

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMMAGARD S/D safely and effectively. See full prescribing information for GAMMAGARD S/D

**GAMMAGARD S/D, Immune Globulin Intravenous (Human)
IgA less than or equal to 1 µg/mL in a 5% Solution
Solvent Detergent Treated
Initial U.S. Approval: 1994**

Warning

See full prescribing information for complete boxed warning

- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the intravenous administration of human immune globulin products, particularly those products that contain sucrose. GAMMAGARD S/D does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer GAMMAGARD S/D at the minimum rate of infusion practicable.

INDICATIONS AND USAGE

GAMMAGARD S/D is an Immune Globulin Intravenous (Human), indicated for:

- Treatment of Primary Immunodeficiency (PI) in adults and pediatric patients two years of age or older. (1.1)
- Prevention of bacterial infections in hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell Chronic Lymphocytic Leukemia (CLL). (1.2)
- Prevention and/or control of bleeding in adult Chronic Idiopathic Thrombocytopenic Purpura (ITP) patients. (1.3)
- Prevention of coronary artery aneurysms associated with Kawasaki syndrome in pediatric patients. (1.4)

DOSAGE AND ADMINISTRATION

Intravenous Use Only

Indication	Recommended Dosage	Duration
PI (2.1)	300-600 mg/kg	Every 3 to 4 weeks
CLL (2.2)	400 mg/kg	Every 3 to 4 weeks
ITP (2.3)	1g/kg	Maximal 3 doses on alternate days
Kawasaki Syndrome (2.4)	Single 1g/kg or 400 mg/kg for 4 consecutive days	Begin within 7 days of onset of fever*

* Administer concomitant Aspirin Therapy: 80-100 mg/kg/day in four divided doses

DOSAGE FORMS AND STRENGTHS

- Freeze-dried preparation containing 5 g or 10 g IgG. (3)

CONTRAINDICATIONS

- History of anaphylactic or severe systemic hypersensitivity reactions to Immune Globulin (Human). (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 severe hypersensitivity reactions and anaphylactic reactions. (5.1)
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of acute renal failure. (5.2)
- Thrombotic and thromboembolic events have been reported with GAMMAGARD S/D. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk for hyperviscosity. (5.3)
- Aseptic Meningitis Syndrome (AMS) has been reported with GAMMAGARD S/D. (5.4)
- Hemolytic anemia can develop. Monitor patients for clinical signs and symptoms of hemolysis and hemolytic anemia. (5.5)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury, TRALI). (5.6)
- Product is made from human plasma and may contain infectious agents, e.g., viruses and theoretically, Creutzfeldt-Jacob disease agent. (5.7)
- Hyperproteinemia, increased serum viscosity and hyponatremia may occur. (5.8)

ADVERSE REACTIONS

- The most common adverse reactions observed in ≥ 5% of patients during the clinical trials were headache, nausea, chills, fatigue, pyrexia, upper abdominal pain, diarrhea, back pain, infusion site pain, hyperhidrosis and flushing. (6.1)
- Severe adverse reactions reported postmarketing include renal failure, thrombotic events (myocardial infarction, cerebrovascular accidents, and pulmonary embolism), anaphylactic shock, aseptic meningitis and hemolysis. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly indicated. (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 GAMMAGARD S/D at the minimum infusion rate practicable. (8.5)

See Section 17 for PATIENT COUNSELING INFORMATION.

Revised: December 2011

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1 FULL PRESCRIBING INFORMATION

WARNING: RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Intravenous use of human immune globulin (IGIV) products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or those receiving known nephrotoxic drugs. GAMMAGARD S/D does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMMAGARD S/D at the minimum concentration available and the minimum rate of infusion practicable.**

2 1 INDICATIONS AND USAGE

3 1.1 Primary Immunodeficiency (PI)

4 GAMMAGARD S/D is indicated for the treatment of primary immunodeficiency (PI)
5 associated with defects in humoral immunity, in adults and children two years and older.
6 This includes, but is not limited to, congenital agammaglobulinemia, common variable
7 immunodeficiency, Wiskott-Aldrich syndrome, and severe combined
8 immunodeficiencies.^{1,2,3}

9 1.2 B-cell Chronic Lymphocytic Leukemia (CLL)

10 GAMMAGARD S/D is indicated for prevention of bacterial infections in patients with
11 hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell
12 Chronic Lymphocytic Leukemia (CLL).⁴

13 1.3 Idiopathic Thrombocytopenic Purpura (ITP)

14 GAMMAGARD S/D is indicated for the treatment of adult Chronic Idiopathic
15 Thrombocytopenic Purpura to increase platelet count and to prevent and/or to control
16 bleeding.

