours after treatment.

Monitor patients for pulmonary adverse reactions. *[see Patient Counseling Information (17)]* 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.

5.8 Volume Overload

The high dose regimen (1 g/kg × 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

5.9 Transmission of Infectious Agents

Because GAMUNEX-C is made from human blood, it 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. No cases of transmission of viral diseases, vCJD or CJD have ever been identified for GAMUNEX-C. ALL infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [1-800-520-2807].

5.10 Hematoma Formation

Do not administer GAMUNEX-C subcutaneously in patients with ITP because of the risk of hematoma formation.

5.11 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of GAMUNEX-C and at appropriate intervals thereafter.
- Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potentially increased risk of thrombosis.
- If signs and/or symptoms of hemolysis are present after an infusion of GAMUNEX-C, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient's serum.

5.12 Interference with Laboratory Tests

After infusion of IgG, the transitory rise of the 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.

6 ADVERSE REACTIONS

PI: Intravenous: The most common adverse reactions observed at a rate ≥5% in subjects with intravenous treatment in the clinical trials were cough increased, rhinitis, pharyngitis, headache, asthma, nausea, fever, diarrhea, and sinusitis.

PI: Subcutaneous: The most common adverse reactions observed at a rate ≥5% of subjects with subcutaneous treatment in the clinical trials were local infusion site reactions, fatigue, headache, upper respiratory tract infection, arthralgia, diarrhea, nausea, sinusitis, bronchitis, depression, allergic dermatitis, erythema, migraine, myalgia, viral infection, and pyrexia.

ITP: The most common adverse reactions observed at a rate ≥5% in subjects in the clinical trials were headache, ecchymosis, vomiting, fever, nausea, rash, abdominal pain, back pain, and dyspepsia.

CIDP: The most common adverse reactions observed at a rate ≥5% in subjects in the clinical trial were headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia.

6.1 Clinical Trials Experience

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

PI: Intravenous Administration

The most serious adverse event observed in clinical study subjects receiving GAMUNEX-C IV for PI was an exacerbation of autoimmune pure red cell aplasia in one subject.

In four different clinical trials to study PI, out of 157 subjects treated with GAMUNEX-C, 4 subjects discontinued due to the following adverse events: Coombs negative hypochromic anemia, autoimmune pure red cell aplasia, arthralgia/hyperhidrosis/fatigue/myalgia/nausea and migraine.

In a study of 87 subjects, 9 subjects in each treatment group were pretreated with non-steroidal medication prior to infusion, such as diphenhydramine and acetaminophen.

Table 2 lists the adverse reactions reported by at least 5% of subjects during the 9-month treatment.

Table 2: Adverse Reactions Occurring in ≥ 5% of Subjects

Adverse Reactions	GAMUNEX®-C No. of subjects: 87 No. of subjects with adverse reaction (percentage of all subjects)	GAMIMUNE® N, 10% No. of subjects: 85 No. of subjects with adverse reaction (percentage of all subjects)
Cough Increased	27 (31.0%)	25 (29.4%)
Rhinitis	21 (24.1%)	24 (28.2%)
Headache	13 (14.9%)	17 (20.0%)
Pharyngitis	14 (16.1%)	16 (18.8%)
Asthma	13 (14.9%)	10 (11.8%)
Fever	6 (6.9%)	10 (11.8%)
Nausea	10 (11.5%)	9 (10.6%)
Diarrhea	6 (6.9%)	9 (10.6%)
Sinusitis	5 (5.7%)	6 (7.1%)

*An adverse reaction is an adverse event that meets any of the following 3 criteria: (a) that began during or within 72 hours of the end of product infusion, (b) that was considered at least possibly related by either the investigator or the applicant, and/or (c) whose causality assessment by the investigator was missing or indeterminate.

Table 3 lists the frequency of adverse reactions (as defined for Table 2), which were reported by at least 5% of subjects.

Table 3: Adverse Reactions Frequency

Adverse Reactions	GAMUNEX®-C No. of infusions: 825 Number (percentage of all infusions)	GAMIMUNE® N, 10% No. of infusions: 865 Number (percentage of all infusions)
Cough Increased	40 (4.8%)	47 (5.4%)
Rhinitis	34 (4.1%)	44 (5.1%)
Headache	17 (2.1%)	24 (2.8%)
Pharyngitis	20 (2.4%)	24 (2.8%)
Fever	8 (1.0%)	20 (2.3%)
Asthma	17 (2.1%)	12 (1.4%)
Diarrhea	10 (1.2%)	10 (1.2%)
Nausea	10 (1.2%)	10 (1.2%)
Sinusitis	6 (0.7%)	7 (0.8%)

The mean number of adverse reactions per infusion that occurred during or within 72 hours of the end of product infusion was 0.33 for the GAMUNEX-C and 0.39 for the GAMIMUNE®N, 10% [Immune Globulin Intravenous (Human) 10%] treatment group.

In all three trials in primary humoral immunodeficiencies, the maximum infusion rate was 0.08 mL/kg/min (8 mg/kg/min). The infusion rate was reduced for 11 of 222 exposed subjects (7 GAMUNEX-C, 4 GAMIMUNE N, 10%) at 17 occasions. In most instances, mild to moderate hives/urticaria, itching, pain or reaction at infusion site, anxiety or headache was the main reason. There was one case of severe chills. There were no anaphylactic or anaphylactoid reactions to GAMUNEX-C or GAMIMUNE N, 10% in clinical trials.

In the IV efficacy and safety study, serum samples were drawn to monitor the virus safety at baseline and one week after the first infusion of IGIV (for parvovirus B19), eight weeks after first and fifth infusion of IGIV (for hepatitis C, hepatitis B, and HIV-1), 16 weeks after the first and fifth infusion of IGIV (for hepatitis C) and at any time of premature discontinuation of the study (for hepatitis C, hepatitis B, HIV-1, and parvovirus B19). Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, Polymerase Chain Reaction [PCR]) and serological testing. There were no treatment related emergent findings of virus transmission for either GAMUNEX-C or GAMIMUNE N, 10%.

PI: Subcutaneous Administration (PK and Safety Studies)

Adverse reactions were divided into 2 types: 1) Local infusion site reactions, and 2) Non-infusion site adverse reactions. Table 4 lists those adverse reactions (as defined for Table 2) occurring in ≥ 2% of infusions during the SC phase of two pharmacokinetic (PK) crossover and safety trials, one in adults and adolescents and the other in children and adolescents. *[see Clinical Pharmacology (12.3)]*

Table 4: Most Frequent Adverse Reactions (≥ 2% of infusions) by Infusion in the SC Phase

Adverse Reactions	Number (Rate*)	
	Adult, Adolescent (Study 060001)	Child, Adolescent (Study T5004-401)
Non-infusion Site Adverse Reactions		
Headache	25 (0.03)	1 (0.01)
Abdominal Pain	1 (<0.01)	2 (0.02)
Local Infusion Site Reactions†,‡		
Mild	389 (0.54)	56 (0.46)
Moderate	29 (0.04)	4 (0.03)
Severe	9 (0.01)	1 (0.01)

*For each trial, rate is calculated by the total number of events divided by the number of infusions received (725 for the adult and adolescent trial and 121 for the children/adolescent trial).

†All local infusion site reactions were *a priori* considered drug-related.

‡At each level of summation (Preferred Term), local infusion site reactions are counted only once if they occur at the same infusion visit.
Mild - usually transient in nature and generally not interfering with normal activities
Moderate - sufficiently discomforting to interfere with normal activities
Severe - prevents normal activities

Table 5 lists the adverse reactions occurring in ≥ 5% of subjects and the frequency of adverse reactions (as defined for Table 2) per infusion.

Table 5: Most Frequent Adverse Reactions (≥ 5% of subjects) by Subject and Infusion in the SC Phase

Adverse Reaction	Adult, Adolescent (Study 060001)		Child, Adolescent (Study T5004-401)	
	No. of Subjects n=32 (%)	No. of Adverse Reactions (Rate*)	No. of Subjects n=11 (%)	No. of Adverse Reactions (Rate*)
Local Infusion Site Reaction†,‡	24 (75.0%)	427 (0.59)	11 (100%)	61 (0.50)
Fatigue	5 (15.6%)	6 (0.01)	0	0
Headache	4 (12.5%)	25 (0.03)	1 (9.1%)	1 (0.01)
Upper respiratory tract infection	4 (12.5%)	5 (0.01)	1 (9.1%)	1 (0.01)
Arthralgia	3 (9.4%)	6 (0.01)	0	0
Diarrhea	3 (9.4%)	6 (0.01)	0	0
Nausea	3 (9.4%)	4 (0.01)	0	0
Sinusitis	3 (9.4%)	4 (0.01)	0	0
Abdominal pain	1 (3.1%)	1 (<0.01)	1 (9.1%)	2 (0.02)
Abdominal pain upper	0	0	1 (9.1%)	1 (0.01)
Autoimmune thryroiditis	0	0	1 (9.1%)	1 (0.01)
Drug hypersensitivity	0	0	1 (9.1%)	1 (0.01)
Influenza	0	0	1 (9.1%)	1 (0.01)
Oropharyngeal pain	0	0	1 (9.1%)	1 (0.01)
Skin chapped	0	0	1 (9.1%)	1 (0.01)
Viral upper respiratory tract infection	0	0	1 (9.1%)	1 (0.01)
Wheezing	1 (3.1%)	1 (<0.01)	1 (9.1%)	1 (0.01)
Bronchitis	2 (6.3%)	2 (<0.01)	0	0
Depression	2 (6.3%)	2 (<0.01)	0	0
Dermatitis allergic	2 (6.3%)	2 (<0.01)	0	0
Erythema	2 (6.3%)	2 (<0.01)	0	0
Migraine	2 (6.3%)	2 (<0.01)	0	0
Myalgia	2 (6.3%)	2 (<0.01)	0	0
Pyrexia	2 (6.3%)	2 (<0.01)	0	0
Viral infection	2 (6.3%)	2 (<0.01)	0	0

*For each trial, rate is calculated by the total number of events divided by the number of infusions received (725 for the adult and adolescent trial and 121 for the children/adolescent trial).

† All local infusion site reactions were *a priori* considered drug-related.

‡ At each level of summation (Preferred Term), infusion site reactions are counted only once if they occur at the same infusion visit.

There were no serious bacterial infections in the SC phase of the PK and safety trials.

Local Infusion Site Reactions

Local infusion site reactions with SC GAMUNEX®-C [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified] consisted of erythema, pain and swelling. One child discontinued due to infusion site pain. The majority of local infusion site reactions resolved within 3 days. The number of subjects experiencing an infusion site reaction and the number of infusion site reactions decreased over time as subjects received continued weekly SC infusions. At the beginning of the SC phase (week 1) in the adult and adolescent trial, a rate of approximately 1 infusion site reaction per infusion was reported, whereas at the end of the study (week 24) this rate was reduced to 0.5 infusion site reactions per infusion, a reduction of 50%. In the children and adolescent trial, the rate of local infusion site reactions decreased from week 1 for all age groups by the end of the study.

ITP

In two different clinical trials to study ITP, out of 76 subjects treated with GAMUNEX-C, 2 subjects discontinued due to the following adverse reactions: Hives and Headache/Fever/Vomiting.

One subject, a 10-year-old boy, died suddenly from myocarditis 50 days after his second infusion of GAMUNEX-C. The death was judged to be unrelated to GAMUNEX-C.

No pre-medication with corticosteroids was permitted by the protocol. Twelve ITP subjects treated in each treatment group were pretreated with medication prior to infusion. Generally, diphenhydramine and/or acetaminophen were used. More than 90% of the observed drug related adverse events were of mild to moderate severity and of transient nature.

The infusion rate was reduced for 4 of the 97 exposed subjects (1 GAMUNEX-C, 3 GAMIMUNE® N, 10% [Immune Globulin Intravenous (Human), 10%]) on 4 occasions. Mild to moderate headache, nausea, and fever were the reported reasons.

Table 6 lists the adverse reactions (as defined for Table 2) reported by at least 5% of subjects during the 3-month efficacy and safety study.

Table 6: Adverse Reactions Occurring in ≥ 5% of Subjects

Adverse Reaction	GAMUNEX®-C No. of subjects: 48 Number (percentage of all subjects)	GAMIMUNE® N, 10% No. of subjects: 49 Number (percentage of all subjects)
Headache	25 (52.1%)	26 (53.1%)
Vomiting	6 (12.5%)	8 (16.3%)
Ecchymosis	7 (14.6%)	2 (4.1%)
Fever	6 (12.5%)	6 (12.2%)
Nausea	6 (12.5%)	5 (10.2%)
Rash	4 (8.3%)	0
Abdominal Pain	3 (6.3%)	3 (6.1.%)
Back Pain	3 (6.3%)	2 (4.1.%)
Dyspepsia	3 (6.3%)	0
Asthenia	2 (4.2%)	3 (6.1%)
Dizziness	2 (4.2%)	3 (6.1%)

Serum samples were drawn to monitor the virus safety of the ITP subjects at baseline, nine days after the first infusion (for parvovirus B19), and 3 months after the first infusion of IGIV and at any time of premature discontinuation of the study. Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, PCR), and serological testing. There were no treatment related emergent findings of virus transmission for either GAMUNEX-C or GAMIMUNE N, 10%.

CIDP

In the CIDP efficacy and safety study, 113 subjects were exposed to GAMUNEX-C and 95 were exposed to Placebo. *[see Clinical Studies (14)]* As a result of the study design, the drug exposure with GAMUNEX-C was almost twice that of Placebo, with 1096 GAMUNEX-C infusions versus 575 Placebo infusions. Therefore, adverse reactions are reported per infusion (represented as frequency) to correct for differences in drug exposure between the 2 groups. The majority of loading-doses were administered over 2 days. The majority of maintenance-doses were administered over 1 day. Infusions were administered in the mean over 2.7 hours.

Table 7 shows the numbers of subjects per treatment group in the CIDP clinical trial, and the reason for discontinuation due to adverse events.

Table 7: Reasons for Discontinuation Due to Adverse Events

Number of Subjects		Number of Subjects Discontinued due to Adverse Events	Adverse Event
GAMUNEX®-C	113	3 (2.7%)	Urticaria, Dyspnea, Bronchopneumonia
Placebo	95	2 (2.1%)	Cerebrovascular Accident, Deep Vein Thrombosis

The most common adverse reactions with GAMUNEX-C were headache and pyrexia. Table 8 lists adverse reactions (as defined for Table 2) reported by at least 5% of subjects in any treatment group.

Table 8: Adverse Reactions Occurring in ≥ 5% of Subjects

	GAMUNEX®-C No. of subjects: 113			Placebo No. of subjects: 95		
MedDRA Preferred Term*	No. of Subjects (%)	No. of Adverse Reactions	Incidence density†	No. of Subjects (%)	No. of Adverse Reactions	Incidence density†
Headache	35 (31.0%)	50	0.046	7 (7.4%)	9	0.016
Pyrexia	15 (13.3%)	27	0.025	0	0	
Hypertension	10 (8.8%)	19	0.017	3 (3.2%)	3	0.005
Chills	9 (8.0%)	10	0.009	0	0	
Nausea	7 (6.2%)	9	0.008	3 (3.2%)	3	0.005
Rash	7 (6.2%)	10	0.009	1 (1.1%)	1	0.002
Arthralgia	6 (5.3%)	7	0.006	0	0	
Asthenia	6 (5.3%)	6	0.005	1 (1.1%)	2	0.003

* Reported in ≥ 5% of subjects in any treatment group.

† Calculated by the total number of adverse reactions divided by the number of infusions received (1096 for GAMUNEX-C and 575 for Placebo).

The most serious adverse reaction observed in clinical study subjects receiving GAMUNEX-C for CIDP was pulmonary embolism (PE) in one subject with a history of PE.

Laboratory Abnormalities

During the course of the clinical program, ALT and AST elevations were identified in some subjects.

- For ALT, in the IV PI study treatment emergent elevations above the upper limit of normal were transient and observed among 14/80 (18%) of subjects in the GAMUNEX-C group versus 5/88 (6%) of subjects in the GAMIMUNE N, 10% group (p=0.026).
- In the SC PI study treatment emergent laboratory abnormalities during the SC phase occurred in several subjects. Four subjects (4/32, 13%) had elevated Alkaline Phosphatase. One subject (1/32, 3%) had an elevated ALT and three subjects (3/32, 9%) had an elevated AST. No elevations were > 1.6 times the upper limit of normal.
- In the ITP study which employed a higher dose per infusion, but a maximum of only two infusions, the reverse finding for elevation of ALT was observed among 3/44 (7%) of subjects in the GAMUNEX-C group versus 8/43 (19%) of subjects in the GAMIMUNE N, 10% group (p=0.118).
- In the CIDP study, 15/113 (13%) of subjects in the GAMUNEX-C group and 7/95 (7%) in the Placebo group (p=0.168) had a treatment emergent transient elevation of ALT.

Elevations of ALT and AST were generally mild (< 3 times upper limit of normal), transient, and were not associated with obvious symptoms of liver dysfunction.

GAMUNEX-C may contain low levels of anti-Blood Group A and B antibodies primarily of the IgG_4 class. Direct antiglobulin tests (DAT or direct Coombs tests), which are carried out in some centers as a safety check prior to red blood cell transfusions, may become positive temporarily. There were 2 cases of hemolytic anemia across these clinical trials. One hemolytic event not associated with positive DAT findings was observed in the IV PI study in a woman with common variable immune deficiency and B12 deficiency (pernicious anemia) at a dose of (450 mg/kg). The other hemolytic event occurred in the CIDP study in a subject with positive DAT at a dose of 1 g/kg.

6.2 Postmarketing Experience

Because adverse reactions are voluntarily reported post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequencies or establish a causal relationship to product exposure.

The following adverse reactions have been identified during post-approval use of IGIV products,[8,20] including GAMUNEX-C:

- *Infusion Reactions:* Hypersensitivity (e.g., anaphylaxis), tachycardia, malaise, flushing, or other skin reactions, chest discomfort, rigors, and changes in blood pressure
- *Renal:* Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures/convulsions, tremor, aseptic meningitis
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, hemolytic anemia, positive direct antiglobulin (Coombs test)
- *General/Body as a Whole:* Rigors
- *Gastrointestinal:* Hepatic dysfunction

7 DRUG INTERACTIONS

GAMUNEX-C may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline. Admixtures of GAMUNEX-C with other drugs and intravenous solutions have not been evaluated. It is recommended that GAMUNEX-C be administered separately from other drugs or medications which the patient may be receiving. The product should not be mixed with IGIVs from other manufacturers.

The infusion line may be flushed before and after administration of GAMUNEX-C with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.

Avoid simultaneous administration of GAMUNEX-C and Heparin through a single lumen delivery device due to GAMUNEX-C, Heparin incompatibilities. Flush Heparin Lock (Hep-Lock) through which GAMUNEX-C was administered with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection, and do not flush with Heparin.

Various passively transferred antibodies in immunoglobulin preparations can confound the results of serological testing.

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 GAMUNEX-C so that appropriate measures may be taken. *[see Patient Counseling Information (17)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with GAMUNEX-C use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with GAMUNEX-C. It is not known whether GAMUNEX-C can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMUNEX-C should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of GAMUNEX-C 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 GAMUNEX-C and any potential adverse effects on the breastfed infant from GAMUNEX-C or from the underlying maternal condition.

8.4 Pediatric Use

PI: Intravenous

GAMUNEX-C was evaluated in 18 pediatric subjects (age range 0-16 years). Twenty-one percent of PI subjects exposed to GAMUNEX-C were children. Pharmacokinetics, safety and efficacy were similar to those in adults with the exception that vomiting was more frequently reported in pediatrics (3 of 18 subjects). No pediatric-specific dose requirements were necessary to achieve serum IgG levels.

PI: Subcutaneous

SC GAMUNEX-C was evaluated in three pediatric subjects (age range 13-15 years) with PI along with adults, and separately in a second trial in 11 children and adolescents (age range 2-16 years). Pharmacokinetics and safety were similar to those in adults. No pediatric-specific dose requirements were necessary to achieve circulating IgG levels. Efficacy and safety in pediatric patients under 2 years of age using the SC route of administration have not been established.