17 1.4 Kawasaki Syndrome

18 GAMMAGARD S/D is indicated for the prevention of coronary artery aneurysms
19 associated with Kawasaki syndrome in pediatric patients.⁵

20 **2 DOSAGE AND ADMINISTRATION**

21 **For Intravenous Use Only**

22 **2.1 Preparation and Handling**

23 **Instruction for Reconstitution:**

24 Allow GAMMAGARD S/D and diluent to reach room temperature before reconstitution
25 and administration if refrigerated.

26 **Reconstitution:**

27 1. Remove caps from concentrate and diluent bottles to expose central portion of rubber
28 stoppers and cleanse stoppers with germicidal solution.

29 **To make a 5% solution:** Use the full volume of the diluent bottle

30 **To make a 10% solution:** Remove half of the volume of the diluent bottle

31 Table 1 indicates the volume of diluent that should be **removed from the vial** before
32 attaching the transfer device to produce a 10% concentration. Using aseptic
33 technique, withdraw the unnecessary volume of diluent using a sterile hypodermic
34 syringe and needle. Discard the filled syringe into a suitable puncture proof container
35 (Sharps Container).

36 **Table 1.**

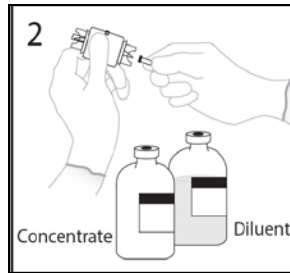
37 **Required Diluent Volume to be Removed**

38

	5 g bottle	10 g bottle
39 Concentration		
40		
41		
42 5%	Do not remove any diluent for reconstitution of 5% Solution	
43 10%	48 mL	96 mL
44		

44

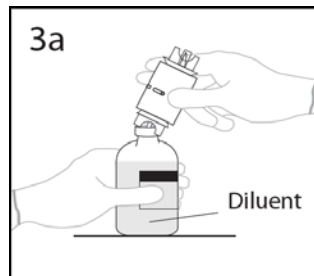
45 2. Remove spike cap from one end of the transfer device. Do not touch spike.



46

47 3a. Place the diluent bottle on a flat surface and hold the bottle to prevent slipping. Use
48 exposed end of transfer device to spike diluent bottle perpendicularly through center
49 of the stopper

50 **CAUTION: Failure to insert spike into center of the stopper may result in**
51 **dislodging of the stopper.**

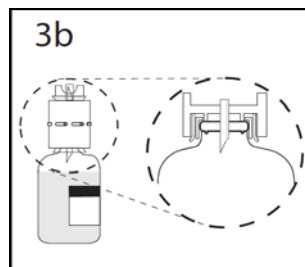


52

53 3b. Ensure that the collar collapses fully into the device by pushing down on the transfer
54 device firmly.

55 While holding onto transfer device, remove remaining spike cover from the other end of
56 the transfer device. Do not touch spike.

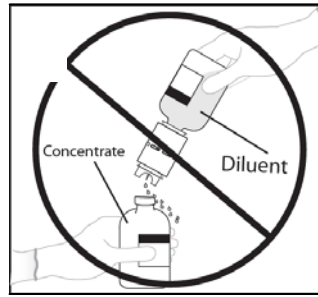
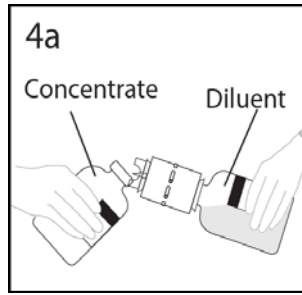
57



58

59 4. Hold diluent bottle with attached transfer device at an angle to the concentrate bottle
60 to prevent spilling the diluent.

61 **Note: Do not hold diluent bottle upside down, for this can lead to diluent spillage.**



62

63 5a. Spike concentrate bottle through center of the stopper while **quickly inverting the**
64 **diluent bottle** to minimize spilling out diluent.

65 **CAUTION: Failure to insert the spike into the center of the stopper may result in**
66 **dislodging of the stopper and loss of vacuum.**

67

68

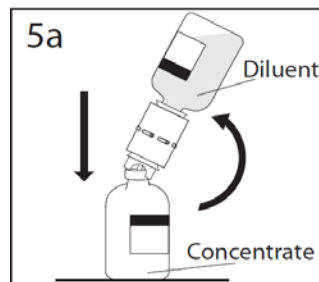
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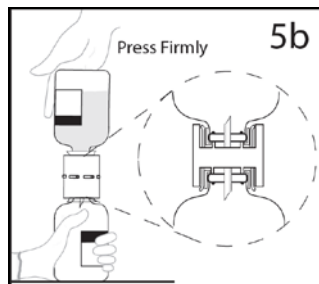
72

73



74 5b. Ensure that the collar collapses fully into the device by pushing down on the diluent
75 bottle firmly.

76

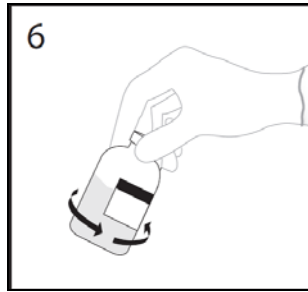


77

78 6. After transfer of diluent is complete, remove transfer device and empty diluent bottle.
79 Immediately swirl the concentrate bottle gently to thoroughly mix contents. Repeat
80 gentle rotation as long as undissolved product is observed.

81 **CAUTION: Do not shake. Avoid foaming.**

82 Discard transfer device after single use per local guidelines.



83

84 Reconstituted GAMMAGARD S/D is a clear to slightly opalescent and colorless to pale
85 yellow solution. Visually inspect parenteral drug product for particulate matter and
86 discoloration prior to administration. Do not use if particulate matter and/or discoloration
87 is observed.

88 Follow directions for use which accompany the administration set provided. If another
89 administration set is used, ensure that the set contains a similar filter.

90 Begin administration as soon as possible within 2 hours if reconstitution is performed
91 aseptically outside of a sterile laminar air flow hood.

92 Administer within 24 hours if reconstitution is performed aseptically inside of a sterile
93 laminar flow hood and stored in the original glass container or pooled into ViaFlex bags
94 under constant refrigeration (2 °C to 8 °C). Record the date and time of
95 reconstitution/pooling. Discard partially used vials.

96 **2.2 Dose**

97 **Primary Immunodeficiency (PI)**

98 The recommended dose of GAMMAGARD S/D for patients with PI is 300-600 mg/kg
99 infused at 3 to 4 week intervals.^{1,2,6} Adjust dose according to the clinical response, the
100 frequency and dose of immunoglobulin may vary from patient to patient. No randomized
101 controlled clinical trials are available to determine an optimum target trough serum IgG
102 level.

103 **B-cell Chronic Lymphocytic Leukemia (CLL)**

104 The recommended dose of GAMMAGARD S/D for patients with
105 hypogammaglobulinemia and/or recurrent bacterial infections due to B-cell CLL is 400
106 mg/kg body weight infused at every 3 to 4 week intervals.⁴

107 **Idiopathic Thrombocytopenic Purpura (ITP)**

108 The recommended dose of GAMMAGARD S/D for patients with chronic ITP is 1 g/kg.
109 The need for additional doses can be determined by clinical response and platelet count.
110 Up to three separate doses may be given on alternate days if required.

111 **Kawasaki Syndrome**

112 The recommended dose of GAMMAGARD S/D for patients with Kawasaki Syndrome is
113 either a single 1 g/kg dose or a dose of 400 mg/kg for four consecutive days beginning
114 within seven days of the onset of fever, administered concomitantly with appropriate
115 aspirin therapy (80-100 mg/kg/day in four divided doses) is recommended.^{5,7,8}

116 **2.3 Administration**

117 Administer GAMMAGARD S/D as soon after reconstitution as possible and administer
118 the reconstituted material at room temperature.

119 The recommended initial 5% solution infusion rate is 0.5 mL/kg/Hr. The infusion rate
120 may be gradually increased to a maximum rate of 4 mL/kg/Hr as tolerated for patients
121 with no history of adverse reactions to IGIV and no significant risk factors for renal
122 dysfunction or thrombotic complications. Patients who tolerate the 5% concentration at 4
123 mL/kg/Hr can be infused with the 10% concentration starting at 0.5 mL/kg/Hr. The rate
124 can be increased gradually up to a maximum of 8 mL/kg/Hr if no adverse effects occur.⁹

125 Monitor patient vital signs throughout the infusion. Certain adverse reactions such as
126 headaches, flushing and changes in pulse rate and blood pressure may be related to the
127 rate of infusion. Slow or stop the infusion if adverse reactions occur. If symptoms
128 subside promptly, the infusion may be resumed at a lower rate that does not result in
129 reoccurrence of the symptoms.