ITP

For treatment of ITP, GAMUNEX-C **must be administered by the intravenous route.**

GAMUNEX-C was evaluated in 12 pediatric subjects with acute ITP. Twenty-five percent of the acute ITP subjects exposed to GAMUNEX-C were children. Pharmacokinetics, safety and efficacy were similar to those in adults with the exception that fever was more frequently reported in pediatrics (6 of 12 subjects). No pediatric-specific dose requirements were necessary to achieve serum IgG levels. One subject, a 10-year-old boy, died suddenly from myocarditis 50 days after his second infusion of GAMUNEX-C. The death was judged to be unrelated to GAMUNEX-C.

CIDP

The safety and effectiveness of GAMUNEX-C have not been established in pediatric subjects with CIDP.

8.5 Geriatric Use

Use caution when administering GAMUNEX-C to patients age 65 and over who are at increased risk for thrombosis or renal insufficiency. *[see Boxed Warning, Warnings and Precautions (5.2, 5.4)]* Do not exceed recommended doses, and administer GAMUNEX-C at the minimum infusion rate practicable. Clinical studies of GAMUNEX-C did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

With intravenous administration, overdose of GAMUNEX-C may lead to fluid overload and hyperviscosity. Patients at risk of complications of fluid overload and hyperviscosity include elderly patients and those with cardiac renal impairment.

11 DESCRIPTION

GAMUNEX-C is a ready-to-use sterile, non-pyrogenic solution of human immune globulin protein for intravenous and subcutaneous (PI indication only) administration. GAMUNEX-C is clear to opalescent, and colorless to pale yellow. GAMUNEX-C consists of 9%–11% protein in 0.16–0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin. The main component of GAMUNEX-C is IgG (≥98%) with a sub-class distribution of IgG_1, IgG_2, IgG_3 and IgG_4 of approximately 62.8%, 29.7%, 4.8%, and 2.7% respectively. The distribution of IgG subclasses is similar to that found in normal serum.

GAMUNEX-C contains trace levels of fragments, IgA (average 0.046 mg/mL), and IgM. GAMUNEX-C doses of 1 g/kg correspond to a glycine dose of 0.15 g/kg. While toxic effects of glycine administration have been reported, the doses and rates of administration were 3–4 fold greater than those for GAMUNEX-C. In another study it was demonstrated that intravenous bolus doses of 0.44 g/kg glycine were not associated with serious adverse effects.[21] Caprylate is a saturated medium-chain (C8) fatty acid of plant origin. Medium chain fatty acids are considered to be essentially non-toxic. Human subjects receiving medium chain fatty acids parenterally have tolerated doses of 3.0 to 9.0 g/kg/day for periods of several months without adverse effects.[22] Residual caprylate concentrations in the final container are no more than 0.216 g/L (1.3 mmol/L). The measured buffer capacity is 35 mEq/L (0.35 mEq/g protein) and the osmolality is 258 mOsmol/kg solvent, which is close to physiological osmolality (285-295 mOsmol/kg). A dose of 1 g/kg body weight therefore represents an acid load of 0.35 mEq/kg body weight. The total buffering capacity of whole blood in a normal individual is 45-50 mEq/L of blood, or 3.6 mEq/kg body weight. Thus, the acid load delivered with a dose of 1 g/kg of GAMUNEX-C would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused instantaneously. The pH of GAMUNEX-C is 4.0–4.5. GAMUNEX-C contains no preservative. GAMUNEX-C is not made with natural rubber latex.

GAMUNEX-C 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. GAMUNEX-C is incubated in the final container (at the low pH of 4.0–4.3). The product is intended for intravenous administration and may be administered subcutaneously in treatment of PI.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model, using the following enveloped and non-enveloped viruses: human immunodeficiency virus, type I (HIV-1) as the relevant virus for HIV-1 and HIV-2; bovine viral diarrhea virus (BVDV) as a model for hepatitis C virus; pseudorabies virus (PRV) as a model for large enveloped DNA viruses (e.g., herpes viruses); Reovirus type 3 (Reo) as a model for non-enveloped viruses and for its resistance to physical and chemical inactivation; hepatitis A virus (HAV) as relevant non-enveloped virus, and porcine parvovirus (PPV) as a model for human parvovirus B19.[23]

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

Table 9: Log_{10} Virus Reduction

Process Step	Log_{10} Virus Reduction					
	Enveloped Viruses			Non-enveloped Viruses		
	HIV	PRV	BVDV	Reo	HAV	PPV
Caprylate Precipitation/Depth Filtration	C/I*	C/I*	2.7	≥3.5	≥3.6	4.0
Caprylate Incubation	≥4.5	≥4.6	≥4.5	NA†	NA†	NA†
Depth Filtration‡	CAP§	CAP§	CAP§	≥4.3	≥2.0	3.3
Column Chromatography	≥3.0	≥3.3	4.0	≥4.0	≥1.4	4.2
Nanofiltration	≥3.7	M/I‖	≥4.1	≥1.8	M/I‖	< 1.0
Low pH Incubation	≥6.5	≥4.3	≥5.1	NA†	NA†	NA†
Global Reduction¶	≥17.7	≥12.2	≥20.4	≥9.3	≥5.0	8.2

* C/I - Interference by caprylate precluded determination of virus reduction for this step. Although removal of viruses is likely to occur at the caprylate precipitation/depth filtration step, BVDV is the only enveloped virus for which reduction is claimed. The presence of caprylate prevents detection of other, less resistant enveloped viruses and therefore their removal cannot be assessed.

† NA – Not Applicable: This step has no effect on non-enveloped viruses.

‡ Some mechanistic overlap occurs between depth filtration and other steps. Therefore, Grifols Therapeutics LLC has chosen to exclude this step from the global virus reduction calculations.

§ CAP - The presence of caprylate in the process at this step prevents detection of enveloped viruses, and their removal cannot be assessed.

‖ M/I - Interference by the process intermediate matrix precluded determination of virus removal capacity for this step.

¶ Sum of reduction factors greater than or equal to 1 log_{10}.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.[23]

Several of the individual production steps in the GAMUNEX-C manufacturing process have been shown to decrease TSE infectivity of that experimental model agent. TSE reduction steps include two depth filtrations (in sequence, a total of ≥ 6.6 log_{10}). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PI

GAMUNEX-C supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacterial, viral, parasitic, and mycoplasmal agents, and their toxins. The mechanism of action in PI has not been fully elucidated.

ITP

The mechanism of action of high doses of immunoglobulins in the treatment of ITP has not been fully elucidated.

CIDP

The precise mechanism of action in CIDP has not been fully elucidated.

12.3 Pharmacokinetics

Two pharmacokinetic crossover trials were carried out with GAMUNEX-C in 44 subjects with Primary Humoral Immunodeficiency to assess intravenous vs subcutaneous administration. In the first study, a single sequence, open-label, crossover trial in adults and adolescents, the pharmacokinetics, safety, and tolerability of SC administered GAMUNEX-C in subjects with PI were evaluated.[24] A total of 32 and 26 subjects received GAMUNEX-C as IV or SC for PK study, respectively, of whom 3 were adolescents. Subjects received GAMUNEX-C 200-600 mg/kg IV every 3-4 weeks for at least 3 months, at which time they entered the IV phase of the study. Subjects were crossed over to weekly SC infusions. The weekly SC dose was determined by multiplying the total IV dose by 1.37 and dividing the resultant new total dose by 3 or 4 depending on the previous IV interval.

In the second study, a single sequence, open-label, crossover trial, the pharmacokinetics, safety, and tolerability of SC administered GAMUNEX-C were evaluated in children and adolescents. The design of the study was essentially the same as above. A total of 11 subjects received GAMUNEX-C as IV and 10 received GAMUNEX-C as SC for PK analysis. Age groups were as follows: age 2 to 5 years, [N=1 both phases]; 6 to 11 years, [N = 5 completing IV phase, N = 4 evaluated in SC phase]; 12-16 years: [N = 5 both phases].

Intravenous Administration

The pharmacokinetic parameters of GAMUNEX-C, measured as total IgG for intravenous administration are shown in Table 10.

Table 10: PK Parameters Following IV Administration of GAMUNEX®-C by Age

Age Group	Statistics	$t_{1/2}$ (hr)	$AUC_{(0\text{-}t)}$ (hr*mg/mL)	$AUC_{(0\text{-}tau)}$ (hr*mg/mL)	$CL_{(0\text{-}t)}$ (mL/hr/kg)	Vss (mL/kg)
2 – 5 years N = 1	Mean SD*	1038.50 NA*	7479.0 NA*	7499.0 NA*	0.05430 NA*	82.040 NA*
6 – 11 years N = 5	Mean SD*	758.52 137.989	5953.6 1573.84	6052.6 1333.59	0.09128 0.027465	94.784 17.6773
12 – 16 years N = 8	Mean SD*	717.90 170.141	8131.9 1173.38	8009.5 1358.76	0.07029 0.015912	73.303 17.2204
≥17 years N = 29	Mean SD*	720.62 130.864	7564.9 1190.68	7524.8 1183.05	0.06243 0.015547	65.494 18.7172

* SD - standard deviation; NA - not applicable.
Source: studies 060001, T5004-401

PI: Subcutaneous Administration

The PK parameter (AUC of total IgG) following IV and SC administration is summarized in Table 11 for subcutaneous vs intravenous administration in the two pharmacokinetic trials. In the adult and adolescent trial, the lower bound of the 90% confidence interval for the geometric mean ratio of AUC (SC vs. IV) was 0.861, therefore, meeting the pre-specified non-inferiority margin between the two modes of administration. The PK analysis results in children and adolescents are consistent to those in the adult and adolescent trial, demonstrating the appropriateness of the conversion factor of 1.37 applied to calculating the SC dose from the IV dose of GAMUNEX-C in pediatric populations.

Table 11: Summary of AUC of Total IgG at Steady State Following IV or SC Administration of GAMUNEX®-C by Age

Route of Administration	IV (N = 43)			SC (N = 36)	
Age Group (N) Statistics	$AUC_{0\text{-}\tau,IV}$ (h*mg/mL) (0-21 days)	$AUC_{0\text{-}\tau,IV}$ (h*mg/mL) (0-28 days)	Adj._$AUC_{0\text{-}\tau,IV}$* (h*mg/mL) (0-7 days)	$AUC_{0\text{-}\tau,SC}$ (h*mg/mL) (0-7 days)	AUC Ratio, SC/IV
2-5 years (N) Mean %CV Range	 NC† NC† NC†	1 7498.7 NC† NC†	1 1874.7 NC† NC†	1 2023.0 NC† NC†	1 1.080 - NC†
6-11 years (N) Mean %CV Range	5 6052.7 22% 4868 - 8308	 NC† NC† NC†	5 2017.6 22% 1623 - 2769	4 2389.2 19% 1971 - 3039	4 1.135 - 1.10 - 1.21
12-16 years (N) Mean %CV Range	5 7396.0 17% 5271 - 8754	3 9032.0 9% 8504 - 9950	8 2387.6 15% 1757 - 2918	7 2361.9 14% 1876 - 2672	7 0.982 - 0.86 - 1.07
≥17 years (N) Mean %CV Range	10 7424.7 14% 5781 - 9552	19 7577.4 17% 5616 - 10400	29 2094.5 20% 1404 - 3184	24 1899.9 20% 1300 - 2758	24 0.882 - 0.70 - 1.04

* Adj._$AUC_{0\text{-}\tau,IV}$: Adjusted weekly IV $AUC_{(0\text{-}7\ days)}$ is calculated as $AUC_{(0\text{-}21\ days)}/3$ or $AUC_{(0\text{-}28\ days)}/4$.
† NC - not calculated
Source: Studies 060001, T5004-401

The mean trough concentrations (mean C_{trough}) of total IgG following IV and SC administration are presented in Table 12 for both studies.

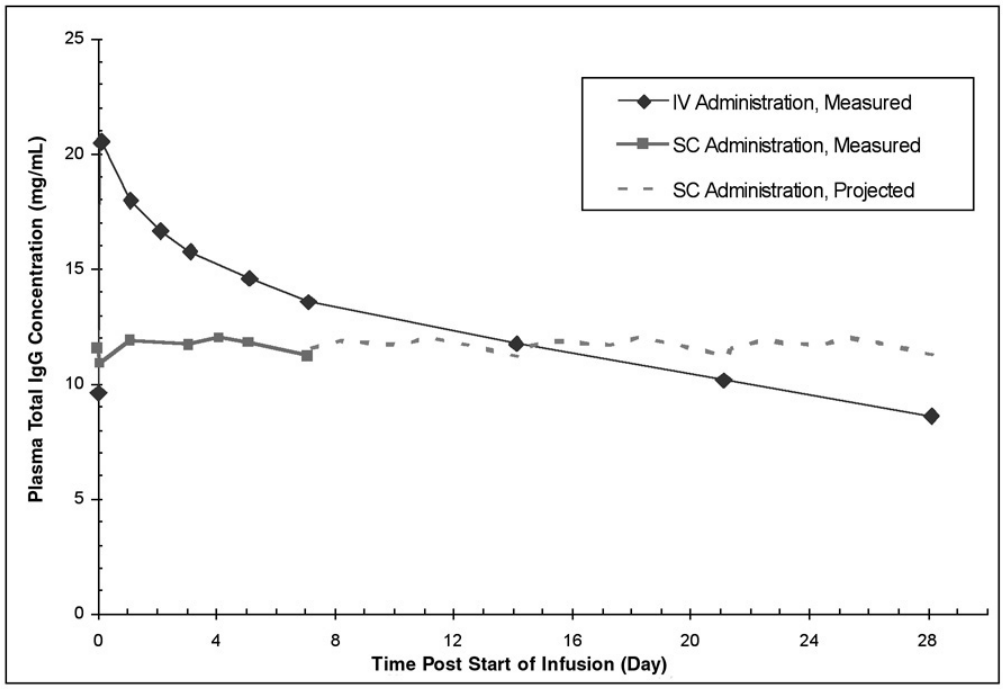
Table 12: Mean Trough Concentrations of Total IgG (mg/mL)

	Adult, Adolescent*		Child, Adolescent†	
	IV Mean C_{trough}	SC Mean C_{trough}	IV Mean C_{trough}	SC Mean C_{trough}
n	32	28	11	10
Mean (mg/mL)	9.58	11.4	9.97	13.25
%CV	22.3	20.4	19	14
Range	6.66-14.0	8.10-16.2	7.84-13.20	10.77-16.90

* Measured in plasma; † Measured in serum

In contrast to plasma total IgG levels observed with monthly IV GAMUNEX-C treatment (rapid peaks followed by a slow decline), the plasma IgG levels in subjects receiving weekly SC GAMUNEX-C therapy were relatively stable (Figure 7, adult and adolescent trial).

Figure 7: Mean Steady-state Plasma Total IgG Concentration vs. Time Curves Following IV Administration or Weekly SC Administration in Adults and Adolescents



14 CLINICAL STUDIES

PI: Intravenous Administration

In a randomized, double-blind, parallel group clinical trial with 172 subjects with primary humoral immunodeficiencies GAMUNEX-C was demonstrated to be at least as efficacious as GAMIMUNE N, 10% in the prevention of any infection, i.e., validated plus clinically defined, non-validated infections of any organ system, during a nine month treatment period.[25] Twenty-six subjects were excluded from the Per Protocol analysis (2 due to non-compliance and 24 due to protocol violations). The analysis for efficacy was based on the annual rate of bacterial infections, pneumonia, acute sinusitis and acute exacerbations of chronic sinusitis.

Table 13: Efficacy Results Per Protocol Analysis

	No. of Subjects with at Least One Infection (%)		Mean Difference (90% Confidence Interval)	p-Value
	GAMUNEX®-C (n = 73)	GAMIMUNE® N, 10% (n = 73)		
Validated Infections	9 (12%)	17 (23%)	-0.117 (-0.220, -0.015)	0.06
Acute Sinusitis	4 (5%)	10 (14%)		
Exacerbation of Chronic Sinusitis	5 (7%)	6 (8%)		
Pneumonia	0 (0%)	2 (3%)		
Any Infection*	56 (77%)	57 (78%)	-0.020 (-0.135, 0.096)	0.78

* Validated infections plus clinically defined, non-validated infections.

The annual rate of validated infections (Number of Infections/year/subject) was 0.18 in the group treated with GAMUNEX-C and 0.43 in the group treated with GAMIMUNE N, 10% (p=0.023). The annual rates for any infection (validated plus clinically-defined, non-validated infections of any organ system) were 2.88 and 3.38, respectively (p=0.300).

ITP

A double-blind, randomized, parallel group clinical trial with 97 ITP subjects was carried out to test the hypothesis that GAMUNEX-C was at least as effective as GAMIMUNE N, 10% in raising platelet counts from less than or equal to 20 $x10^9$/L to more than 50 $x10^9$/L within 7 days after treatment with 2 g/kg IGIV. Twenty-four percent of the subjects were less than or equal to 16 years of age.[26]

GAMUNEX-C was demonstrated to be at least as effective as GAMIMUNE N, 10% in the treatment of adults and children with acute or chronic ITP.

Table 14: Platelet Response of Per Protocol Analysis

	Number of Responders (percent of all subjects)		Mean Difference (90% Confidence Interval)
	GAMUNEX®-C (n=39)	GAMIMUNE® N, 10% (n=42)	
By Day 7	35 (90%)	35 (83%)	0.075 (-0.037, 0.186)
By Day 23	35 (90%)	36 (86%)	0.051 (-0.058, 0.160)
Sustained for 7 days	29 (74%)	25 (60%)	0.164 (0.003, 0.330)

A trial was conducted to evaluate the clinical response to rapid infusion of GAMUNEX-C in patients with ITP. The study involved 28 chronic ITP subjects, wherein the subjects received 1 g/kg GAMUNEX-C on three occasions for treatment of relapses. The infusion rate was randomly assigned to 0.08, 0.11, or 0.14 mL/kg/min (8, 11 or 14 mg/kg/min). Pre-medication with corticosteroids to alleviate infusion-related intolerability was not permitted. Pre-treatment with antihistamines, anti-pyretics and analgesics was permitted. The average dose was approximately 1 g/kg body weight at all three prescribed rates of infusion (0.08, 0.11 and 0.14 mL/kg/min). All patients were administered each of the three planned infusions except seven subjects. Based on 21 patients per treatment group, the a posteriori power to detect twice as many drug-related adverse events between groups was 23%. Of the seven subjects that did not complete the study, five did not require additional treatment, one withdrew because he refused to participate without concomitant medication (prednisone) and one experienced an adverse event (hives); however, this was at the lowest dose rate level (0.08 mL/kg/min).

CIDP

A multi-center, randomized, double-blind, Placebo-controlled trial (The Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified CIDP Efficacy or ICE study) was conducted with GAMUNEX-C.[27] This study included two separately randomized periods to assess whether GAMUNEX-C was more effective than Placebo for the treatment of CIDP (assessed in the Efficacy Period for up to 24 weeks) and whether long-term administration of GAMUNEX-C could maintain long-term benefit (assessed in the 24 week Randomized Withdrawal Period).

In the Efficacy Period, there was a requirement for Rescue (crossover) to the alternate study drug if the subject did not improve and maintain this improvement until the end of the 24 week treatment period. Subjects entering the Rescue phase followed the same dosing and schedule as in the Efficacy period. Any subject who was rescued (crossed over) and did not improve and maintain this improvement was withdrawn from the study.

Subjects who completed 24 weeks treatment in the Efficacy period or Rescue phase and responded to therapy were eligible for entry into a double-blind Randomized Withdrawal Period. Eligible subjects were re-randomized to GAMUNEX-C or Placebo. Any subject who relapsed was withdrawn from the study.

The Efficacy Period and the Rescue treatment started with a loading dose of 2 g/kg body weight of GAMUNEX-C or equal volume of Placebo given over 2-4 consecutive days. All other infusions (including the first infusion of the Randomized Withdrawal Period) were given as maintenance doses of 1 g/kg body weight (or equivalent volume of Placebo) every three weeks.

The Responder rates of the GAMUNEX-C and Placebo treatment groups were measured by the INCAT score. The INCAT (Inflammatory Neuropathy Cause and Treatment) scale is used to assess functional disability of both upper and lower extremities in demyelinating polyneuropathy. The INCAT scale has upper and lower extremity components (maximum of 5 points for upper (arm disability) and maximum of 5 points for lower (leg disability)) that add up to a maximum of 10-points (0 is normal and 10 is severely incapacitated).[28] At the start of the efficacy portion of the study, the INCAT scores were as follows: Upper Extremity mean was 2.2 $\pm$ 1.0, and median was 2.0 with a range of 0 to 5; Lower Extremity mean was 1.9 $\pm$ 0.9, and median was 2.0 with a range of 1 to 5; Total Overall Score mean was 4.2 $\pm$ 1.4, and median was 4.0 with a range of 2 to 9. A Responder was defined as a subject with at least 1-point improvement from baseline in the adjusted INCAT score that was maintained through 24 weeks.

More subjects with CIDP responded to GAMUNEX-C: 28 of 59 subjects (47.5%) responded to GAMUNEX-C compared with 13 of 58 subjects (22.4%) administered Placebo (25% difference; 95% CI 7%-43%; **p=0.006**). The study included both subjects who were IGIV naïve and subjects who had previous IGIV experience. The outcome was influenced by the group of subjects who experienced prior therapy with IGIV, as shown by the outcomes table, below.

Time to relapse for the subset of 57 subjects who previously responded to GAMUNEX-C was evaluated: 31 were randomly reassigned to continue to receive GAMUNEX-C and 26 subjects were randomly reassigned to Placebo in the Randomized Withdrawal Period. Subjects who continued to receive GAMUNEX-C experienced a longer time to relapse versus subjects treated with Placebo (**p=0.011**). The probability of relapse was 13% with GAMUNEX-C versus 45% with Placebo (hazard ratio, 0.19; 95% confidence interval, 0.05, 0.70).

Table 15: Outcomes in Intent-to-Treat Population Efficacy Period

Efficacy Period	GAMUNEX®-C		Placebo		p-value*
	Responder	Non-Responder	Responder	Non-Responder	
All Subjects	28/59 (47.5%)	31/59 (52.5%)	13/58 (22.4%)	45/58 (77.6%)	0.006
IGIV – Naïve Subjects	17/39 (43.6%)	22/39 (56.4%)	13/46 (28.3%)	33/46 (71.7%)	0.174
IGIV – Experienced Subjects	11/20 (55.0%)	9/20 (45.0%)	0/12 (0%)	12/12 (100%)	0.002

* p-value based on Fisher's exact method

The following table shows outcomes for the Rescue Phase (which are supportive data):

Table 16: Outcomes in Rescue Phase

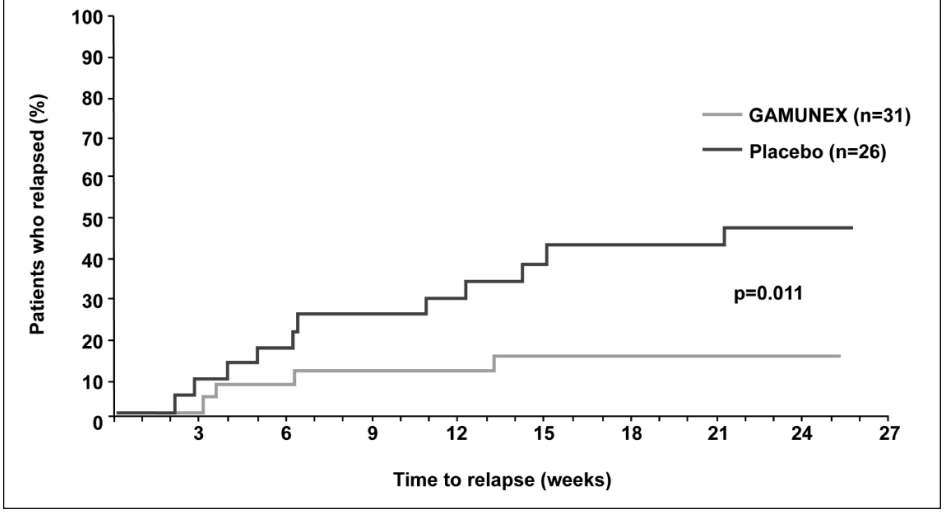
Rescue Period	GAMUNEX®-C		Placebo		p-value*
	Success	Failure	Success	Failure	
All Subjects	25/45 (55.6%)	20/45 (44.4%)	6/23 (26.1%)	17/23 (73.9%)	0.038
IGIV – Naïve Subjects	19/33 (57.6%)	14/33 (42.4%)	6/18 (33.3%)	12/18 (66.7%)	0.144
IGIV – Experienced Subjects	6/12 (50%)	6/12 (50%)	0/5 (0%)	5/5 (100%)	0.102

* p-value based on Fisher's exact method

The following Kaplan-Meier curves show the outcomes for the Randomized Withdrawal Period:

Figure 8: Outcome for Randomized Withdrawal Period

Secondary Endpoint Randomized Withdrawal Period	Time to Relapse	p-value* p=0.011



* p-value based on log-rank test

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16 HOW SUPPLIED/STORAGE AND HANDLING

GAMUNEX-C is supplied in single-use, tamper evident vials (shrink band) containing the labeled amount of functionally active IgG. The four larger vial size labels incorporate integrated hangers. GAMUNEX-C is not made with natural rubber latex.

GAMUNEX-C is supplied in the following sizes:

NDC Number	Size	Grams Protein
13533-800-12	10 mL	1
13533-800-15	25 mL	2.5
13533-800-20	50 mL	5
13533-800-71	100 mL	10
13533-800-24	200 mL	20
13533-800-40	400 mL	40

- **DO NOT FREEZE**
- Keep the vial in the carton to protect from light.
- GAMUNEX-C may be stored for 36 months at 2–8°C (36–46°F) from the date of manufacture, AND product may be stored at temperatures not to exceed 25°C (77°F) for up to 6 months anytime during the 36 month shelf life, after which the product must be immediately used or discarded.
- Do not use after expiration date.

17 PATIENT COUNSELING INFORMATION

[see Boxed Warning and Warnings and Precautions]

Instruct patients to immediately report the following signs and symptoms to their healthcare provider:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath *[see Warnings and Precautions (5.2)]*
- Symptoms of thrombosis which may include: pain and/or 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 *[see Warnings and Precautions (5.4)]*
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting *[see Warnings and Precautions (5.5)]*
- Increased heart rate, fatigue, yellowing of the skin or eyes, and dark-colored urine *[see Warnings and Precautions (5.6)]*
- Trouble breathing, chest pain, blue lips or extremities, and fever *[see Warnings and Precautions (5.7)]*

Inform patients that GAMUNEX-C is made from human plasma and may contain infectious agents that can cause disease. While the risk GAMUNEX-C can transmit an infectious agent has been reduced by screening plasma donors for prior exposure, testing donated plasma, and by inactivating or removing pathogens during manufacturing, patients should report any symptoms that concern them. *[see Warnings and Precautions (5.9)]*

Inform patients that GAMUNEX-C can interfere with their immune response to live virus vaccines such as measles, mumps and rubella. Inform patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations. *[see Drug Interactions (7)]*

PI: Self-Administration: Subcutaneous Administration Only

Advise the patient to read the FDA-approved patient labeling (Instructions for Use: Subcutaneous Infusion for Primary Humoral Immunodeficiency).

Provide the patient with instructions on subcutaneous infusion for home treatment, if the physician believes that home administration is appropriate for the patient.

- The type of equipment to be used along with its maintenance,
- proper infusion techniques, selection of appropriate infusion sites (e.g., abdomen, thighs, upper arms, and/or lateral hip),
- maintenance of a treatment diary, and
- measures to be taken in case of adverse reactions in the patient instructions.

Manufactured by:

GRIFOLS

Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

3054846/3054847

GAMUNEX®-C

Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified

Instructions for Use: Subcutaneous Infusion for Primary Humoral Immunodeficiency

Information for Patients

Please read this information about GAMUNEX-C carefully before using this medicine. This information does not take the place of talking with your healthcare professional, and it does not include all of the important information about GAMUNEX-C. If you have any questions after reading this, contact your healthcare professional.

What is the most important information I should know about GAMUNEX-C?

GAMUNEX-C should be infused under your skin (in the subcutaneous tissue). DO NOT inject GAMUNEX-C into a blood vessel or directly into a muscle.

What is GAMUNEX-C?

GAMUNEX-C (Găm-yo͞o-nĕx) is an immunoglobulin used to treat primary immune deficiency (PI). Immunoglobulin is another name for the purified antibodies from human plasma that defend the body against infections such as viruses and bacteria. People with PI lack the healthy antibodies needed to fight off these infections. GAMUNEX-C provides those healthy antibodies and will help lower the number and severity of infections you could get.

Who should NOT take GAMUNEX-C?

Do not take GAMUNEX-C if you have known severe allergic reactions or a severe response to Immune Globulin (Human). Tell your doctor if you have had a serious reaction to other medicines that contain immune globulin. Also tell your doctor if you have an immunoglobulin A (IgA) deficiency.

How should I take GAMUNEX-C?

You will take GAMUNEX-C through infusions given just below the skin (in the subcutaneous tissue). As directed by your physician, one or more injection sites on your body will be selected. The number and location of the injection sites depends on the amount you need to receive. Typically, adults may use 1 to 4 needles in different locations at one time. You may use up to 8 needles as directed by your doctor. For children, use up to 6 infusion sites simultaneously. For patients of all ages ensure that the infusion sites are at least 2 inches (5 cm) apart. The needles are attached with a tube to the pump. You will need to have infusions once a week.

Instructions for administering GAMUNEX-C are at the end of this patient Instructions for Use (see "Steps for Administration"). Only use GAMUNEX-C by yourself after you have been instructed by your doctor or healthcare professional.

What should I avoid while taking GAMUNEX-C?

Certain types of vaccines (ones containing a live virus) may not work as well for you if you are also receiving immunoglobulin products like GAMUNEX-C. The antibodies in GAMUNEX-C may prevent the vaccine from working. Before you get a vaccine, tell the doctor or nurse that you are taking GAMUNEX-C.

Tell your doctor or healthcare professional if you are pregnant or plan to become pregnant, or if you are nursing.

What are possible side effects of GAMUNEX-C?

The most common side effects with GAMUNEX-C when given under the skin (subcutaneously) are:

- Redness, swelling, and itching at the injection site
- Fatigue
- Headache
- Pain (including pain in the joints, arms, legs)
- Diarrhea
- Nausea
- Migraine
- Fever

Tell your doctor right away or go to the emergency room if you have hives, trouble breathing, wheezing, dizziness, or fainting. These could be signs of a bad allergic reaction.

Tell your doctor right away if you have any of the following symptoms. They could be signs of a rare, but serious problem.

- Decreased urination, sudden weight gain, fluid retention/swelling in your legs, and/or shortness of breath. They could be signs of a serious kidney problem called renal failure.
- Pain and/or 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. These could be signs of a blood clot in your body (thrombosis). Immediately report symptoms of thrombosis.
- Severe headache, stiff neck, fatigue, fever, sensitivity to light, painful eye movements, nausea and vomiting. These could be signs of a type of brain inflammation called aseptic meningitis.
- Increased heart rate, fatigue, yellow skin or eyes, and dark colored urine. These could be signs of a type of blood problem called hemolytic anemia.
- Chest pains, trouble breathing, blue lips or extremities, and fever. These could be signs of a lung problem called TRALI (transfusion-related acute lung injury).
- Fever over 100°F (37.8°C). This could be a sign of an infection.

Tell your doctor about any side effects that concern you. You can ask your doctor to give you the full prescribing information available to healthcare professionals.

Steps for Administration

Infuse GAMUNEX-C only after you have been trained by your doctor or healthcare professional. Below are step-by-step instructions to help you remember how to use GAMUNEX-C. Ask your doctor or healthcare professional about any instructions you do not understand.

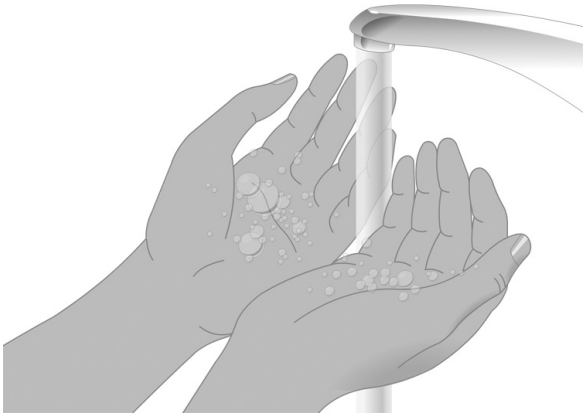
Before Using GAMUNEX-C

- GAMUNEX-C comes in single-use vials.
- Keep it refrigerated. **Do not let it freeze.**
- Keep the vial in the carton to protect from light.
- GAMUNEX-C can be stored at room temperature for up to 6 months but you must use it within that time or you must throw it away.
- Do not shake the vials.
- Prior to use, allow the solution to come to room temperature (68-77°F or 20-25°C). This can take 60 minutes or longer.
- Do not use the vial if:
  - the solution is cloudy, discolored or contains particles. The solution should be clear to opalescent, and colorless to pale yellow.
  - the protective cap or plastic shrink band around the cap is missing, or there is any evidence of tampering. Tell your healthcare provider immediately.
  - the expiration date has passed.
- 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 GAMUNEX-C

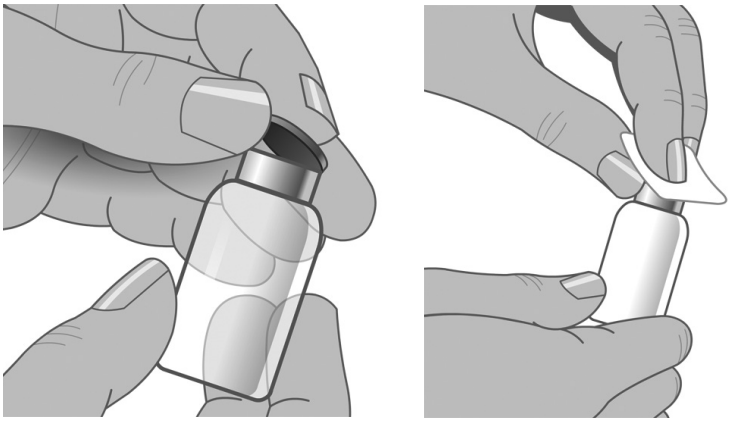
- Your healthcare provider may recommend that you use antibacterial soap or that you wear gloves.



Step 2:

Remove the protective cap and sanitize the stopper

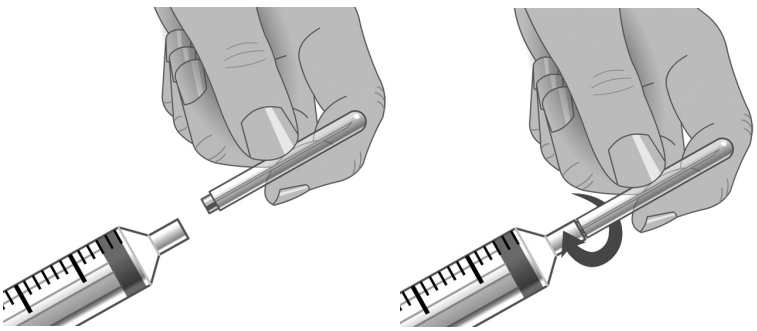
- Remove the protective cap from the vial to expose the central portion of the stopper.
- Wipe the stopper with alcohol and allow to dry.



Step 3:

Use aseptic technique when preparing and administering GAMUNEX-C

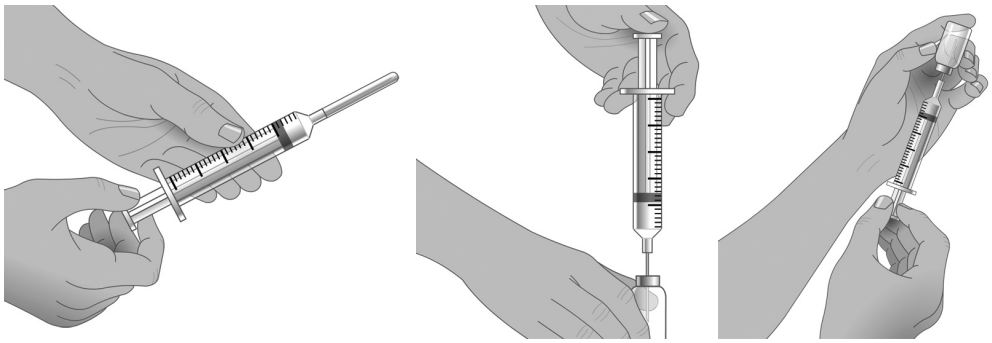
- Do not allow your fingers or other objects to touch the inner stem of the plunger, the syringe tip, or other areas that will come in contact with your GAMUNEX-C solution. This is called aseptic technique and is designed to prevent transmission of germs.
- Using aseptic technique, attach each needle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



Step 4:

Prepare the syringe and draw GAMUNEX-C solution into syringe

- Remove cap from needle.
- Pull the syringe plunger back to the level matching the amount of GAMUNEX-C to be withdrawn from the vial.
- Place the GAMUNEX-C vial 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 GAMUNEX-C to be withdrawn.
- Turn the vial upside down and withdraw the correct amount of GAMUNEX-C. If multiple vials are required to achieve the correct dose, repeat Step 4.

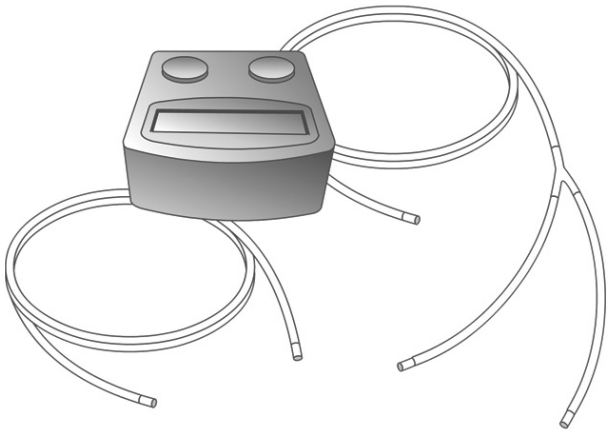


Step 5:

Fill the pump reservoir and prepare the 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 GAMUNEX-C. 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 GAMUNEX-C exit from the needle.

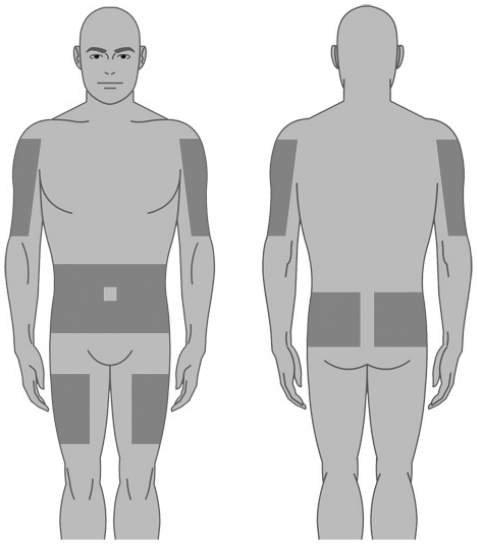
Example Equipment



Step 6:

Select the number and location of infusion sites

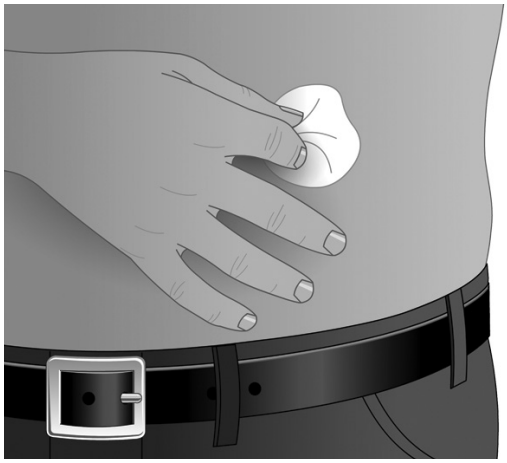
- Select one or more infusion sites as directed by your healthcare provider.
- The number and location of injection sites depends on the volume of the total dose.



Step 7:

Prepare the infusion site

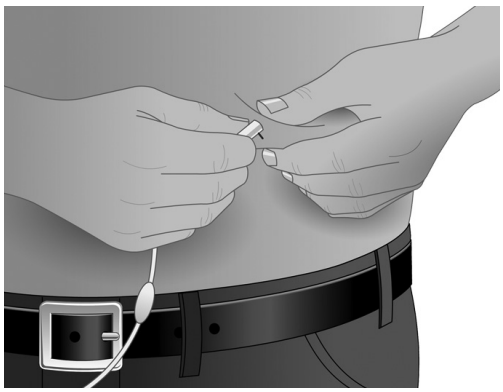
- Cleanse the infusion site(s) with antiseptic solution using a circular motion working from the center of the site and moving to the outside.
- Sites should be clean, dry, and at least 2 inches apart.