130 It is recommended that, if possible, the antecubital veins are used, especially for 10%
131 solutions, to reduce the likelihood of discomfort at the infusion site (see *ADVERSE*
132 *REACTIONS* [5.3]).

133 Adverse reactions may occur more frequently in patients who receive human IGIV for
134 the first time, upon switching brands, or if there has been a long hiatus since the previous
135 infusion. In such cases, start at a lower rate and gradually increase as tolerated.

136 There are no prospective studies demonstrating that any concentration or rate of infusion
137 is completely safe. However, the risk may be decreased at lower rates of infusion.¹⁰ For
138 patients who are judged to be at risk of renal dysfunction or thrombotic complications,

139 administered GAMMAGARD S/D at the minimum allowable rate of infusion and
140 gradually titrated up to a more conservative maximal rate of less than 3.3 mg/kg/min
141 (< 2mL/kg/hr of a 10% or < 4mL/kg/hr of a 5% solution) (see *WARNINGS AND*
142 *PRECAUTIONS [5.3]*).

143 **3 DOSAGE FORMS AND STRENGTHS**

144 GAMMAGARD S/D with an IgA concentration of less than 1 µg/mL is a freeze-dried
145 preparation containing 5 g or 10 g IgG.

146 **4 CONTRAINDICATIONS**

147 GAMMAGARD S/D is contraindicated in patients who have had a history of
148 anaphylactic or severe systemic hypersensitivity reactions to the administration of
149 GAMMAGARD S/D with <1µg/mL IgA in a 5 % solution.

150 **5 WARNINGS AND PRECAUTIONS**

151 **5.1 Hypersensitivity**

152 Severe hypersensitivity reactions and anaphylactic reactions with a fall in blood pressure
153 have occurred in patients receiving GAMMAGARD S/D, including patients who
154 tolerated previous treatments with GAMMAGARD S/D, even though it contains low
155 levels of IgA. If hypersensitivity reaction develops, discontinue GAMMAGARD S/D
156 infusion immediately and institute appropriate treatment.

157 This product has an IgA concentration less than 1 µg/mL. Preparations depleted of IgA
158 (0.4 to 2.9 µg/mL) were shown to be better tolerated by a limited number of patients who
159 reacted to IGIV preparations with higher IgA concentrations. However, the
160 concentration of IgA that will not provoke a reaction is not known, and therefore **all**
161 **IGIV preparations carry the risk of inducing an anaphylactic reaction to IgA.** In
162 such instances, a risk of anaphylaxis may exist despite the fact that GAMMAGARD S/D,
163 IgA < 1 µg/mL, contains trace amounts of IgA.

164 **5.2 Renal Dysfunction/Failure**

165 Acute renal failure has been reported in association with GAMMAGARD S/D. Acute
166 renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic
167 nephrosis and death have been reported in patients receiving IGIV, particularly those
168 products containing sucrose.¹⁰ GAMMAGARD S/D does not contain sucrose.

169 Assure that patients are not volume depleted prior to the initiation of the infusion of
170 GAMMAGARD S/D. In patients who are at risk of developing renal dysfunction,

171 because of pre-existing renal insufficiency or predisposition to acute renal failure (such as
172 diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or
173 patients receiving known nephrotoxic drugs, etc.), administer GAMMAGARD S/D at an
174 infusion rate less than 4 mL/kg/Hr (< 3.3 mg IG/kg/min) for a 5% solution or at a rate
175 less than 2 mL/kg/Hr (< 3.3 mg IG/kg/min) for a 10 % solution (see *DOSAGE AND*
176 *ADMINISTRATION* [2]).

177 Periodic monitoring of renal function and urine output is particularly important in
178 patients judged to be at increased risk for developing acute renal failure. Assess renal
179 function, including measurement of blood urea nitrogen (BUN) and serum creatinine,
180 before the initial infusion of GAMMAGARD S/D and again at appropriate intervals
181 thereafter. If renal function deteriorates, consider discontinuation of GAMMAGARD
182 S/D.

183 **5.3 Thromboembolic Events**

184 Thromboembolic events, including myocardial infarction, cerebral vascular accident,
185 deep vein thrombosis, and pulmonary embolism, have been reported in association with
186 IGIV therapy, including GAMMAGARD S/D (see *ADVERSE REACTIONS* [6]).^{10,11}
187 Patients at risk for thromboembolic events include those with a history of atherosclerosis,
188 multiple cardiovascular risk factors, advanced age, impaired cardiac output, known or
189 suspected hyperviscosity, hypercoagulable disorders, prolonged periods of
190 immobilization, obesity, diabetes mellitus, acquired or inherited thrombophilic disorder, a
191 history of vascular diseases, and a history of a previous thrombotic or thromboembolic
192 event (see *WARNING AND PRECAUTIONS* [5.9]).

193 Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity,
194 including those with cryoglobulins, fasting chylomicronemia/markedly high
195 triacylglycerols (triglycerides), or monoclonal gammopathies (see *WARNING AND*
196 *PRECAUTIONS* [5.9]). For patients judged to be at risk of developing thrombotic
197 events, administer GAMMAGARD S/D at the minimum rate of infusion practicable (see
198 *DOSAGE AND ADMINISTRATION* [2.3]).

199 **5.4 Aseptic Meningitis Syndrome (AMS)**

200 AMS has been reported to occur in association with IGIV therapy, including
201 GAMMAGARD S/D. Discontinuation of IGIV treatment has resulted in remission of
202 AMS within several days without sequelae. The syndrome of AMS usually begins within
203 several hours to two days following IGIV treatment.

204 AMS is characterized by the following symptoms and signs: severe headache, nuchal
205 rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting.
206 Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several
207 thousand cells per cubic mm, predominantly from the granulocytic series, and with
208 elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct
209 a thorough neurological examination on patients exhibiting such symptoms and signs,
210 including CSF studies, to rule out other causes of meningitis.

211 AMS may occur more frequently with high dose (2 g/kg) IGIV treatment.¹²

212 **5.5 Hemolysis**

213 Hemolytic anemia can develop subsequent to IGIV therapy, including GAMMAGARD
214 S/D¹³ (see *ADVERSE REACTIONS* [6.2]). GAMMAGARD S/D contains blood group
215 antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells
216 (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely,
217 hemolysis.⁹ Acute intravascular hemolysis has been reported, and delayed hemolytic
218 anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration (see
219 *ADVERSE REACTIONS* [6.2]).

220 Monitor patients for clinical signs and symptoms of hemolysis. If signs and/or symptoms
221 of hemolysis are present after GAMMAGARD S/D infusion, perform appropriate
222 confirmatory laboratory testing.

223 **5.6 Transfusion-Related Acute Lung Injury (TRALI)**

224 Non-cardiogenic pulmonary edema (TRALI) has been reported in patients following the
225 administration of gammaglobulin products, including GAMMAGARD S/D therapy (see
226 *ADVERSE REACTIONS* [6.2]). TRALI is characterized by severe respiratory distress,
227 pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms
228 typically occur within 1 to 6 hours after treatment.

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

233 **5.7 Transmissible Infectious Agents**

234 Because GAMMAGARD S/D is made from human plasma, it may carry a risk of
235 transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob
236 disease (CJD) agent. This also applies to unknown or emerging viruses and other

237 pathogens. No cases of transmission of viral diseases or CJD have ever been identified
238 for GAMMAGARD S/D.

239 All infections thought by a physician possibly to have been transmitted by this product
240 should be reported by the physician or other healthcare provider to Baxter Healthcare
241 Corporation at 1-800-423-2862 (in the U.S.) or FDA at 1-800-FDA-1088 or
242 www.fda.gov/medwatch. The physician should discuss the risks and benefits of this
243 product with the patient.

244 **5.8 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia**

245 Hyperproteinemia and increased serum viscosity may occur in patients receiving
246 GAMMAGARD S/D.

247 The amount of sodium in the product may add materially to the recommended daily
248 allowance of dietary sodium for patients on a low sodium diet. In these patients,
249 calculate the amount of sodium from the product and use it when determining dietary
250 sodium intake. GAMMAGARD S/D contains approximately 0.85% NaCl or
251 approximately 3340 mg sodium/liter at a 5% concentration. A 70 kg patient receiving
252 1g/kg (1.4 L) of the product would receive 4676 mg of sodium.

253 **5.9 Monitoring: Laboratory Tests**

- 254 • Periodic monitoring renal function and urine output should be considered in patients
255 judged to be at increased risk of developing acute renal failure. Assess renal function,
256 including measurement of BUN and serum creatinine, before the initial infusion of
257 GAMMAGARD S/D and at appropriate intervals thereafter.¹⁰

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

- 262 • If signs and/or symptoms of hemolysis are present after an infusion of
263 GAMMAGARD S/D, perform appropriate laboratory testing for confirmation.

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

266 **5.10 Interference with Laboratory Tests**

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

271 **5.11 Rubber Latex Sensitivity**

272 Certain components used in the packaging of this product contain natural rubber latex.
273 Use GAMMAGARD S/D cautiously in patients with sensitivity to rubber latex.