Step 8:

Insert the needle

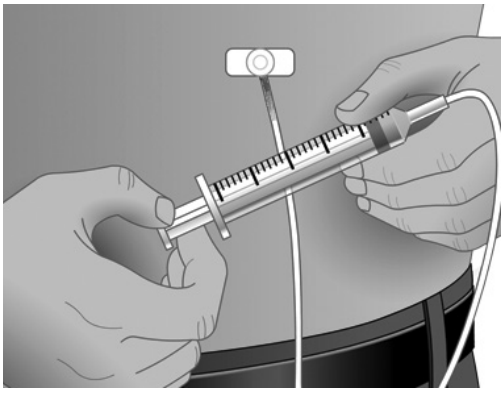
- Grasp the skin between two fingers and insert the needle into the subcutaneous tissue.



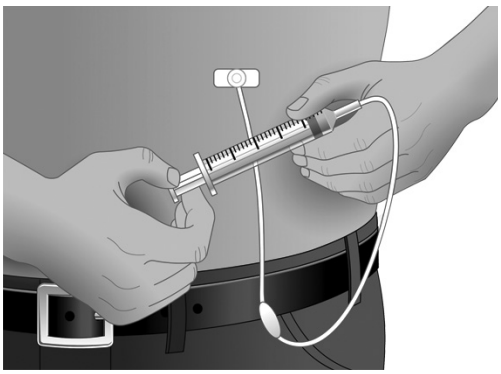
Step 9:

Do not inject GAMUNEX-C 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.

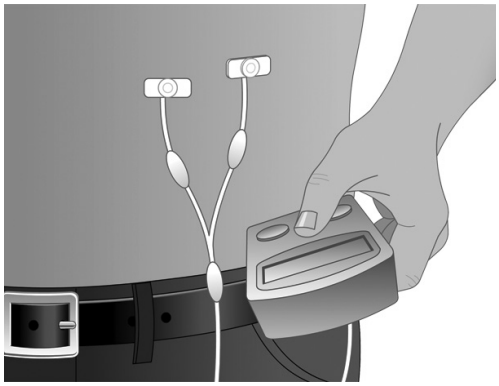


Step 10:

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 GAMUNEX-C following the pump manufacturer's instructions for the infusion pump



Step 12:
After infusion, turn off pump 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.

Step 13:
Record each infusion

- Remove the peel-off label with the product lot number from the GAMUNEX-C 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 journal, so be sure to take it with you each time you visit the doctor's office.

Call your doctor for medical advice about side effects. You can also report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured by:

GRIFOLS

Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

3054846/3054847
Revised 1/2020

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).

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

- 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.

---------- 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 ≥ 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 LLC at 1-800-520-2807 or FDA at 1-800-FDA-1088 or 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**

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS

- **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 central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.** ***[see Warnings and Precautions (5.2), Patient Counseling Information (17)]***
- **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.** ***[see Warnings and Precautions (5.2)]***

1 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. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[1-4]

2 DOSAGE AND ADMINISTRATION

For subcutaneous infusion only.

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

2.1 Dose

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

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

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

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

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

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

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

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).

Switching to XEMBIFY from IVIG

Begin treatment with XEMBIFY one week after the patient's last IVIG infusion.

Calculate the initial weekly dose of XEMBIFY. Divide the previous monthly (or every 3 weeks) IVIG dose in grams by the number of weeks between IVIG infusions, then multiply this dose by the dose adjustment factor of 1.37.

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

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

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

Switching to XEMBIFY from subcutaneous immune globulin (IGSC)

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

2.2 Preparation and Handling

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

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

Do not use if the solution is cloudy or turbid.

Do not shake.

Do not dilute.

The XEMBIFY vial is for single use only.

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

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

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

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

Do not use after expiration date.

Discard unused portion.

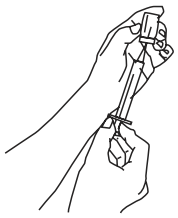
2.3 Administration
For subcutaneous infusion only.

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

Do not shake.

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

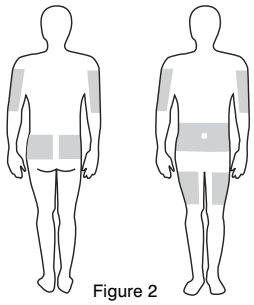
1. Inspect the vials: inspect for clarity, color, and expiration date(s).
2. Prepare for infusion:
   Gather supplies: XEMBIFY vial(s), ancillary supplies, sharps container, patient's treatment diary/logbook, and the infusion pump.
   Prepare a clean work area.
   Wash hands.
3. Remove the protective 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 Therapeutics LLC immediately [1-800-520-2807].
4. Wipe the stopper with alcohol and allow to dry.
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)


Figure 1

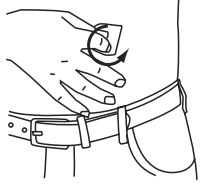
6. Use XEMBIFY as soon as practicable, within 2 hours to avoid the potential formation of particles caused by siliconized syringes.
7. Follow the manufacturer's instructions for preparing the pump and administration tubing. Be sure to prime the administration tubing to ensure that no air is left in the tubing or needle by filling the tubing/needle with XEMBIFY.
8. Select the number and location of injection sites. Rotate sites for each administration. (Figure 2)

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

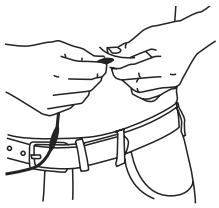
   Avoid bony areas, scars, areas of inflammation, superficial infection or blood vessels.


Figure 2

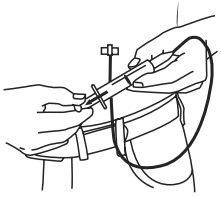
9. Cleanse the injection site(s) with antiseptic solution using a circular motion working from the center of the site and moving to the outside. Sites should be clean, dry, and at least 2 inches (5 cm) apart. (Figure 3)
10. Grasp the skin between 2 fingers (pinch at least one inch (2.5 cm) of skin) and insert the needle at a 90-degree angle into the subcutaneous tissue. (Figure 4)


Figure 3

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)
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.


Figure 4

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.


Figure 5

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

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).

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

XEMBIFY is contraindicated in:

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

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

5.2 Thrombosis

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

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. 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. *[see Boxed Warning, Dosage and Administration (2.3), Patient Counseling Information (17)]*

5.3 Aseptic Meningitis Syndrome (AMS)

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

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

5.4 Renal Dysfunction/Failure

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

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

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

5.5 Hemolysis

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

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

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

5.6 Transfusion-related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following treatment with human immune globulin products.[16] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically occur within 1 to 6 hours after treatment.

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

5.7 Transmissible Infectious Agents

Because XEMBIFY is made from human blood, it 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. This also applies to unknown or emerging viruses and other pathogens. No cases of transmission of viral diseases or CJD have been associated with the use of XEMBIFY. ALL infections suspected by a physician to have possibly been transmitted by XEMBIFY should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [1-800-520-2807].

5.8 Interference with Laboratory Tests

After infusion with XEMBIFY, the transitory rise of various passively transferred antibodies in the patient's blood may yield false-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.

6 ADVERSE REACTIONS

The most common adverse reactions in ≥ 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 Clinical Trials Experience

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

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

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

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

Table 2: Adverse Reactions in ≥ 5% of Subjects During Infusions of XEMBIFY

Adverse Reaction*	By Subject n (%)† (N=49 subjects)	By Infusion n (rate)‡ (N=1053 infusions)
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.
† 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.

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

6.2 Postmarketing Experience

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

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

Cardiac disorders: Tachycardia

Nervous system disorders: Tremor and paresthesia

Respiratory, thoracic and mediastinal disorders: Dyspnea and laryngospasm

7 DRUG INTERACTIONS

7.1 Serological Testing

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

7.2 Live Attenuated Virus Vaccines

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 healthcare provider of recent therapy with XEMBIFY so that appropriate measures may be taken.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No human data are available to indicate the presence or absence of 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. Immune globulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4%and 15-20%, respectively.

8.2 Lactation

Risk Summary

No human data are available to indicate the presence or absence of drug associated risk. 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.

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

11 DESCRIPTION

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

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

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).

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

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

Table 3: Summary of Virus Clearance Capacity (Log_{10})

Process Step	Enveloped Viruses				Non-enveloped Viruses		
	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‡
Overall Clearance Capacity	**≥16.5**	**≥20.2**	**≥13.0**	**≥10.4**	**≥9.3**	**≥5.0**	**8.2**

* 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_{10} 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.

Additionally, the manufacturing process was 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.

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

12 CLINICAL PHARMACOLOGY

12.1 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 XEMBIFY are not fully understood.

12.2 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. XEMBIFY 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.

12.3 Pharmacokinetics

Pharmacokinetic (PK) parameters of subcutaneously administered XEMBIFY were evaluated in subjects with primary immunodeficiency (PI) during a clinical trial. *[see Clinical Studies (14)]* Subjects were treated intravenously with a comparator product [GAMUNEX-C®, immune globulin 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-C 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-C (957 mg/dL) (average mean trough ratio SC/IV of 1.3). PK parameters of XEMBIFY are summarized in Table 4. PK parameters did not significantly differ between age groups (Table 5).

Table 4: PK Parameters of Total IgG at Steady-State in IV and SC Phases (PK Population) in Children and Adults

Phase	Statistics	$AUC_{(0\text{-}7\ days)}$ (h*mg/mL)*	C_{max} (mg/mL)	t_{max} (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†

* $AUC_{(0\text{-}7\ days)}$ in the IV Phase is calculated as $AUC_{(0\text{-}21\ days)}/3$ for subjects on an every-3-week IV dosing schedule (n=6), and as $AUC_{(0\text{-}28\ days)}/4$ for subjects on an every-4-week IV dosing schedule (n=43).

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

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

Age Group (years)	Statistics	$AUC_{(0\text{-}7\ days)}$ (h*mg/mL)*	C_{max} (mg/mL)	Mean Trough (mg/mL)	t_{max} (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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 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-C 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-C 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-C, and were within the norms of this route of administration in this species.

14 CLINICAL STUDIES

Study 1 was a prospective, open-label single-arm, multi-center clinical trial designed to evaluate pharmacokinetics and safety of XEMBIFY as compared to GAMUNEX-C. Efficacy was based on annualized serious bacterial infection (SBI) rate during the 6 months on XEMBIFY. The GAMUNEX-C run-in phase prior to XEMBIFY (subcutaneous phase) lasted 3 or 4 months to achieve steady state prior to pharmacokinetic profiling. The definition of SBI was either bacteremia/sepsis, bacterial meningitis, bacterial pneumonia, osteomyelitis/septic arthritis, or visceral abscess.

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

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

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

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

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

Parameters	**Results**
Number of Subjects (efficacy period)	49
Total number of subject days on treatment	7,407
Total number of subject-years on treatment	20.28
Infections 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.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

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

Package NDC Number	Container NDC Number	Size	Gram Protein
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

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

Store XEMBIFY at 2–8°C (36–46°F).

Note: XEMBIFY may be stored at temperatures not to exceed 25°C (77°F) for up to 6 months any time prior to the expiration date. Following 25°C (77°F) storage, use the product immediately or discard.

Do not freeze.

Do not use solutions that have been frozen.

Do not use after expiration date.

Discard unused portion.

17 PATIENT COUNSELING INFORMATION

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

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

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

- Hypersensitivity reaction including hives, generalized urticaria, tightness of the chest, wheezing, low blood pressure, and anaphylaxis *[see Warnings and Precautions (5.1)]*
- Symptoms of thrombosis which may include: pain and/or 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 *[see Warnings and Precautions (5.2)]*
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting *[see Warnings and Precautions (5.3)]*
- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath *[see Warnings and Precautions (5.4)]*
- Increased heart rate, fatigue, yellowing of the skin or eyes, and dark-colored urine *[see Warnings and Precautions (5.5)]*
- Trouble breathing, chest pain, blue lips or extremities, and fever *[see Warnings and Precautions (5.6)]*

Inform patients/caregivers that because XEMBIFY is made from human blood, it 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. *[see Warnings and Precautions (5.7)]*

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

Self-administration

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

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

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

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

Instruct patient to rotate infusion sites for subsequent infusions.

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

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

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

Manufactured by:
GRIFOLS
Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

3054808
Revised 7/2019

INFORMATION FOR PATIENTS

XEMBIFY™

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

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

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

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

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

Tell your healthcare provider if you have or ever had:
- a serious reaction to other medicines that contain immune globulin.
- an immunoglobulin A (IgA) deficiency.
- a history of heart or blood vessel disease.
- blood clots or "thick blood".
- inability to move for some time.

How should I take XEMBIFY?
XEMBIFY is given under the skin (subcutaneously). Most of the time, infusions under the skin are given at home by self-infusion or by infusion with a caregiver's help. Self-infusion is different from giving yourself a shot.

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

What should I tell my healthcare provider before using XEMBIFY?
Tell your healthcare provider if you have had a serious reaction to other medicines that contain immune globulin. Also tell your healthcare provider if you have an immunoglobulin A (IgA) deficiency.

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

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

What are possible or reasonably likely side effects of XEMBIFY?
The most common side effects with XEMBIFY are:
- Infusion site reactions, including but not limited to
  - 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
- Cough
- Diarrhea

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

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

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

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

Pain, swelling, warmth, redness, or a lump in your legs or arms. These could be signs of a blood clot.

Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a liver problem or a blood problem.

Chest pain or trouble breathing, or blue lips or extremities. These could be signs of a serious heart or lung problem.

Severe headache, stiff neck, fatigue, fever, sensitivity to light, painful eye movements, nausea and vomiting. These could be signs of a type of brain inflammation called aseptic meningitis.

Fever over 100°F (37.8°C). This could be a sign of an infection.

Tell your healthcare provider about any side effects that concern you. You can ask your healthcare provider to give you the full prescribing information available to healthcare providers. You are encouraged to report side effects to Grifols Therapeutics LLC [1-800-520-2807].

How do I store XEMBIFY?

XEMBIFY comes in single use vials.

- Keep XEMBIFY refrigerated. Do not freeze.
- If needed, you can store XEMBIFY at room temperature for up to 6 months, but you must use it within that time or you must throw it away.
- Do not return XEMBIFY to the refrigerator if it was warmed to room temperature.
- Check the expiration date on the carton and vial label.
- Do not use XEMBIFY after the expiration date.

What else should I know about XEMBIFY?

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

INSTRUCTIONS FOR USE

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

Before Using XEMBIFY

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

Do not apply heat or place in the microwave.

Step 1: Assemble supplies

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

Step 2: Clean surface

Set up your infusion area on 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 3: Wash hands

Wash and dry your hands thoroughly before using XEMBIFY.

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



Step 4: Check vials

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

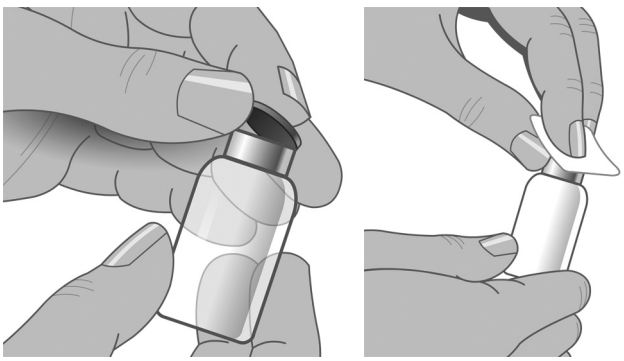
Do not use the vial if:

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

Step 5: Remove the protective cap

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

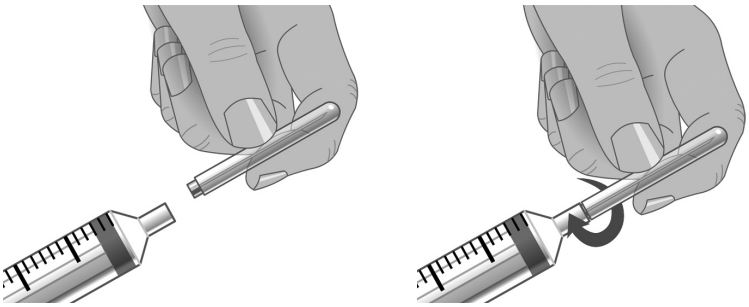
Wipe the stopper with alcohol and allow to dry.



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

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 "aseptic technique" to prevent germs from getting into the XEMBIFY.

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



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

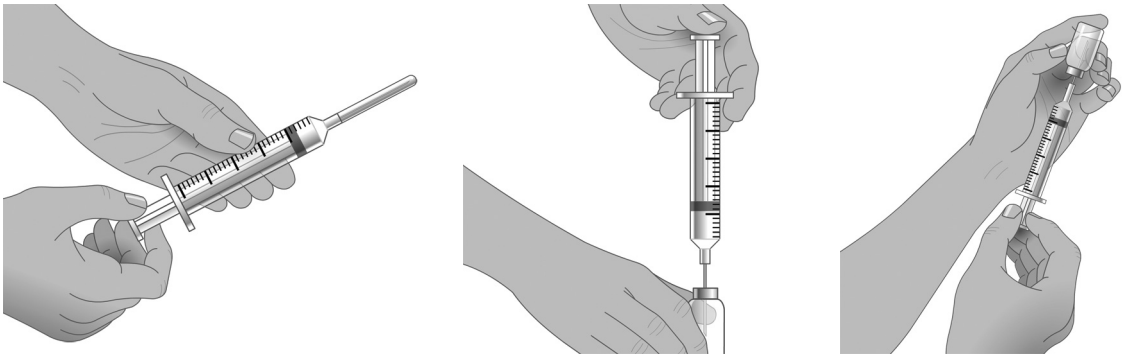
Remove cap from needle.

Pull the syringe plunger back to the level matching the amount of XEMBIFY™ (immune globulin subcutaneous, human-klhw) to be withdrawn from the vial.

Place the XEMBIFY vial 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.

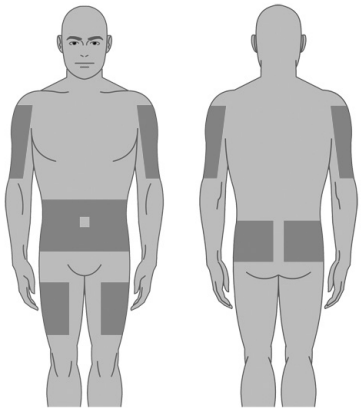
Turn the vial upside down and withdraw the correct amount of XEMBIFY. If multiple vials are required to get the correct dose, repeat Step 4.



Step 8: Fill the pump reservoir and prepare the 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.

Prime the administration tubing with XEMBIFY to take out any air left in the tubing or needle. 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 come out of the needle.



Step 9: 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.

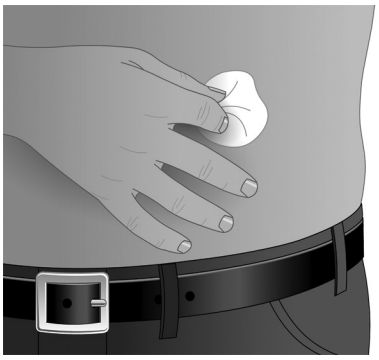
Avoid: bony areas, visible blood vessels, scars, and any areas of inflammation (irritation) or infection.

Rotate sites between future infusions.

Step 10: Prepare the infusion site

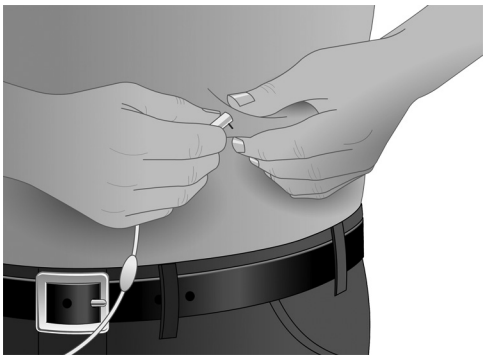
Wipe the infusion site(s) with a sterile alcohol wipe beginning at the center of each infusion site and moving outward in circular motion. Allow the infusion site(s) to dry (at least 30 seconds).

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



Step 11: Insert the needle

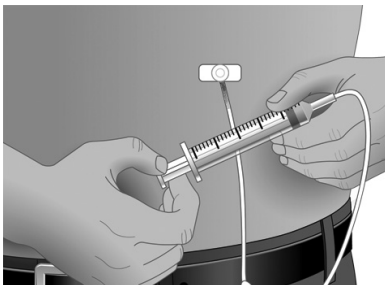
Grasp the skin between two fingers (pinch at least 1 inch (2.5 cm) of skin) and insert the needle at a 90-degree angle into the tissue underneath the skin or subcutaneous tissue.



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

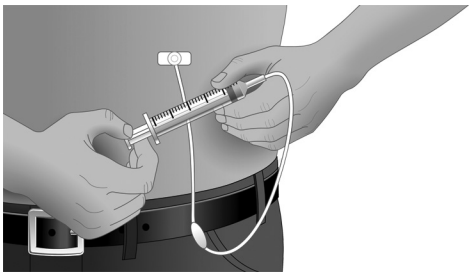
After inserting each needle into tissue (and before your infusion), make sure that a blood vessel has not been accidentally entered. To do this, attach a sterile syringe to the end of the primed administration tubing. Pull back on the syringe plunger and watch for any blood flowing back into administration 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 13: Repeat for other sites, as needed

Step 14: Infuse XEMBIFY
Infuse XEMBIFY as soon as possible after it is prepared.

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

Step 15: After infusion
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.

Step 16: 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. Include information about each infusion such as: the time, date, dose, lot number(s), infusion sites, and any reactions.

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

Tell your healthcare provider about any problems you have during your infusions. Call your healthcare provider for medical advice about side effects. You can also report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured by:
GRIFOLS
Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

3054808
Revised 7/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLEBOGAMMA 5% DIF safely and effectively. See full prescribing information for FLEBOGAMMA 5% DIF.

FLEBOGAMMA 5% DIF (immune globulin intravenous [human]), solution for intravenous administration
Initial U.S. Approval: 2006

WARNING: THROMBOSIS, RENAL DYSFUNCTION, and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including FLEBOGAMMA 5% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **For patients at risk of thrombosis administer FLEBOGAMMA 5% DIF 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 of hyperviscosity.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis and death may occur with the administration of human immune globulin intravenous (IGIV) products, particularly those products that contain sucrose. FLEBOGAMMA 5% DIF does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer FLEBOGAMMA 5% DIF at the minimum dose and infusion rate practicable. (5.2)**

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration (2) 9/2019

----------INDICATIONS AND USAGE----------

Flebogamma 5% DIF is an immune globulin intravenous (human), indicated for treatment of primary (inherited) immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------

For Intravenous Use Only

Indication	Dose	Initial Infusion Rate	Maintenance Dose Rate (if tolerated)
PI	300-600 mg per kg every 3-4 weeks	0.01 mL per kg per minute (0.5 mg per kg per min)	Increase to 0.10 mL per kg per minute (5 mg per kg per min)

- For patients at risk of renal dysfunction or thrombosis, administer Flebogamma 5% DIF at the minimum dose and infusion rate practicable. (5.2, 5.4)
- Ensure that patients with pre-existing renal insufficiency are not volume-depleted and discontinue Flebogamma 5% DIF if renal function deteriorates. (5.2)

----------DOSAGE FORMS AND STRENGTHS----------

Solution for intravenous injection containing 5% IgG (50 mg per mL). (3)

----------CONTRAINDICATIONS----------

- History of anaphylactic or severe systemic reactions to human immunoglobulin. (4)
- IgA-deficient patients with antibodies against IgA and a history of hypersensitivity. (4)

----------WARNINGS AND PRECAUTIONS----------

- IgA-deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. (5.1)
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure. (5.2)
- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Flebogamma 5% DIF therapy. (5.3)
- Thrombosis may occur. Monitor patients with known risk factors for thrombosis and consider baseline assessment of blood viscosity for those at risk of hyperviscosity. (5.4)
- Aseptic meningitis syndrome (AMS) may occur in patients receiving Flebogamma 5% DIF therapy, especially with high doses or rapid infusion. (5.5)
- Hemolysis, either intravascular or due to enhanced red blood cell sequestration, can develop subsequent to Flebogamma 5% DIF treatments. Risk factors include high doses and non-O blood group. Monitor patients for hemolysis and hemolytic anemia. (5.6)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury, TRALI). (5.7)
- Patients receiving Flebogamma 5% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for development of fever, chills, nausea, and vomiting. (5.8)
- Flebogamma 5% DIF is made from human plasma and may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.9)
- Passive transfer of antibodies may confound serologic testing. (5.11)
- Flebogamma 5% DIF contains sorbitol. The presence of sorbitol presents a risk to those with hereditary fructose intolerance (HFI). (5.12)

----------ADVERSE REACTIONS----------

The most common adverse reactions (reported in at least 5% of clinical trial adult subjects) were headache, pyrexia/fever, pain, infusion site reactions, diarrhea, rigors or chills, urticaria, and infusion site inflammation. (6)

The most common adverse reactions (reported in at least 5% of clinical trial pediatric subjects) were headache, pyrexia, hypotension, tachycardia, diastolic hypotension, nausea, abdominal pain, diarrhea, pain, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines, such as measles, mumps, and rubella. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No human or animal data. Use only if clearly needed. (8.1)
- Geriatric: In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Flebogamma 5% DIF at the minimum dose and infusion rate practicable and at less than 0.06 mL per kg per minute (3 mg per kg per min). (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2019

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FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION, and ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including FLEBOGAMMA 5% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. (*see Warnings and Precautions [5.4] and Patient Counseling Information [17]*)**
- **For patients at risk of thrombosis, administer FLEBOGAMMA 5% DIF 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 patient at risk for hyperviscosity. (*see Dosage and Administration [2.3] and Warnings and Precautions [5.4]*)**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death[1] have been related to intravenous immune globulin (IGIV) products. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.**
- **Administer FLEBOGAMMA 5% DIF at the minimum dose and rate of infusion practicable in patients at risk for renal dysfunction or failure.**
- **Reports of renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose as a stabilizer. They account for a disproportionate share of the total number of reported cases of renal dysfunction and acute renal failure. FLEBOGAMMA 5% DIF does not contain sucrose. (*see Dosage and Administration [2.3] and Warnings and Precautions [5.2]*)**

1 INDICATIONS AND USAGE

Flebogamma 5% DIF is an immune globulin intravenous (human) solution indicated in adults and pediatric patients 2 years of age and older for the treatment of primary immunodeficiency (PI), including the humoral immune defects in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome.

2 DOSAGE AND ADMINISTRATION

For Intravenous Use Only

2.1 Dosage

Treatment of Primary Immunodeficiency (PI)

Dose	Initial Infusion Rate	Maintenance Dose Rate (if tolerated)
300-600 mg per kg body weight (6.0-12.0 mL per kg) administered every 3-4 weeks	0.01 mL per kg per minute (0.5 mg per kg per min)	Increase to 0.10 mL per kg per minute (5 mg per kg per min)

If a patient has been exposed to measles, it may be prudent to administer an extra dose of IGIV as soon as possible and within 6 days of exposure. A dose of 400 mg/kg should provide a serum level > 240 mIU/mL of measles antibodies for at least two weeks.

If a patient is at risk of future measles exposure and receives a dose of less than 530 mg/kg every 3-4 weeks, the dose should be increased to at least 530 mg/kg. This should provide a serum level of 240 mIU/mL of measles antibodies for at least 22 days after infusion.

As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. Adjust the dose according to the clinical response.

Adjust the dosage over time to achieve the desired trough IgG levels and clinical responses. No randomized controlled trial data are available to determine an optimum target trough serum IgG level.

2.2 Preparation and Handling

- Inspect Flebogamma 5% DIF visually for particulate matter and color prior to administration. Do not use the vial if particles are detected. Do not use if turbid.
- Several vials of Flebogamma 5% DIF may be pooled into an empty sterile solution container by using aseptic technique, if large doses are to be administered.
- Do not dilute with intravenous fluids. Do not inject other medications into intravenous tubing being used for Flebogamma 5% DIF.
- Infuse Flebogamma 5% DIF through a separate intravenous line. Do not add any medications or intravenous fluids to the Flebogamma 5% DIF infusion container. Do not mix IGIV products of different formulations or from different manufacturers.
- Discard unused contents and administration devices after use.
- Use promptly any vial that has been entered.
- Discard partially used vials. Do not save for future use because the solution contains no preservative.
- Do not use solution that has been frozen.

2.3 Administration

The recommended initial infusion rate of Flebogamma 5% DIF is 0.01 mL per kg body weight per minute (0.5 mg per kg per min). If the infusion is well-tolerated during the first 30 minutes, the rate may be gradually increased to a maximum of 0.10 mL per kg per minute (5 mg per kg per min).

Monitor patient vital signs throughout the infusion. Slow or stop infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient.

3 DOSAGE FORMS AND STRENGTHS

Flebogamma 5% DIF is a liquid preparation containing 5% IgG (50 mg per mL).

4 CONTRAINDICATIONS

- Flebogamma 5% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of human immune globulin.
- Flebogamma 5% DIF is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity. (*see Warnings and Precautions [5.1]*)

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions and anaphylactic reactions with a fall in blood pressure may occur, even in patients who had tolerated previous treatment with IGIV. (*see Contraindications [4]*) If hypersensitivity reaction develops, discontinue Flebogamma 5% DIF infusion immediately and institute appropriate treatment.

Flebogamma 5% DIF contains trace amounts of IgA (less than 50 µg/mL). (*see Description [11]*) Patients with antibodies to IgA have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Flebogamma 5% DIF is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction. (*see Contraindications [4]*)

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, and death have been reported in patients receiving IGIV, particularly those products containing sucrose[2]. Flebogamma 5% DIF does not contain sucrose.

Ensure that patients are not volume-depleted before administering Flebogamma 5% DIF. For patients judged to be at risk for developing renal dysfunction, including patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs, administer Flebogamma 5% DIF at the minimum dose and rate of infusion practicable[3]. (*see Boxed Warning, Dosing and Administration [2.3]*)

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure[1]. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Flebogamma 5% DIF and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of the product.

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Flebogamma 5% DIF therapy. It is clinically critical to distinguish true hyponatremia from a pseudohyponatremia that is temporally or causally related to hyperproteinemia with concomitant decreased calculated serum osmolarity or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a higher risk of thrombosis.

5.4 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including Flebogamma 5% DIF. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. (*see Warnings and Precautions [5.10]*) For patients at risk of thrombosis, administer Flebogamma 5% DIF 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. (*see Boxed Warning, Dosage and Administration [2.3], and Patient Counseling Information [17]*)

5.5 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae[4-7]. The symptoms of AMS usually begin within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. (*see Patient Counseling Information [17]*) Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination to patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently following high-dose (e.g. over 1.0 g per kg body weight) or rapid infusion of IGIV.

5.6 Hemolysis

Flebogamma 5% DIF may contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test (DAT) (Coombs' test) result and hemolysis[8-11]. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration and acute hemolysis, consistent with intravascular hemolysis, has been reported[12]. Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of IGIV.

The following risk factors may be associated with the development of hemolysis following IGIV administration: high doses (e.g., at least 2 g per kg), given either as a single administration or divided over several days, and non-O blood group[13]. Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV[14], but their role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP and PI[11]. Monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within 36 to 96 hours post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis. (*see Patient Counseling Information [17]*)

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Non-cardiogenic pulmonary edema has been reported in patients following IGIV treatment[15]. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours after transfusion.

Monitor patients for pulmonary adverse reactions. (*see Patient Counseling Information [17]*) If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient serum. TRALI may be managed by using oxygen therapy with adequate ventilatory support.

5.8 Infusion Reactions

Individuals receiving Flebogamma 5% DIF for the first time, or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at a higher risk for the development of fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events. (*see Dosage and Administration [2.3]*)

5.9 Transmissible Infectious Agents

Because Flebogamma 5% DIF is made from human plasma, it 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. This also applies to unknown or emerging viruses and other pathogens. No cases of transmission of viral diseases or CJD have been associated with the use of Flebogamma 5% DIF. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Biologicals at 1-888-474-3657.

Before prescribing or administering Flebogamma 5% DIF, the physician should discuss the risks and benefits of its use with the patient. (*see Patient Counseling Information [17]*)

5.10 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of Flebogamma 5% DIF and at appropriate intervals thereafter.
- Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies because of the potentially increased risk of thrombosis.
- If signs and/or symptoms of hemolysis are present after an infusion of Flebogamma 5% DIF, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient serum.

5.11 Interference with Laboratory Tests

After infusion of IgG, the transitory rise of the 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.

5.12 Hereditary Fructose Intolerance

Flebogamma 5% DIF contains sorbitol. The presence of sorbitol presents a risk to those with hereditary fructose intolerance (HFI). The incidence of HFI is estimated at 1 in 20,000 births and is usually diagnosed at the time of weaning when fructose or sucrose is introduced into the diet. Clinical symptoms include recurrent vomiting, abdominal pain and hypoglycemia. Flebogamma 5% DIF must not be administered to subjects with HFI.

6 ADVERSE REACTIONS

The most common adverse reactions (reported in at least 5% of clinical trial adult subjects) were headache, pyrexia/fever, pain, infusion site reactions, diarrhea, rigors or chills, urticaria, and infusion site inflammation.

The most common adverse reactions (reported in at least 5% of clinical trial pediatric subjects) were headache, pyrexia, hypotension, tachycardia, diastolic hypotension, nausea, abdominal pain, diarrhea, pain, and vomiting.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

6.1 Clinical Trials Experience

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

Adverse reactions were reported in a study of 46 individuals with PI receiving infusions every 3 to 4 weeks of 300-600 mg per kg body weight. Thirty-one subjects (67.4%) had at least one adverse reaction at some time during the study that was considered product-related. None of the 46 subjects who participated in this study discontinued the study prematurely due to an adverse drug reaction.

Adverse reactions that occurred with an incidence of at least 5% on a per-subject basis are summarized in Table 1.

Table 1. Adverse Reactions Occurring in at Least 5% of Subjects

Adverse Reaction	Subjects (%) N = 46	Number of Events
Headache	**10 (21.7)**	**24**
Pyrexia[a]	**9 (19.6)**	**12**
Pain[b]	**7 (15.2)**	**11**
Injection site reaction	**6 (13.0)**	**10**
Diarrhea	**4 (8.7)**	**5**
Rigors	**4 (8.7)**	**7**
Urticaria	**3 (6.5)**	**3**
Infusion site inflammation[c]	**3 (6.6)**	**3**

a. include combined reported terms of pyrexia and body temperature increase.

b. include combined reported terms of pain such as pain (not otherwise specified), injection site pain, back pain, abdominal pain (not otherwise specified), and abdominal pain upper.

c. include combined reported terms of infusion site inflammation and others such as injection site oedema and injection site swelling.

Other common adverse drug reactions reported in fewer than 5% of the subjects included hypertension, sinusitis, nausea/vomiting, positive Coombs test, arthralgia, myalgia, dizziness, bronchitis, and hypotension.

The total number of adverse reactions reported whose onset were within 72 hours after the end of an infusion of Flebogamma 5% DIF was 94. There were a total of 709 infusions, resulting in a ratio of 0.13 temporally associated adverse reactions per infusion (the upper bound of the 1-sided 95% confidence interval = 0.18). Of the 709 total infusions, 70 (9.7%, 1-sided 95% upper bound CI = 12.4%) were associated with at least one adverse reaction that began within 72 hours after the completion of an infusion. In this analysis, each infusion is only counted once, regardless of the number of adverse reactions that occurred during the infusion, when during the 72-hour period after the infusion the adverse reaction started, or the intensity of those adverse reactions.

Factoring adverse reaction intensity into the analysis of the 709 infusions shows that there were 58 infusions with at least one mild adverse reaction (8.2% [upper bound 95% CI=10.5%]), 25 infusions with at least one moderate adverse reaction (3.5% [upper bound 95% CI=5.2%]), and 1 infusion with a severe adverse reaction (0.1% [upper bound 95% CI=0.8%]). In this analysis, if a subject reported multiple events with different intensities during the same infusion (e.g., mild headache and moderate pyrexia), that infusion would be counted in all relevant categories. Therefore, the number of infusions counted is 84.

Three subjects (6.5%) experienced a treatment-emergent rise in AST (> 3x the upper-limit of normal), and 1 subject (2.2%) experienced a treatment-emergent rise in ALT (> 3x the upper-limit of normal). None of these abnormal lab values were long-lasting (i.e. they occurred at 1 or 2 infusions), and none of these subjects had a concomitant treatment-emergent rise in total bilirubin.

A clinical study with Flebogamma 5% DIF for the treatment of PI was conducted in 24 pediatric subjects aged 2-16 years to determine whether they respond differently from adult subjects. Pediatric subjects received intravenous infusions of 262-625 mg per kg body weight every 3-4 weeks. Twenty subjects (83.3%) had at least one adverse reaction at some time during the study that was considered product-related. There were no deaths or serious adverse reactions.

In 317 infusions, 20 pediatric subjects reported 159 treatment-related adverse drug reactions (ADR). Treatment-related adverse reactions that occurred with an incidence of at least 5% on a per-subject basis included headache (42%), pyrexia (29%), hypotension (25%), tachycardia (25%), diastolic hypotension (21%), nausea (8%), abdominal pain (8%), diarrhea (8%), pain (8%), and vomiting (8%). Of these, 99 ADRs were mild, 54 were moderate, and 6 were severe in intensity. The most common severe ADR was headache. Tachycardia was defined as mild, moderate, or severe by ratio of heart rate over baseline of 1.2-1.4, 1.41-1.6, or >1.6, respectively. Two episodes of tachycardia were moderate and 14 were mild, 1 mild case had the infusion interrupted and the rest had no action taken, and all resolved. Hypotension was defined as mild, moderate, or severe by the decrease in pressure below baseline of 10-15%, 16-25%, and >25%, respectively. Ten episodes of hypotension/diastolic hypotension were moderate and 29 were mild, one moderate case had the infusion interrupted and the rest had no action taken, and all resolved. None of the ADRs related to fluctuation in vital signs were severe, all resolved without sequelae, and none were considered clinically significant.

One subject (6.5%) experienced a treatment-emergent rise in ALT (over 2.5x the upper-limit of normal). This was considered a mild treatment-related AE and resolved without sequelae. All other lab values were within normal limits. One subject experienced one positive Coombs' test result after baseline (experienced 14 days after the final infusion). No subjects experienced clinically significant abnormal lab values for LDH, bilirubin, serum creatinine. In addition, no subjects experienced positive test results for HBsAg, HCV, or HIV.

6.2 Post-marketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

The following adverse reactions have been identified during the post-approval use of IGIV products[16, 17], including Flebogamma 5% DIF.

Infusion Reactions	Hypersensitivity (e.g. anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
Renal	Acute renal dysfunction/failure, osmotic nephropathy
Respiratory	Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion-Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
Cardiovascular	Cardiac arrest, thromboembolism, vascular collapse, hypotension
Neurological	Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
Integumentary	Stevens-Johnson Syndrome, epidermolysis, erythema multiformae, dermatitis (e.g. bullous dermatitis)
Hematologic	Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test
Musculoskeletal	Back pain
Gastrointestinal	Hepatic dysfunction, abdominal pain
General/Body as a Whole	Pyrexia, rigors

7 DRUG INTERACTIONS

Passive transfer of antibodies may transiently impair the immune response to live attenuated virus vaccines, such as measles, mumps, and rubella. Inform the immunizing physician of recent therapy with Flebogamma 5% DIF so that appropriate measures can be taken (*see Patient Counseling Information [17]*)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies of Flebogamma 5% DIF use in pregnant women. Animal reproduction studies have not been performed with Flebogamma 5% DIF. It is also not known whether Flebogamma 5% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. Flebogamma 5% DIF should be given to a pregnant woman only if clearly needed.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Flebogamma 5% DIF in human milk, its effects on the breastfed infant, or its effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Flebogamma 5% DIF and any potential adverse effects on the breastfed infant from Flebogamma 5% DIF or from the underlying maternal condition.