274 **6 ADVERSE REACTIONS**

275 The most common adverse reactions reported in $\geq 5\%$ of clinical trial subjects occurring
276 during or within 48 hours of an infusion were headache, nausea, chills, asthenia (fatigue),
277 pyrexia, upper abdominal pain, diarrhea, back pain, hyperhidrosis, and flushing.

278

279 There were no serious adverse events that were attributed to GAMMAGARD S/D in the
280 clinical trials.

281

282 In postmarketing surveillance, serious adverse reactions reported with GAMMAGARD
283 S/D were anaphylaxis, acute renal failure, myocardial infarction, cerebral vascular
284 accident, transient ischemic attack, deep vein thrombosis, pulmonary embolism; aseptic
285 meningitis, acute hemolysis, and TRALI.

286 **6.1 Clinical Trials Experience**

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

290 **Primary Immunodeficiency Diseases (PI)**

291 In 17 patients receiving GAMMAGARD (5% solution) for 56 to 77 months, 12 (71%)
292 were adults, and 5 (29%) were children (16 years or younger).³ Adverse reactions are
293 those adverse events (AEs) that were deemed by the investigators as causally related to
294 the infusion of GAMMAGARD. Twenty-one adverse reactions occurred in 6 of the 17
295 subjects of the total 341 infusions (6%). There was one death in a woman from a cerebral
296 vascular hemorrhage secondary to thrombocytopenia and was considered unrelated to
297 study product. Of the 5 subjects who received an infusion with 600 mg/kg at a rate of 0.3
298 g/kg/hr, two subjects experienced adverse reactions, with an adverse reaction rate of
299 40%.

300

301 The adverse reactions occurred in $\geq 5\%$ of subjects during or within 48 hours of infusion
302 are listed in Table 2.

303

Table 2.
Adverse Reactions that Occurred in $\geq 5\%$ of Subjects
During or within 48 Hours of Infusion

Adverse Reaction	By Subjects (%)	By Infusions (%)
	Total number of subjects: 17	Total number of infusions: 341
Headache	3 (17.6)	3 (0.9)
Chills	2 (11.8)	6 (1.8)
Backache	2 (11.8)	2 (0.6)
Emesis	1 (5.9)	1 (0.3)
Flushing	1 (5.9)	1 (0.3)
Fatigue	1 (5.9)	4 (1.2)
Dizziness	1 (5.9)	1 (0.3)

304

305 In a double blind, cross over study, 36 subjects with PI were treated for 6 months with
306 GAMMAGARD S/D and 6 months with Gamimune N. One hundred AEs were
307 considered to be possibly or probably related to treatment with GAMMAGARD S/D. Of
308 these, 72 were mild, 24 were moderate, and 4 were severe. The numbers and percentages
309 of AEs were similar for GAMMAGARD S/D and Gamimune-N. There were no deaths
310 during the study. The adverse reactions occurred during GAMMAGARD S/D treatment
311 in $\geq 5\%$ of subjects in the study are shown in Table 3.

Table 3.
Adverse Reactions that Occurred in $\geq 5\%$ of Subjects Treated with GAMMAGARD S/D

Adverse Reactions	By Subject (%)	By Infusion (%)
	Total number of subjects: 36	Total number of infusions: 211
Headache	11 (30.56)	23 (10.9)
Nausea	8 (22.22)	14 (6.64)
Chills	7 (19.44)	14 (6.64)
Fatigue	4 (11.11)	11 (5.21)
Pyrexia	4 (11.11)	6 (2.84)
Upper Abdominal Pain	3 (8.33)	3 (1.42)
Diarrhea	3 (8.33)	3 (1.42)
Back Pain	3 (8.33)	4 (1.90)

Table 3.
Adverse Reactions that Occurred in $\geq 5\%$ of Subjects Treated with GAMMAGARD S/D

Adverse Reactions	By Subject (%) Total number of subjects: 36	By Infusion (%) Total number of infusions: 211
Infusion Site Pain	2 (5.56)	3 (1.42)
Hyperhidrosis	2 (5.56)	4 (1.90)
Flushing	2 (5.56)	2 (0.95)

312

313 In 10 subjects who participated in a PK cross over study of GAMMAGARD and
 314 GAMMAGARD S/D, 5 adverse reactions were reported to be associated with the total 28
 315 infusions (17.5%). Three of the adverse reactions AEs were associated with 10
 316 GAMMAGARD infusions and 2 were associated with 18 GAMMAGARD S/D infusions.
 317 Two subjects withdrew from the study. One subject developed a recurrence of chronic
 318 cellulitis and was hospitalized and the event was not considered to be related to study
 319 drug. The other subject withdrew due to the experience of moderate severe adverse
 320 reactions such as chills, anxiety and increased temperature after infusion of
 321 GAMMAGARD.