8.4 Pediatric Use

Flebogamma 5% DIF was studied in a multicenter clinical trial for the treatment of PI in 24 subjects aged 2-16 years (seven were 2-5 years of age, seven were 6-11 years, and ten were 12-16 years), and found to be efficacious for the prevention of acute serious bacterial infections. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Twenty subjects (83.3%) had at least one adverse reaction at some time during the study that was considered product-related. There were no deaths or serious adverse reactions. Treatment-related adverse reactions that occurred with an incidence of at least 5% on a per-subject basis included headache (42%), pyrexia (29%), hypotension (25%), tachycardia (25%), diastolic hypotension (21%), nausea (8%), abdominal pain (8%), diarrhea (8%), pain (8%), and vomiting (8%).

Safety and efficacy of Flebogamma 5% DIF in pediatric patients below the age of 2 years have not been established.

8.5 Geriatric Use

Limited information is available for the geriatric use of Flebogamma 5% DIF. Clinical studies of Flebogamma 5% DIF did not include sufficient numbers of subjects over the age of 65 to determine whether they respond differently from younger subjects. Use caution when administering Flebogamma 5% DIF to patients age 65 and over who are judged to be at increased risk for developing thrombosis or renal insufficiency. Do not exceed recommended dose, and administer Flebogamma 5% DIF at the minimum dose and infusion rate practicable, and at less than 0.06 mL per kg per minute (3 mg per kg per min). (*see Boxed Warning, Warning and Precautions [5.2, 5.4], and Dosage and Administration [2.3]*)

10 OVERDOSAGE

Overdose may lead to fluid overload and hyperviscosity. Patients at particular risk of complications of fluid overload and hyperviscosity include elderly patients and patients with cardiac or renal impairment.

11 DESCRIPTION

Flebogamma 5% DIF is a ready to use, sterile, clear or slightly opalescent and colorless to pale yellow, liquid preparation of purified immunoglobulin (IgG) obtained from human plasma pools. The purification process includes cold ethanol fractionation, polyethylene glycol precipitation, ion exchange chromatography, low pH treatment, pasteurization, solvent detergent treatment, and Planova nanofiltration using 20 nanometer (nm) filters.

Flebogamma 5% DIF is a purified (at least 97% IgG), unmodified, human IgG. The distribution of the four IgG subclasses is approximately 66.6% IgG_1, 28.5% IgG_2, 2.7% IgG_3, and 2.2% IgG_4. Flebogamma 5% DIF contains trace amounts of IgA (typically less than 50 µg/mL) and trace amounts of sodium and IgM.

Flebogamma 5% DIF contains 5 g human normal immunoglobulin and 5 g D-sorbitol (as stabilizer) in 100 mL of water for injection, and ≤ 3 mg/mL polyethylene glycol. There is no preservative in the formulation. The pH of the solution ranges from 5 to 6 and the osmolality from 240 to 370 mOsm/kg, which is within the normal physiological range.

Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collections and plasma preparation. Each individual plasma donation used in the manufacture of Flebogamma 5% DIF is collected only at FDA-approved blood establishments and is tested by FDA-licensed serological test for hepatitis B virus (HBV) surface antigen (HBsAg), and for antibodies to human immunodeficiency virus (HIV-1/HIV-2) and hepatitis C virus (HCV) in accordance with U.S. regulatory requirements. As an additional safety measure, mini-pools of plasma are tested for the presence of HBV, HIV-1 and HCV by FDA-licensed nucleic acid testing (NAT) and found to be negative. In addition, plasma is tested by in-process NAT for hepatitis A virus (HAV) and parvovirus B19 (B19) on mini-pools and the viral load limit for B19 in the manufacturing pool is set not to exceed 10^4 IU/mL. NAT for the presence of HCV and HIV in the manufacturing plasma pool is also performed and found to be negative.

To further improve the margin of safety, three dedicated, independent virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely pasteurization at 60°C, 10 hours, solvent-detergent treatment for 6 hours, and nanofiltration down to 20 nm Planova filters.

In vitro virus spiking studies have been used to validate the capability of the manufacturing process to inactivate and remove viruses. To establish the minimum applicable virus clearance capacity of the manufacturing process, these virus clearance studies were performed on seven steps of the production process (pasteurization, solvent-detergent treatment, nanofiltration, Fraction I precipitation, Fraction II+III precipitation, 4% PEG precipitation, and pH treatment for 4 hours at 37°C).

The viral reduction data (in $\log_{10}$) from these experiments are summarized in Table 2.

Table 2. Flebogamma 5% DIF: Viral Reduction Capacity of Combined Steps ($\log_{10}$)

Target virus	HIV-1, HIV-2 (env. RNA)	HBV Herpesvirus (env. DNA)		HCV (env. RNA)		WNV (env. RNA)	HAV (non-env. RNA)	Virus B19 (non-env. DNA)
Model virus	**HIV-1**	**PRV**	**IBR**	**BVDV**	**SINDBIS**	**WNV**	**EMC**	**PPV**
Fraction I precipitation	**< 1.00***	**nd**	**nd**	**nd**	**nd**	**2.78**	**nd**	**< 1.00***
Ethanol incubation (Fraction II+III)	**1.48**	**nd**	**nd**	**nd**	**nd**	**< 1.00***	**nd**	**nd**
PEG precipitation	**≥ 6.10**	**≥ 5.92**	**nd**	**≥ 5.78**	**nd**	**nd**	**≥ 6.41**	**6.35**
Acid pH treatment	**2.47**	**≥ 5.32**	**nd**	**< 1.00***	**nd**	**nd**	**1.36**	**na**
Pasteurization	**≥ 5.64**	**≥ 4.96**	**≥ 6.33**	**≥ 4.69**	**≥ 6.49**	**≥ 5.42**	**≥ 5.56**	**4.08**
Solvent Detergent	**≥ 4.61**	**≥ 6.95**	**nd**	**≥ 6.14**	**nd**	**≥ 5.59**	**na**	**na**
Nanofiltration 20 nanometer	**≥ 4.81**	**≥ 4.63**	**nd**	**≥ 4.67**	**nd**	**≥ 3.63**	**≥ 5.92**	**4.61**
Overall Reduction Capacity	**≥ 25.11**	**≥ 27.78**	**≥ 6.33**	**≥ 21.28**	**≥ 6.49**	**≥ 17.42**	**≥ 19.25**	**15.04**

* When the RF is < 1 $\log_{10}$, it is not taken into account for the calculation of the overall reduction capacity.

≥ is no residual infectivity detected; nd = not done; na = non-applicable, since the virus is theoretically resistant to this treatment.

Abbreviations: HIV = Human immunodeficiency virus; PRV = Pseudorabies virus; IBR = Infectious bovine rhinotracheitis virus; BVDV = Bovine viral diarrhea virus; SINDBIS = Sindbis virus; WNV = West Nile virus; EMC = Encephalomyocarditis virus; PPV = Porcine parvovirus.

Additionally, the manufacturing process was investigated for its capacity to decrease infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents. Several individual production steps in the Flebogamma 5% DIF manufacturing process have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include 4% polyethylene glycol precipitation [at least 6.19 $\log_{10}$] and Planova nanofiltration using a 20 nanometer filter [at least 5.45 $\log_{10}$]. These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Flebogamma 5% DIF, immune globulin intravenous (human), is a replacement therapy for PI. It supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. Flebogamma 5% DIF also contains a spectrum of antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in Flebogamma 5% DIF have not been fully elucidated.

12.3 Pharmacokinetics

In the clinical study assessing safety and efficacy in PI, Flebogamma 5% DIF was administered as an IV infusion (300-600 mg per kg) to subjects every 3 (n = 8) or 4 (n = 12) weeks for 12 months. The pharmacokinetics of total IgG was determined after the 7th infusion for the 3-week dosing interval and after the 5th infusion for the 4-week dosing interval (Table 3).

Table 3. Pharmacokinetic Variables of Total IgG in Subjects with PI

Variable	3-Week Dosing Interval (n = 8)		4-Week Dosing Interval (n = 12)	
	Mean [Range]	SD	Mean [Range]	SD
Cmax (mg/dL)	1,929 [1,300-2,420]	441	2,069 [1,590-2,800]	338
$AUC_{0 - last}$ (day·mg/dL)	31,159 [20,458-40,104]	6,572	32,894 [27,650-41,814]	3,886
Clearance (mL/day)	139 [81-243]	57	109 [59-161]	33
Half-life (days)[a]	30 [19-41]	9	32 [25-39]	5
Trough IgG level (mg/dL)[b]	951.38 [773.17-1143.15]	132.42	899.89 [776.70-1,137.14]	92.03

a. This half-life is an apparent value derived from a period of measurement of 28 days.

b. For subjects on the 3-week schedule, the average of the trough levels from Infusion 7 to the end of the study was calculated; for those on a 4-week schedule, the average of the trough levels from Infusion 5 to the end of the study was calculated. The means of the subject means are presented in this table.

There were 3 adolescent (up to 16 years of age) subjects who underwent pharmacokinetic testing, all of whom were on the 3-week infusion schedule. There were no clinically relevant differences among the adults and adolescents that were tested.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effect of Flebogamma 5% DIF or its effects on fertility.

13.2 Animal Toxicology and/or Pharmacology

Acute toxicity studies were performed in mice and rats at doses up to 2.5 g per kg body weight with infusion rates 6-37 times higher than the maximum rates recommended for humans. The most common clinical observations in mice studies were piloerection, ptosis, ataxia, and increase in respiration all lasting 90 minutes or less. No relevant adverse effects could be confirmed affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity, and behavior of the treated mice and rats.

Five of the 25 rats treated with the highest dose, approximately 8 times the maximum infusion rate recommended for humans, showed a transient “reddish urine” sign which was not confirmed as a relevant toxicity-causing phenomenon after renal macroscopic and microscopic analysis. This phenomenon was ascribed to hemolysis when serum was analyzed, suggesting a possible relation to cross reactivity of rodent red cells with human antibodies. No “reddish urine” was detected in any mouse, a much smaller animal where the rate of infusion was comparatively much higher than in rats. The macroscopic inspection of all treated mice did not show any renal alteration.

14 CLINICAL STUDIES

A multicenter, open-label, historically controlled study was conducted in the United States to assess the efficacy, safety, and pharmacokinetics of Flebogamma 5% DIF in adult and pediatric subjects with PI. A total of 46 subjects aged 15-75 years (63% male, 37% female) were enrolled and treated with Flebogamma 5% DIF at a dose of 300-600 mg per kg per infusion every 3-4 weeks for 12 months.

Since the subjects in the clinical study were assigned to two different treatment intervals (3-week vs. 4-week infusion schedules), the dosage had to be adjusted to ensure that the subjects received approximately the same dosage on an annualized basis. Therefore, subjects in the 3-week schedule received 75% of the monthly (4-week) dosage per infusion. This resulted in a mean annualized dosage of 451 mg per kg per month for subjects in the 3-week schedule (n=13, range 288-588 mg per kg per month) and 448 mg per kg per month for subjects in the 4-week schedule (n=33, range 298-591 mg per kg per month).

During the study period, the annual rate of acute serious bacterial infection, defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per subject per year, was 0.021 (with an upper 1-sided 98% confidence interval of 0.112). One subject had one episode of bacterial pneumonia and there were no other episodes of serious bacterial infections reported (Table 4).

Table 4. Summary of Bacterial Infections (Intention-to-Treat Population, N = 46)

Infections	Subjects (N=46) N (%)	Episodes	Estimates[a]	98% CI[b]
Bacterial pneumonia	1 (2.2)	1		
Bacteremia or sepsis	0 (0.0)	0		
Osteomyelitis/septic arthritis	0 (0.0)	0		
Bacterial meningitis	0 (0.0)	0		
Total subjects	**1 (2.2)**	**1**	**0.021**	**(0.001-0.112)**

a. Estimate = Total episodes/Total subject years.

b. The confidence interval is obtained by using a generalized linear model procedure for Poisson distribution.

The number of days of work/school missed, hospitalizations and days of each hospitalization, the number of visits to physicians or emergency rooms, other infections documented by positive radiographic findings and fever, and days on therapeutic and prophylactic oral/parenteral antibiotic use were also evaluated. These variables were annualized by using the subject-years exposure data of those subjects experiencing the events, but not the entire study cohort. With regard to the number of other validated infections, the mean rate was less than 2 days per subject per year (this calculation used all subjects, including those who had no infections). (Table 5)

Table 5. Summary of Annualized Efficacy Variables

Variable	Subjects		Mean number of events, days or visits per subject per year[a]
	N	%	
Work/school days missed	**23**	**50.0**	**12.95**
Days of normal activities missed	**18**	**39.1**	**7.28**
Days in hospital	**4**	**8.7**	**0.77**
Visits to physician/ER	**29**	**63.0**	**4.31**
Number of other documented infectious episodes	**33**	**71.7**	**1.96**
Days of therapeutic oral antibiotic use	**35**	**76.1**	**55.52**
Days of therapeutic parenteral antibiotic use	**2**	**4.3**	**0.14**
Days of other therapeutic antibiotic use	**16**	**34.8**	**44.30**
Days of prophylactic oral antibiotic use	**19**	**41.3**	**81.08**
Days of prophylactic parenteral antibiotic use	**1**	**2.3**	**0.02**
Days of other prophylactic antibiotic use	**0**	**0.0**	**0.00**

a. Days of work/school missed per subject year are derived as total days of work/school missed divided by total days in study multiplied by 365. If data are missing for a period (e.g. between Infusion 2 and Infusion 3), then number of days in this period is not counted in the denominator. All other endpoints are derived similarly.

A multicenter, open-label, historically controlled study was conducted in the United States to assess the efficacy of Flebogamma 5% DIF in pediatric subjects with PI. A total of 24 subjects aged 2-16 years (79% male, 21% female) were enrolled and treated with Flebogamma 5% DIF at a dose of 262-625 mg per kg per infusion every 3-4 weeks for 12 months.

The annual rate of acute serious bacterial infections, defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per subject per year, was 0.051 (with an upper 1-sided 99% confidence limit of 0.53). One subject had one episode of bacterial pneumonia and there were no other episodes of serious bacterial infections reported.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

Flebogamma 5% DIF is supplied in single-use, individually laser-etched vials containing the labeled amount of functionally active IgG. The following presentations of Flebogamma 5% DIF are available:

NDC Number	Size	Grams Protein
61953-0004-1	10 mL	0.5 g
61953-0004-2	50 mL	2.5 g
61953-0004-3	100 mL	5.0 g
61953-0004-4	200 mL	10.0 g
61953-0004-5	400 mL	20.0 g

Each vial has an integral suspension band and a label with two peel-off strips showing the product name and lot number.

Flebogamma 5% DIF may be stored at room temperature at 2 to 25°C (36 to 77°F) for 24 months, as indicated by the expiration date printed on the outer carton and container label. Discard after expiration date. **Do not freeze.**

Keep Flebogamma 5% DIF in its original carton to protect it from light.

Not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Instruct patients to immediately report the following signs and symptoms to their physician:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (*see Renal Failure [5.2]*)
- Symptoms of thrombosis which may include: pain and/or 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 (*see Thrombosis [5.4]*)
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting (*see Aseptic Meningitis Syndrome [5.5]*)
- Fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine (*see Hemolysis [5.6]*)
- Trouble breathing, chest pain, blue lips or extremities, fever (*see TRALI [5.7]*)

Inform patients that Flebogamma 5% DIF is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses, the vCJD agent and, theoretically, the CJD agent). The risk of Flebogamma 5% DIF transmitting an infectious agent has been reduced by screening plasma donors for prior exposure, testing the donated plasma, and inactivating and/or removing certain viruses during manufacturing. (*see Warnings and Precautions [5.8]*) Instruct patients to report any symptoms that concern them and might be caused by infections.

Inform patients that Flebogamma 5% DIF may interfere with their immune response to live viral vaccines such as measles, mumps, and rubella. Inform patients to notify their health care professional of this potential interaction when they are receiving vaccinations. (*see Drug Interactions [7]*)

Manufactured by:
INSTITUTO GRIFOLS, S.A.
BARCELONA - SPAIN
U.S. License No. 1181

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLEBOGAMMA 10% DIF safely and effectively. See full prescribing information for FLEBOGAMMA 10% DIF

FLEBOGAMMA 10% DIF (immune globulin intravenous [Human]), solution for intravenous administration
Initial U.S. Approval: 2010

WARNING: THROMBOSIS, RENAL DYSFUNCTION, and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including FLEBOGAMMA 10% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **For patients at risk of thrombosis administer FLEBOGAMMA 10% DIF 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 of hyperviscosity.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis and death may occur with the administration of human immune globulin intravenous (IGIV) products, particularly those products that contain sucrose. FLEBOGAMMA 10% DIF does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer FLEBOGAMMA 10% DIF at the minimum dose and infusion rate practicable. (5.2)**

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration (2) 9/2019

----------INDICATIONS AND USAGE----------

Flebogamma 10% DIF is an immune globulin intravenous (human), indicated for treatment of:

- Primary (inherited) Immunodeficiency (PI). (1.1)
- Chronic Primary Immune Thrombocytopenia (ITP) in patients 2 years of age and older. (1.2)

----------DOSAGE AND ADMINISTRATION----------

For Intravenous Use Only

Indication	Dose	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
PI	300-600 mg per kg every 3-4 weeks	0.01 mL per kg per minute (1 mg/kg/min)	0.08 mL per kg per minute (8 mg per kg per min)
ITP	1 g per kg daily for 2 consecutive days	0.01 mL per kg per minute (1 mg per kg per min)	0.08 mL per kg per minute (8 mg per kg per min)

- Ensure that patients with pre-existing renal insufficiency are not volume-depleted and discontinue Flebogamma 10% DIF if renal function deteriorates. (5.2)
- For patients at risk of renal dysfunction or thrombosis, administer Flebogamma 10% DIF at the minimum dose and infusion rate practicable. (5.2, 5.4)

----------DOSAGE FORMS AND STRENGTHS----------

Solution for intravenous injection containing 10% IgG (100 mg per mL). (3)

---------- CONTRAINDICATIONS ----------

- History of anaphylactic or severe systemic reactions to human immunoglobulin. (4)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity. (4)

----------WARNINGS AND PRECAUTIONS----------

- IgA deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. (5.1)
- Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving Flebogamma 10% DIF therapy. (5.3)
- Aseptic meningitis syndrome (AMS) may occur in patients receiving Flebogamma 10% DIF therapy, especially with high doses or rapid infusion rates. (5.5)
- Hemolysis, either intravascular or due to enhanced red blood cell sequestration, can develop subsequent to Flebogamma 10% DIF treatment. Risk factors include high doses and non-O blood group. Monitor patients for hemolysis and hemolytic anemia. (5.6)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury, TRALI). (5.7)
- Patients receiving Flebogamma 10% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for development of fever, chills, nausea, and vomiting. (5.8)
- Flebogamma 10% DIF is made from human plasma and may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.9)
- Passive transfer of antibodies may confound serologic testing. (5.11)
- Flebogamma 10% DIF contains sorbitol. The presence of sorbitol presents a risk to those with hereditary fructose intolerance (HFI). (5.12)

----------ADVERSE REACTIONS----------

The most common adverse reactions (reported in ≥5% of clinical trial subjects) were:

PI: headache, fever/pyrexia, shaking, tachycardia, hypotension, back pain, myalgia, hypertension, chest pain, pain, nausea, infusion site reactions and pain in extremities.

ITP: headache, pyrexia, nausea, chills, vomiting, body temperature increased, dizziness, back pain, hypotension, hypertension, heart rate increased and diarrhea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines, such as measles, mumps, and rubella. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: no human or animal data. (8.1)
- Pediatrics: increased risk of adverse reactions compared with adults. (8.4)
- Geriatric: in patients aged 65 years or older or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose. Infuse Flebogamma 10% DIF at the minimum dose and infusion rate practicable and at <0.04 mL per kg per min (<4 mg per kg per min). (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION, and ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including FLEBOGAMMA 10% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. *(see Warnings and Precautions (5.4)* and *Patient Counseling Information (17))***
- **For patients at risk of thrombosis, administer FLEBOGAMMA 10% DIF 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 patient at risk for hyperviscosity. *(see Dosage and Administration (2.3)* and *Warnings and Precautions (5.4))***
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death[1] have been related to intravenous immune globulin (IGIV) products. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.**
- **Administer FLEBOGAMMA 10% DIF at the minimum dose and rate of infusion practicable in patients at risk for renal dysfunction or failure.**
- **Reports of renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose as a stabilizer. They account for a disproportionate share of the total number of reported cases of renal dysfunction and acute renal failure. FLEBOGAMMA 10% DIF does not contain sucrose. *(see Dosage and Administration (2.3)* and *Warnings and Precautions (5.2))***

1 INDICATIONS AND USAGE

Flebogamma 10% DIF is an immune globulin intravenous (human) solution indicated for the treatment of:

1.1 Primary Immunodeficiency (PI)

Flebogamma 10% DIF is indicated as replacement therapy in primary immunodeficiency (PI) including the humoral immune defects in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome.

1.2 Chronic Primary Immune Thrombocytopenia (ITP)

Flebogamma 10% DIF is indicated for the treatment of patients 2 years of age and older with chronic primary immune thrombocytopenia to raise platelet count.

2 DOSAGE AND ADMINISTRATION

For Intravenous Use Only

2.1 Dosage

Table 1. Recommended Infusion Rates for Flebogamma 10% DIF

Indication	Dose	Initial Infusion Rate	Maintenance Dose Rate (if tolerated)
PI	300 to 600 mg per kg body weight (3.0 to 6.0 mL per kg) administered every 3 to 4 weeks	0.01 mL per kg per minute (1 mg per kg per min)	0.08 mL per kg per minute (8 mg per kg per min)
ITP	1 g per kg body weight (10 mL per kg) daily for 2 consecutive days	0.01 mL per kg per minute (1 mg per kg per min)	0.08 mL per kg per minute (8 mg per kg per min)

If a patient with PI has been exposed to measles, it may be prudent to administer an extra dose of IGIV as soon as possible and within 6 days of exposure. A dose of 400 mg/kg should provide a serum level > 240 mIU/mL of measles antibodies for at least two weeks.

If a patient with PI is at risk of future measles exposure and receives a dose of less than 530 mg/kg every 3-4 weeks, the dose should be increased to at least 530 mg/kg. This should provide a serum level of 240 mIU/mL of measles antibodies for at least 22 days after infusion.

As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. Adjust the dose according to clinical response.

Adjust the dosage over time to achieve the desired serum trough IgG levels and clinical responses. No randomized controlled trial data are available to determine an optimum target trough serum IgG level.

2.2 Preparation and Handling

- Inspect Flebogamma 10% DIF visually for particulate matter and color prior to administration. Do not use the vial if particles are detected. Do not use if turbid.
- Several vials of Flebogamma 10% DIF may be pooled into an empty sterile solution container by using aseptic technique, if large doses are to be administered.
- Do not dilute with intravenous fluids. Do not inject other medications into intravenous tubing being used for Flebogamma 10% DIF.
- Infuse Flebogamma 10% DIF through a separate intravenous line. Do not add any medications or intravenous fluids to the Flebogamma 10% DIF infusion container. Do not mix IGIV products of different formulations or from different manufacturers.
- Discard unused contents and administration devices after use.
- Use promptly any vial that has been entered.
- Discard partially used vials. Do not save for future use because the solution contains no preservative.
- Do not use solution that has been frozen.

2.3 Administration

The recommended initial infusion rate of Flebogamma 10% DIF is 0.01 mL per kg body weight per minute (1 mg per kg per min) for the first thirty minutes. If tolerated, the rate may be gradually increased to 0.04 mL per kg body weight per minute (4 mg per kg per min) and if tolerated, gradually increased to a maximum of 0.08 mL per kg body weight per min (8 mg per kg per min).

Monitor patient vital signs throughout the infusion. Slow or stop the infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient.

For the first 2-3 infusions, Flebogamma 10% DIF may be administered at infusion rates slower than recommended rates. If after administration of the first few infusions no adverse drug reactions are observed, the infusion rate for subsequent infusions may be slowly increased to the maximum rate. For patients experiencing adverse drug reactions, reduce the infusion rate in subsequent infusions or administer IGIV at 5% concentration.

3 DOSAGE FORMS AND STRENGTHS

Flebogamma 10% DIF is a liquid preparation containing 10% IgG (100 mg per mL).

4 CONTRAINDICATIONS

- Flebogamma 10% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of human immune globulin.
- Flebogamma 10% DIF is contraindicated in IgA deficient patients with antibodies to IgA and a history of hypersensitivity. *(see Warnings and Precautions (5.1))*

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions and anaphylactic reactions with a fall in blood pressure may occur, even in patients who tolerated treatment with IGIV in the past. *(see Contraindications (4))* If a hypersensitivity reaction develops, discontinue Flebogamma 10% DIF infusion immediately and institute appropriate treatment.

Flebogamma 10% DIF contains trace amounts of IgA (less than 100 µg/mL). *(see Description (11))* Patients with antibodies to IgA have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Flebogamma 10% DIF is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction. *(see Contraindications (4))*

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis and death have been reported in patients receiving IGIV, particularly those products containing sucrose.[2] Flebogamma 10% DIF does not contain sucrose.

Ensure that patients are not volume-depleted before administering Flebogamma 10% DIF. For patients judged to be at risk for developing renal dysfunction, including patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia or patients receiving known nephrotoxic drugs, administer Flebogamma 10% DIF at the minimum dose and rate of infusion practicable.[3] *(see Boxed Warning) (see Dosing and Administration (2.3))*

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.[1] Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Flebogamma 10% DIF and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of the product.

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving Flebogamma 10% DIF therapy. It is critical to distinguish true hyponatremia from pseudohyponatremia that is temporally or causally related to hyperproteinemia with concomitant decreased calculated serum osmolarity or elevated osmolar gap. This is because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and increased risk of thrombosis.

5.4 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including Flebogamma 10% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. *(see Warnings and Precautions (5.10))* For patients at risk of thrombosis, administer Flebogamma 10% DIF 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. *(see Boxed Warning, Dosage and Administration (2.3) and Patient Counseling Information (17))*

5.5 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.[4,5] The symptoms of AMS usually begin within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. *(see Patient Counseling Information (17))* Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL but negative culture results. Conduct a thorough neurological examination of patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently following high doses (e.g., >2 g per kg body weight) or rapid infusion of IGIV.

5.6 Hemolysis

Flebogamma 10% DIF may contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test (DAT) (Coombs' test) and hemolysis.[6,7] Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration and acute hemolysis, consistent with intravascular hemolysis.[8] Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of IGIV.

The following risk factors may be associated with the development of hemolysis following IGIV administration: high doses (e.g., >2 g per kg), given either as a single administration or divided over several days, and non-O blood group.[9] Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV,[10] but their role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP and PI.[11] Monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within 36 to 96 hours post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis. *(see Patient Counseling Information (17))*

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Non-cardiogenic pulmonary edema has been reported in patients following IGIV treatment.[12] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. *(see Patient Counseling Information (17))* If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Infusion Reactions

Individuals receiving Flebogamma 10% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for the development of fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events. *(see Dosage and Administration (2.3))*

5.9 Transmissible Infectious Agents

Because Flebogamma 10% DIF is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and theoretically, the Creutzfeldt-Jakob (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. No cases of transmission of viral diseases or CJD have been associated with the use of Flebogamma 10% DIF. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Biologicals at 1-888-474-3657. Before prescribing or administering Flebogamma 10% DIF, the physician should discuss the risks and benefits of its use with the patient. *(see Patient Counseling Information (17))*

5.10 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of Flebogamma 10% DIF and at appropriate intervals thereafter.
- Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potential for increased risk of thrombosis.
- If signs and/or symptoms of hemolysis are present after an infusion of Flebogamma 10% DIF, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient serum.

5.11 Interference with Laboratory Tests

After infusion of IgG, the transitory rise of the 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.

5.12 Hereditary Fructose Intolerance

Flebogamma 10% DIF contains sorbitol. The presence of sorbitol presents a risk to those with hereditary fructose intolerance (HFI). The incidence of HFI is estimated at 1 in 20,000 births and is usually diagnosed at the time of weaning when fructose or sucrose is introduced into the diet. Clinical symptoms include recurrent vomiting, abdominal pain and hypoglycemia. Flebogamma 10% DIF must not be administered to subjects with HFI.

6 ADVERSE REACTIONS

The most common adverse reactions (reported in ≥5% of clinical trial subjects) were:

PI: headache, fever/pyrexia, shaking, tachycardia, hypotension, back pain, myalgia, hypertension, chest pain, pain, nausea, infusion site reactions and pain in extremities.

ITP: headache, pyrexia, nausea, chills, vomiting, body temperature increased, dizziness, back pain, hypotension, hypertension, heart rate increased and diarrhea.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

6.1 Clinical Trials Experience

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

Primary Immunodeficiency (PI)

In a multicenter, open-label, non-randomized, historically controlled clinical study, 46 individuals with PI received infusions of Flebogamma 10% DIF at doses of 300 to 600 mg/kg body weight every 3 weeks (mean dose 469 mg/kg) or 4 weeks (mean dose 457 mg/kg) for up to 12 months. *(see Clinical Studies (14.1))*

One subject experienced four serious adverse events (SAE) (bacterial pneumonia, subcutaneous abscess and two episodes of cellulitis) and withdrew from the study. Two other subjects discontinued prematurely due to AEs (back pain/chest pain/headache; and chills/tachycardia). Three subjects experienced four SAEs (drug abuse/depression; hernia; and sinusitis) unrelated to the product.

One or more product-related adverse reactions were reported in 38 (83%) subjects.

Adverse reactions that occurred with an incidence of ≥5% on a per-subject basis are summarized in Table 2.

Table 2. Adverse Reactions Occurring in ≥5% of Subjects

Adverse Reaction	Subjects (%) N=46	Number of Events
Headache	24 (52.2)	71
Pyrexia[a]	19 (41.3)	11
Rigors	17 (37.0)	38
Tachycardia/heart rate increased	11 (23.9)	20
Hypotension	9 (19.6)	11
Back Pain	8 (17.4)	27
Myalgia	8 (17.4)	21
Hypertension[b]	7 (15.2)	12
Chest pain[c]	6 (13)	25
Pain	4 (8.7)	8
Nausea	4 (8.7)	6
Infusion site reaction	3 (6.5)	6
Pain in extremities	3 (6.5)	3

a. includes combined reported terms of pyrexia and body temperature increase.

b. includes combined reported terms of hypertension, diastolic hypertension, blood pressure increased, systolic blood pressure increased and systolic hypertension.

c. includes combined reported terms of chest pain and chest discomfort.

Other common adverse drug reactions reported in <5% of the subjects included flatulence, fatigue, feeling cold, malaise, neck pain, dizziness, wheezing, muscle spasms/tightness and abdominal distension/pain.

The total number of temporally associated adverse reactions (i.e., reported within 72 hours post-infusion) was 291. Since a total of 601 infusions were administered, the ratio of temporally associated adverse reactions per infusion was 0.48 (upper bound of the 1-sided 95% confidence interval: 0.52). A total of 166 infusions (30.3%, 1-sided 95% upper bound CI = 37.6%) were associated with one or more temporally associated adverse reactions. In this analysis, each infusion is only counted once, regardless of the number of adverse reactions that occurred during the infusion, when during the 72-hour period after the infusion the adverse reaction started, or the intensity of those adverse reactions. In the 21 subjects who received pre-medication, 12 (57%) reported temporally associated adverse reactions for 48 of 130 infusions (37%).

Factoring adverse reaction intensity into the analysis of the 601 infusions shows that there were 117 infusions with at least one mild adverse reaction (19.5% [upper bound 95% CI=22.9%]), 74 infusions with at least one moderate adverse reaction (12.3 % [upper bound 95% CI=15.2%]), and 8 infusions with at least one severe adverse reaction (1.3% [upper bound 95% CI=2.6%]). In this analysis, if a subject reported multiple events with different intensities during the same infusion (e.g., mild headache and moderate pyrexia), that infusion would be counted in all relevant categories. Therefore, the number of infusions counted is 199.

Forty-three of 46 subjects had a negative Coombs' test at baseline. Of these 43 subjects, 10 (23.3%) developed a positive Coombs' test at some time during the study. However, no subjects showed evidence of hemolytic anemia.

Chronic Primary Immune Thrombocytopenia (ITP)

In a prospective, open-label, multicenter study, 58 subjects (46 adult and 12 pediatric) with chronic ITP were treated with Flebogamma 10% DIF, administered intravenously at a dose of 1 g per kg per day for 2 consecutive days, for a total dose of 2 g per kg, at a starting rate of 0.01 mL per kg per minute for 30 minutes.

Three SAEs of moderate to severe intensity were reported in 3 adult subjects during the 30 day follow-up period: soft tissue inflammation (unrelated) of unknown etiology in one subject on Day 29 and headache in two subjects (possibly related) on Day 2. All subjects recovered without sequelae.

Forty-eight (82.8%) subjects had one or more product related adverse reactions at some time during the study. Adverse reactions that occurred with an incidence of at least 5% on a per subject basis are summarized in Table 3. The proportion of subjects who experienced treatment-emergent adverse events (TEAE) was higher in the pediatric cohort than in the adult cohort. *(see Pediatric Use (8.4) and Clinical Studies (14.2))*

Table 3. Adverse Reactions Occurring in ≥5% of Subjects

Adverse Reaction	Adults (N = 46)		Pediatrics (N = 12)		All Subjects (N = 58)	
	n (%)	Number of Events	n (%)	Number of Events	n (%)	Number of Events
Headache	24 (52.2)	34	11 (91.7)	19	35 (60.3)	53
Nausea	4 (8.7)	4	8 (66.7)	9	12 (20.7)	13
Pyrexia	8 (17.4)	11	4 (33.3)	5	12 (20.7)	16
Chills	7 (15.2)	8	4 (33.3)	4	11 (19.0)	12
Vomiting	4 (8.7)	4	5 (41.7)	5	9 (15.5)	9
Body temperature increased	3 (6.5)	3	2 (16.7)	2	5 (8.6)	5
Back pain	2 (4.3)	2	2 (16.7)	2	4 (6.9)	4
Dizziness	4 (8.7)	4	0	0	4 (6.9)	4
Diarrhea	3 (6.5)	3	0	0	3 (5.2)	3
Heart rate increased	1 (2.2)	1	2 (16.7)	2	3 (5.2)	3
Hypertension	2 (4.3)	2	1 (8.3)	1	3 (5.2)	3
Hypotension	1 (2.2)	1	2 (16.7)	3	3 (5.2)	4

In a supportive study of Flebogamma 10% DIF in adults (N=18) with ITP, three SAEs in 2 subjects were reported over the 3 month follow-up period: one case of thrombosis (possibly related) in one subject, and leukopenia (from 5.3 x 10^9/L pre-infusion to 2.7 x 10^9/L at Day 3; probably related) and decreased hemoglobin (from 11.7 g/dL pre-infusion to 9.8 g/dL on Day 2; probably related) in a second subject. All subjects recovered without sequelae.

6.2 Post-marketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. The following adverse reactions have been identified during post-approval use of IGIV products,[13-14] including Flebogamma 5% and 10% DIF.

Infusion reactions Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure

Renal Acute renal dysfunction/failure, osmotic nephropathy

Respiratory Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion-Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm

Cardiovascular Cardiac arrest, thromboembolism, vascular collapse, hypotension

Neurological Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome

Integumentary Stevens-Johnson Syndrome, epidermolysis, erythema multiformae, dermatitis (e.g., bullous dermatitis)

Hematologic Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test

Musculoskeletal Back pain

Gastrointestinal Hepatic dysfunction, abdominal pain

General/Body as a Whole Pyrexia, rigors

7 DRUG INTERACTIONS

Passive transfer of antibodies may transiently impair the immune response to live attenuated virus vaccines such as measles, mumps and rubella. Inform the immunizing physician of recent therapy with Flebogamma 10% DIF so that appropriate measures can be taken. *(see Patient Counseling Information (17))*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies of Flebogamma 10% DIF use in pregnant women. Animal reproduction studies have not been performed with Flebogamma 10% DIF. It is also not known whether Flebogamma 10% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. Flebogamma 10% DIF should be given to a pregnant woman only if clearly needed.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Flebogamma 10% DIF in human milk, its effects on the breastfed infant, or its effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Flebogamma 10% DIF and any potential adverse effects on the breastfed infant from Flebogamma 10% DIF or from the underlying maternal condition.

8.4 Pediatric Use

Primary Immunodeficiency (PI)

Three (3) pediatric subjects with PI (two between the ages of 6 and 10, and one 16 years old) were included in the clinical evaluation of Flebogamma 10% DIF. This number is too small to establish safety and efficacy in the pediatric population. *(see Clinical Studies (14))*

Chronic Primary Immune Thrombocytopenia (ITP)

Twelve (12) pediatric subjects with chronic ITP were enrolled and treated with Flebogamma 10% DIF in a clinical trial. Of the 12 subjects enrolled and treated, 4 were children and 8 were adolescents. The proportion of subjects who experienced treatment-emergent adverse events (TEAE) was higher in the pediatric cohort than in the adult cohort. *(see Clinical Trials Experience (6.1))*

The safety and effectiveness of Flebogamma 10% DIF has not been established in pediatric subjects under the age of 2.

8.5 Geriatric Use

Limited information is available for the geriatric use of Flebogamma 10% DIF. Clinical studies of Flebogamma 10% DIF did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects. Use caution when administering Flebogamma 10% DIF to patients aged ≥65 years who are judged to be at increased risk for developing thrombosis or renal insufficiency. Do not exceed the recommended dose, and infuse Flebogamma 10% DIF at the minimum dose and infusion rate practicable and at less than 0.04 mL per kg per minute (4 mg per kg per min). *(see Boxed Warning, Warning and Precautions (5.2, 5.4) and Dosage and Administration (2.3))*

10 OVERDOSAGE

Overdose may lead to fluid overload and hyperviscosity. Patients at particular risk of complications of fluid overload and hyperviscosity include elderly patients and patients with cardiac or renal impairment.

11 DESCRIPTION

Flebogamma 10% DIF is a ready to use, sterile, clear or slightly opalescent and colorless to pale yellow, liquid preparation of purified immunoglobulin (IgG) obtained from human plasma pools. The purification process includes cold ethanol fractionation, polyethylene glycol precipitation, ion exchange chromatography, low pH treatment, pasteurization, solvent detergent treatment and Planova nanofiltration using 20 nanometer (nm) filters.

Flebogamma 10% DIF is a purified (at least 97% IgG), unmodified, human IgG. The distribution of the four IgG subclasses is approximately 66.6% IgG_1, 27.9% IgG_2, 3.0% IgG_3 and 2.5% IgG_4. Flebogamma 10% DIF contains trace amounts of IgA (typically less than 100 µg/mL) and trace amounts of sodium and IgM.

Flebogamma 10% DIF contains 10 g human normal immunoglobulin and 5 g D-sorbitol (as stabilizer) in 100 mL of water for injection, and ≤ 6 mg/mL polyethylene glycol. There is no preservative in the formulation. The pH of the solution ranges from 5 to 6 and the osmolality from 240 to 370 mOsm/kg, which is within the normal physiological range.

Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collections and plasma preparation. Each individual plasma donation used in the manufacture of Flebogamma 10% DIF is collected only at FDA-approved blood establishments and is tested by FDA licensed serological test for hepatitis B surface antigen (HBsAg), and for antibodies to human immunodeficiency virus (HIV-1/HIV-2) and hepatitis C virus (HCV) in accordance with U.S. regulatory requirements. As an additional safety measure, mini-pools of plasma are tested for the presence of HBV, HIV-1 and HCV by FDA licensed nucleic acid testing (NAT) and found to be negative. In addition, plasma is tested by in-process NAT for hepatitis A virus (HAV) and parvovirus B19 (B19) on mini-pools and the viral load limit for B19 in the manufacturing pool is set not to exceed 104 IU/mL. NAT for the presence of HCV and HIV in the manufacturing plasma pool is also performed and found to be negative.

To further improve the margin of safety, three dedicated, independent virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely pasteurization at 60°C, 10 hours, solvent-detergent treatment for 6 hours and nanofiltration down to 20 nm Planova filters.

In vitro virus spiking studies have been used to validate the capability of the manufacturing process to inactivate and remove viruses. To establish the minimum applicable virus clearance capacity of the manufacturing process, these virus clearance studies were performed on seven steps of the production process (pasteurization, solvent-detergent treatment, nanofiltration, Fraction I precipitation, Fraction II+III precipitation, 4% PEG precipitation and pH treatment for 4 hours at 37°C).