322

323 Adverse reactions occurred in the PK study and in the safety study are shown in Table 4.

324

Table 4.
Adverse Reactions that occurred during or within 48 hours of an Infusion of GAMMAGARD S/D

Event	By Infusion (%) Total number: 394
Headache	20 (5.1)
Chills	11 (2.7)
Elevated Temperature	7 (1.8)
Nausea	6 (1.5)
Emesis	5 (1.3)
Hypertension	4 (1.0)
Fatigue	4 (1.0)
Flushing	4 (1.0)
Leg Cramps	3 (0.8)
Flu-Like Symptoms	2 (0.5)
Exanthema	2 (0.5)
Loss of Appetite	2 (0.5)

Table 4.
Adverse Reactions that occurred during or within 48 hours of an Infusion of
GAMMAGARD S/D

Event	By Infusion (%) Total number: 394
Anxiety	1 (0.25)
Backache	1 (0.25)
Urticaria	1 (0.25)

325

326 The tolerability and viral safety of GAMMAGARD S/D were evaluated in a study of 38
 327 subjects, who were treated with GAMMAGARD S/D for an average of 7.7 months.
 328 Adverse reactions were reported from 20 of the 38 subjects (52.6%) in 50 of the total 394
 329 infusions (12.7%) during or within 48 hours of an infusion. Twenty-four (48%) of the
 330 adverse reactions occurred in 3 subjects and 26 occurred in the other 35 subjects in 350
 331 infusions. No subject withdrew during the study. Five subjects had a transient borderline
 332 elevation in liver enzyme (AST). No subject developed a positive serologic response to
 333 Hepatitis C or HIV. There were no other significant laboratory abnormalities.

334 The adverse experiences of GAMMAGARD S/D reconstituted as a 10% solution and the
 335 maximal tolerated infusion rate were examined in a post-marketing study of 27 subjects.
 336 Local pain and/or irritation occurred in 42 of the total 276 infusions (15.2%). Ninety
 337 percent of the reactions occurred when the patients received the 10% solution compared
 338 to the 5% control. These local reactions tended to be more common following hand vein
 339 infusions and their incidence may be reduced by infusions via the antecubital vein.
 340 Application of a warm compress to the infusion site alleviated local symptoms.
 341 Twenty-six subjects were able to achieve the maximal infusion rate of 8 mL/kg/hr with
 342 the GAMMAGARD S/D reconstituted to a 10% solution.

343 **B-cell Chronic Lymphocytic Leukemia (CLL)**

344 In the study of 81 patients with B-cell CLL, the incidence of adverse reactions following
 345 GAMMAGARD infusions was approximately 1.3% compare to the rate of the placebo
 346 (normal saline) group which was 0.6%.³ There were 23 adverse reactions associated with
 347 the 1235 infusions in the study. Sixteen of the adverse reactions occurred in the
 348 GAMMAGARD group (1.6%) and 7 in the control group (0.6%). The most common
 349 reactions were fever and chills. Sleepiness was noted during 4 infusions. One subject
 350 had a myocardial infarction which was considered to be unrelated to the
 351 GAMMAGARD. Twenty-four of the subjects did not complete all 17 infusions. Three

352 subjects in each group died during the study, five of whom were due to infection. The
353 other 18 subjects withdrew for reasons unrelated to the treatment.

354 **Idiopathic Thrombocytopenic Purpura (ITP)**

355 During the clinical study of GAMMAGARD for the treatment of ITP, headache which
356 occurred in 12 of 16 patients (75%) and was the only adverse reaction reported. Of these
357 12 patients, 11 had chronic ITP (9 adults, 2 children), and one child had acute ITP. Oral
358 antihistamines and analgesics alleviated the symptoms and were used as pretreatment for
359 those patients requiring additional IGIV therapy.