The viral reduction data (in $\log_{10}$) from these experiments are summarized in Table 4.

Table 4. Flebogamma 10% DIF: viral reduction capacity of combined steps ($\log_{10}$)

Target virus	HIV-1, HIV-2 (env. RNA)	HBV Herpesvirus (env. DNA)		HCV (env. RNA)		WNV (env. RNA)	HAV (non-env. RNA)	B19 Virus (non-env. DNA)
Model virus	HIV-1	PRV	IBR	BVDV	SINDBIS	WNV	EMC	PPV
Fraction I precipitation	< 1.00*	nd	nd	nd	nd	2.78	nd	< 1.00*
Ethanol incubation (Fraction II+III)	1.48	nd	nd	nd	nd	< 1.00*	nd	nd
PEG precipitation	≥ 6.10	≥ 5.92	nd	≥ 5.78	nd	nd	≥ 6.41	6.35
Acid pH treatment	2.47	≥ 5.32	nd	< 1.00*	nd	nd	1.36	na
Pasteurization	≥ 5.64	≥ 4.96	≥ 6.33	≥ 4.69	≥ 6.49	≥ 5.42	≥ 5.56	4.08
Solvent Detergent	≥ 4.61	≥ 6.95	nd	≥ 6.14	nd	≥ 5.59	na	na
Nanofiltration 20 nanometer	≥ 4.81	≥ 4.63	nd	≥ 4.67	nd	≥ 3.63	≥ 5.92	4.61
Overall Reduction Capacity	≥ 25.11	≥ 27.78	≥ 6.33	≥ 21.28	≥ 6.49	≥ 17.42	≥ 19.25	15.04

*When the RF is <1 $\log_{10}$, it is not taken into account for the calculation of the overall reduction capacity.

≥=no residual infectivity detected; nd= not done; na= non-applicable, since the virus is theoretically resistant to this treatment.

Abbreviations: HIV= Human immunodeficiency virus; PRV= Pseudorabies virus; IBR= Infectious bovine rhinotracheitis virus, BVDV; Bovine viral diarrhea virus; SINDBIS= Sindbis virus; WNV= West Nile virus; EMC= Encephalomyocarditis virus; PPV= Porcine parvovirus.

Additionally, the manufacturing process was investigated for its capacity to decrease infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.

Several individual production steps in the Flebogamma 10% DIF manufacturing process have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include 4% polyethylene glycol precipitation [at least 6.19 $\log_{10}$] and Planova nanofiltration using a 20 nanometer filter [at least 5.45 $\log_{10}$]. These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PI: Flebogamma 10% DIF supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. Flebogamma 10% DIF also contains a spectrum of antibodies capable of reacting with cells, such as erythrocytes. The role of these antibodies and the mechanism of action of IgG in Flebogamma 10% DIF have not been fully elucidated.

Chronic ITP: the mechanism of action of immunoglobulins in the treatment of chronic ITP has not been fully elucidated.

12.3 Pharmacokinetics

In the clinical study assessing safety and efficacy in PI, the pharmacokinetics of Flebogamma 10% DIF were assessed for 21 or 28 days after administration in 19 subjects. PK analysis was performed for 10 subjects receiving Flebogamma 10% DIF on a 21-day schedule and for 9 subjects receiving treatment on a 28-day schedule.

The mean dose (range) for those on the 21-day schedule was 476 mg/kg (range: 339-597) and 496 mg/kg (range: 434-588) for those on the 28-day schedule. Blood samples for PK analysis were obtained after Infusion #7 for subjects on a 28-day schedule and after Infusion #9 for subjects on a 21-day schedule. Table 5 summarizes the pharmacokinetic parameters of Flebogamma 10% DIF, measured as serum concentrations of total IgG. The half-life of IgG can vary considerably among patients.

Table 5. Pharmacokinetic Variables of Total IgG in Subjects with PI

Variable	3-Week Dosing Interval (n = 10)		4-Week Dosing Interval (n = 9)	
	Mean ± SD	Range	Mean ± SD	Range
Cmax (mg/mL)	19.50 ± 2.83	15.10 – 24.40	20.92 ± 3.66	16.80 – 29.20
$AUC_{0 - last}$ (day · mg/mL)	339.51 ± 45.27	241.12 – 380.21	342.37 ± 39.72	276.83 – 408.25
Clearance (mL/day)	115 ± 31	81 – 186	144 ± 47	77 – 237
Half-life (days)[a]	34 ± 10	21 – 58	37 ± 13	24 – 59
Trough IgG level (mg/mL)[b]	9.76 ± 1.65	6.45 – 11.40	8.77 ± 1.26	7.59 – 11.70

a. This half-life is an apparent value derived from a 28 day period of measurement

b. For subjects on the 3-week schedule, average trough levels from Infusion #9 to the end of the study was calculated; for those on a 4-week schedule, the average of the trough levels from Infusion #7 to the end of the study was calculated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effect of Flebogamma 10% DIF or its effects on fertility.

13.2 Animal Toxicology and/or Pharmacology

Acute toxicity studies were performed in mice and rats at doses up to 2.5 g per kg body weight with infusion rates 6-37 times higher than the maximum rates recommended for humans. The most common clinical observations in mice studies were piloerection, ptosis, ataxia and increase in respiration all lasting 90 minutes or less. No relevant adverse effects could be confirmed affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity, and behavior of the treated mice and rats.

Five of the 25 rats treated with the highest dose at approximately 8 times the maximum infusion rate recommended for humans, showed a transient “reddish urine” sign which was not confirmed as a relevant toxicity-causing phenomenon after renal macroscopic and microscopic analysis. This phenomenon was ascribed to hemolysis that occurred when the serum was analyzed, suggesting a possible relation to cross-reactivity of rodent red cells with human antibodies. No “reddish urine” was detected in any mouse, a much smaller animal where the rate of infusion was comparatively much higher than in rats. The macroscopic inspection of all treated mice did not show any renal alteration.

14 CLINICAL STUDIES

14.1 Treatment of Primary Immunodeficiency (PI)

A phase 3, multicenter, open-label, historically controlled study to assess the efficacy, safety and pharmacokinetics of Flebogamma 10% DIF in subjects with PI was conducted in the United States. Forty-six subjects were treated with Flebogamma 10% DIF for 12 months at a 3-week or 4-week dosing interval. Subjects ranged in age from 6 to 65 years; 65% were male and 35% were female; 96% were Caucasian and 4% were Hispanic. Pre-medication to alleviate potential adverse drug reactions was only allowed after the first infusions only in those subjects that exhibited adverse reactions. Of 601 infusions administered during the study, 130 (22%) infusions in 21 (47%) subjects were preceded by pre-medication (antipyretic, antihistamine, or antiemetic agent) because of experience with consecutive infusion-related adverse reactions.

If the infusion was well tolerated (no adverse reaction temporally associated with the infusion), the infusion rate was increased to 0.02 mL per kg per minute for 30 minutes and then to 0.04 mL per kg per minute for another 30 minutes. If well tolerated, additional increments of 0.02 mL per kg per minute were made at 30-minute intervals up to a maximum rate of 0.08 mL per kg per minute.

Since subjects in the clinical study were assigned to two different treatment intervals (3-week vs. 4-week infusion schedules), the dosage had to be adjusted to ensure that subjects received approximately the same dosage on an annualized basis. Therefore, subjects in the 3-week schedule received 75% of the monthly (4-week) dosage per infusion. This resulted in a mean annualized dosage of 468.5 mg per kg per month for subjects in the 3-week schedule (N=16, range 320-597 mg per kg per month) and 457.4 mg per kg per month for subjects in the 4-week schedule (N=30, range 307-588 mg per kg per month). Subjects received a total of 601 infusions of Flebogamma 10% DIF. The maximum infusion rate allowed during the study was 0.08 mL per kg per minute.

During the study period, the annual rate of acute serious bacterial infections, defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess and bacterial meningitis per subject per year, was 0.025 (upper 1-sided 98% confidence interval: 0.001 to 0.133). One subject had one episode of bacterial pneumonia. There were no other serious bacterial infections (Table 6).

Table 6. Summary of Bacterial Infections (Intention-to-Treat Population, N = 46)

Infections	Subjects (N=46) N (%)	Episodes	Estimates[a]	98% CI[b]
Bacterial pneumonia	1 (2.2)	1		
Bacteremia or sepsis	0 (0.0)	0		
Osteomyelitis/septic arthritis	0 (0.0)	0		
Visceral abscess	0 (0.0)	0		
Bacterial meningitis	0 (0.0)	0		
Subjects with at least 1 serious bacterial infection	**1 (2.2)**	**1**	**0.025**	**(0.001, 0.133)**

a. Estimate = Total episodes/Total subject years.

b. The confidence interval is obtained by using a generalized linear model procedure for Poisson distribution.

The number of days of work/school missed, hospitalizations and days of each hospitalization, the number of visits to physicians or emergency rooms, other infections documented by positive radiographic findings and fever, and days on therapeutic and prophylactic oral/parenteral antibiotic use also were evaluated. These variables were annualized by using subject-years exposure data of those subjects experiencing the events, but not the entire study cohort. The mean rate of other validated infections was <2 days per subject per year (this calculation used all subjects, including those who had no infections). (Table 7)

Table 7. Summary of Annualized Efficacy Variables

Variable	Subjects		Mean number of events, days or visits per subject per year[a]
	N	%	
Work/school days missed	20	43.5	3.0
Days in hospital	5	11.0	0.6
Visits to physician/ER	24	52.2	2.1
Number of other documented infectious episodes	7	15.2	0.2
Days of therapeutic oral antibiotic use	36	78.3	56.4
Days of therapeutic parenteral antibiotic use	2	4.3	1.3
Days of other therapeutic antibiotic use	14	30.4	60.5
Days of prophylactic oral antibiotic use	19	41.3	45.8
Days of prophylactic parenteral antibiotic use	1	2.2	0.02
Days of other prophylactic antibiotic use	1	2.2	3.3

a. Days of work/school missed per subject year are derived as total days of work/school missed divided by total days in study multiplied by 365. If data are missing for a period, e.g., between Infusion #2 and Infusion #3, then number of days in this period is not counted in the denominator. All other endpoints are derived similarly.

14.2 Treatment of Chronic Primary Immune Thrombocytopenia (ITP)

A phase 3, prospective, open-label, single-arm, multicenter study assessed the efficacy, safety and tolerability of Flebogamma 10% DIF in 58 subjects (46 adult and 12 pediatrics) with chronic ITP and a platelet count of ≤20 x 10^9/L. Subjects ranged in age from 3 to 70 years (median age: 28 years). Females (67.2%) outnumbered males (32.8%). A majority of the subjects were Asian (67.4%); the remainder was Caucasian (26.1%), Hispanic (4.3%) and African American (2.2%).

Median age of the pediatric cohort was 13 years. The ratio of males to females was 1:1. Only Caucasian subjects were enrolled. See Table 8 for the number of pediatric subjects stratified by age.

Table 8. Summary of Pediatric Subjects by Age Groups

Age group	Number of subjects (N)
3-5 years	1
6-11 years	3
12-16 years	8

Subjects received a 2 g per kg dose of Flebogamma 10% DIF administered intravenously as 1 g per kg on 2 consecutive days. Pre-medication to alleviate potential adverse drug reactions was not allowed. The starting rate of 0.01 mL per kg per minute was to be maintained for 30 minutes. If the infusion was well tolerated, the infusion rate was increased to 0.02 mL per kg per minute for 30 minutes and then to 0.04 mL per kg per minute for another 30 minutes. If well tolerated, additional increments of 0.02 mL per kg per minute were made at 30-minute intervals up to a maximum rate of 0.08 mL per kg per minute.

Platelet counts were measured on infusion visits (Days 1 and 2), in clinical follow-up visits (Day 3, Day 5 $\pm$ 1, Day 8 $\pm$ 1, Day 15 $\pm$ 1, Day 22 $\pm$ 1), at final study visit (Day 30 $\pm$ 1) and daily on Day 4 through Day 8 or until counts reached or exceeded 50 $\times$ 10^9/L, whichever occurred first, and then every 4 $\pm$ 1 days through Day 22 $\pm$ 1.

The primary efficacy endpoint was the response rate, defined as the proportion of treated subjects in whom platelet counts increased from ≤ 20 $\times$ 10^9/L to ≥ 50 $\times$ 10^9/L by Day 8 $\pm$ 1 (the day of the first infusion was Day 1) in the modified intent-to-treat population (mITT). The mITT consisted of all subjects who received at least one infusion (at any dose) of Flebogamma 10% DIF.

Table 9. Response Rate (mITT Population)

	Adults (N = 46)	Pediatrics (N = 12)	All Subjects (N = 58)
Number of responders (%)	35 (76.1)	12 (100.0)	47 (81.0)
95% confidence interval[a]	(63.5, 86.0)	(77.9, 100.0)	(70.6, 89.0)

mITT: modified intention to treat; N: number of subjects.

a. The lower and upper bound of the exact one-sided 95% confidence interval.

Secondary efficacy endpoints included:

- Time to platelet count recovery, as determined by the number of days elapsed from Day 1 to the day on which the platelet count was first found to be ≥ 50 × 10^9/L during the clinical follow-up period ending on Day 30 ± 1.
- Duration of response, as determined by the number of consecutive days for which the platelet count remained ≥50 × 10^9/L during the clinical follow-up period ending on Day 30 ± 1.
- Regression of hemorrhage/bleeding, as determined by the proportion of treated subjects with hemorrhage/bleeding on Day 1 who improved their diathesis, assessed using a categorized rating scale, during the clinical follow-up period ending on Day 15 ± 1.

A total of 47 out of 58 subjects (81%) in the mITT population were responders. The responder rate was 76.1% (35/46) in adults and 100% (12/12) in children. Analysis of the primary efficacy endpoint showed that the lower limit of the exact one-sided 95% CI was 70.6%, which was above the predefined response rate of 50%.

Mean time to platelet count recovery (≥50 × 10^9/L) was ≤ 1.7 days among all responders (≤ 1.8 days in adults and ≤ 1.4 days in pediatrics). Median time to platelet count recovery was ≤ 2 days for all responders and adults, and ≤ 1 day for pediatrics. (The symbol "≤" is used because actual time to platelet count recovery could have occurred prior to the study visit since this endpoint was assessed only at study visits.)

Table 10. Time to Platelet Count Recovery in Responders (mITT Population)

		Adults (N = 46)	Pediatrics (N = 12)	All Subjects (N = 58)
Number of responders		35	12	47
Time to platelet count recovery (days)	Mean ± SD	1.8 ± 1.0	1.4 ± 0.5	1.7 ± 0.9
	Median (Min, Max)	2 (0, 4)	1 (1, 2)	2 (0, 4)

mITT=modified intention to treat; N=number of subjects; SD=standard deviation of the mean; Min=minimum; Max=maximum.

Mean duration of response was ≥ 10.8 days among all responders, ≥ 9.6 days in adult responders and ≥ 14.3 days in pediatric responders. (The symbol "≥" is used because actual duration of response could have persisted after the study visit since this endpoint was assessed only at study visits.)

Table 11. Duration of Response in Responders (mITT Population)

		Adults (N = 46)	Pediatrics (N = 12)	All Subjects (N = 58)
Number of responders		35	12	47
Duration of response (days)	Mean ± SD	9.6 ± 7.8	14.3 ± 8.0	10.8 ± 8.0
	Median (Min, Max)	7 (1, 29)	14 (3, 29)	10 (1, 29)

mITT= modified intention to treat; N= number of subjects; SD=standard deviation of the mean; Min= minimum; Max=maximum.

Approximately 67% of all subjects (39/58) presented with signs of hemorrhage/bleeding at Day 1 before the first infusion of Flebogamma 10% DIF. This cohort included 59% of adults (27/46) and all pediatric subjects (12/12, 100%). Approximately 92% of these subjects experienced improvement in bleeding diathesis during the follow-up period by Day 15 regardless of whether they were responders in terms of platelet count.

Table 12. Regression of Hemorrhage (mITT population)

Parameters	Adults (N = 46)	Pediatrics (N = 12)	All Subjects (N = 58)
Subjects with hemorrhage at Day 1	27	12	39
Improvement in diathesis of subjects with hemorrhage at Day 1	24/27 (88.9%)	12/12 (100.0%)	36/39 (92.3%)
95% confidence interval[a]	(70.8, 97.6)	(73.5, 100.0)	(79.1, 98.4)

mITT: modified intention to treat; N: number of subjects.

a. Lower and upper bound of the exact two-sided 95% confidence interval.

Mean maximum platelet count among all responders ranged from 205.3 $\times$ 10^9/L (adults) to 335.2 $\times$ 10^9/L (pediatrics). All responders, adults and pediatrics combined, showed a mean maximum platelet count of 238.4 $\times$ 10^9/L. All responders, including adult and pediatric responders, had a mean time to maximum platelet count of 4.8 days. Maximum platelet count was 4.7 days for adult responders and 5.3 days for pediatric responders. The mean maximum increase in platelet count in all responders was 226.3 $\times$ 10^9/L, with 193.3 $\times$ 10^9/L in adult responders and 322.6 $\times$ 10^9/L in pediatric responders.

Three SAEs were reported in the adult cohort, 1 case of soft-tissue inflammation and 2 cases of headache. No SAEs were reported in the pediatric cohort but the incidence of treatment-emergent adverse events was higher in pediatric subjects than in adults. *(see Adverse Events (6.1))*

A supportive, prospective, open-label, single-arm, multicenter study assessed the efficacy, safety and tolerability of Flebogamma 10% DIF in 18 adult subjects with chronic ITP and a platelet count of ≤20 x 10^9/L. A total of 12 females and 6 males ranging in age from 18 to 82 years were enrolled. Their median age was 43 years. All subjects were Caucasian.

The primary efficacy endpoint was the response rate, defined as the proportion of treated subjects in whom platelet counts increased from ≤ 20 $\times$ 10^9/L to ≥ 50 $\times$ 10^9/L at any time during the study period. The study achieved its primary endpoint: 13/18 subjects (72.2%; 95% confidence interval: 50.2, 88.4) met the criteria for treatment responders.

Three SAEs were reported in two subjects and assessed as possibly related: leukopenia (mild) and decreased hemoglobin (mild) in the one subject and axillary vein thrombosis (severe) in the second subject. Both subjects recovered without sequelae. The proportion of subjects who experienced treatment-emergent adverse events (TEAE) was higher in the pediatric cohort than in the adult cohort. *(see Clinical Trials Experience, (6.1) and Pediatric Use (8.4))*

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16 HOW SUPPLIED/STORAGE AND HANDLING

Flebogamma 10% DIF is supplied in single-use, individually laser-etched vials containing the labeled amount of functionally active IgG.

The following presentations of Flebogamma 10% DIF are available:

NDC Number	Fill Size	Grams Protein
61953-0005-1	50 mL	5 g
61953-0005-2	100 mL	10 g
61953-0005-3	200 mL	20 g

Each vial has an integral suspension band and a label with two peel-off strips showing the product name and lot number.

Flebogamma 10% DIF may be stored at room temperature at 2 to 25°C (36 to 77°F) for up to 24 months, as indicated by the expiration date printed on the outer carton and container label. Discard after expiration date. **Do not freeze.**

Keep Flebogamma 10% DIF in its original carton to protect it from light.

Not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Instruct patients to immediately report the following signs and symptoms to their physician:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath *(see Renal Failure (5.2))*
- Symptoms of thrombosis which may include: pain and/or 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 *(see Thrombosis (5.4))*
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea and vomiting *(see Aseptic Meningitis Syndrome (5.5))*
- Increased heart rate, fatigue, yellowing of skin or eyes and dark-colored urine *(see Hemolysis (5.6))*
- Trouble breathing, chest pain, blue lips or extremities, fever *(see TRALI (5.7))*

Inform patients that Flebogamma 10% DIF is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses, the vCJD agent and, theoretically, the CJD agent). The risk of Flebogamma 10% DIF transmitting an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating and/or removing certain viruses during manufacturing. *(see Warnings and Precautions (5.8))* Instruct patients to report any symptoms that concern them and might be caused by infections.

Inform patients that Flebogamma 10% DIF may interfere with their immune response to live viral vaccines such as measles, mumps and rubella. Inform patients to notify their health care professional of this potential interaction when they are receiving vaccinations. *(see Drug Interactions (7))*

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