360 **Kawasaki Syndrome**

361 In a study of 51 patients with Kawasaki Syndrome, no hypersensitivity-type reactions
362 (urticaria, bronchospasm or generalized anaphylaxis) were reported in patients receiving
363 either a single 1g/kg dose or 400 mg/kg of GAMMAGARD for four consecutive days.
364 Adverse reactions, including chills, flushing, cramping, headache, hypotension, nausea,
365 rash and wheezing, were reported with both dose regimens. These adverse reactions
366 occurred in 7 of the 51 (13.7%) patients associated with 7 of the total 129 (5.4%)
367 infusions. Of the 25 patients who received a single 1 g/kg dose, 4 patients (16%)
368 experienced adverse reactions. Of the 26 patients who received 400 mg/kg/day over 4
369 days, 3 (11.5%) experienced adverse reactions.

370 **6.2 Postmarketing Experience**

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

374 The following adverse reactions have been reported during postmarketing use of
375 GAMMAGARD S/D (Table 5).

376

Table 5.
Adverse Reactions from Postmarketing Experience

Infections and Infestations	Aseptic Meningitis Syndrome
Blood and Lymphatic System Disorders	Anemia, Hemolysis, Lymphadenopathy, Thrombocytopenia
Immune System Disorders	Anaphylactic Shock, Anaphylactic/Anaphylactoid Reaction, Hypersensitivity

Psychiatric Disorders	Restlessness
Nervous System Disorders	Cerebrovascular Accident, Transient Ischemic Attack, Convulsion, Dizziness, Migraine, Paresthesia, Syncope, Tremor
Eye Disorders	Retinal Vein Thrombosis, Eye Pain, Photophobia, Visual Disturbance
Cardiac Disorders	Myocardial Infarction, Cyanosis, Tachycardia, Bradycardia
Vascular Disorders	Vena Cava Thrombosis, Arterial Thrombosis, Deep Vein Thrombosis, Hypotension, Hypertension, Pallor, Thrombophlebitis
Respiratory, Thoracic And Mediastinal Disorders	Pulmonary Embolism, Pulmonary Edema, Bronchospasm, Wheezing, Cough, Hyperventilation, Hypoxia, Throat Tightness
Gastrointestinal Disorders	Abdominal Pain, Dyspepsia
Hepatobiliary Disorders	Hepatitis*
Skin and Subcutaneous Tissue Disorders	Angioedema, Dermatitis, Erythema, Rash
Musculoskeletal And Connective Tissue Disorders	Arthralgia, Myalgia
Renal and Urinary Disorders	Renal Failure
General Disorders And Administration-Site Conditions	Infusion Site Reaction, Asthenia, Edema, Rigors
Investigations	Positive Direct Coombs Test

377 *non-infectious hepatitis

378

379 In addition to the events listed above which were observed for GAMMAGARD S/D, the
380 following events have been identified for IGIV products in general:

381

Renal	Osmotic nephropathy
Respiratory	Cyanosis, apnea, Acute Respiratory Distress Syndrome (ARDS)
Integumentary	Bullous dermatitis, epidermolysis, erythema multiforme, Stevens-Johnson Syndrome
Cardiovascular	Cardiac arrest, vascular collapse
Neurological	Coma, loss of consciousness
Hematologic	Pancytopenia
Gastrointestinal	Hepatic dysfunction

382

383 **7 DRUG INTERACTIONS**

384 Admixtures of GAMMAGARD S/D with other drugs and intravenous solutions have not
385 been evaluated. It is recommended that GAMMAGARD S/D be administered separately
386 from other drugs or medications which the patient may be receiving. Do not mix the
387 product with human IGIV products from other manufacturers.

388 Passive transfer of antibodies may transiently impair the immune responses to live
389 attenuated vaccines, such as measles, mumps, rubella, and varicella. Inform the
390 immunizing physician of recent therapy with GAMMAGARD S/D so that appropriate
391 precautions can be taken.

392 **8 USE IN SPECIFIC POPULATIONS**

393 **8.1 Pregnancy**

394 Pregnancy Category C. Animal reproduction studies have not been conducted with
395 GAMMAGARD S/D. It is also not known whether GAMMAGARD S/D can cause fetal
396 harm when administered to a pregnant woman or can affect reproduction capacity.
397 Immunoglobulins cross the placenta from maternal circulation increasingly after 30
398 weeks of gestation. GAMMAGARD S/D should be given to a pregnant woman only if
399 clearly needed.

400 **8.3 Nursing Mothers**

401 GAMMAGARD S/D has not been evaluated in nursing mothers. GAMMAGARD S/D
402 should be given to nursing women only if clearly indicated.

403 **8.4 Pediatric Use**

404 Clinical studies of GAMMAGARD S/D for the treatment of PI did not include sufficient
405 numbers of subjects aged 16 and younger to determine whether they respond differently
406 from adults. Five children under the age of 16 were treated in the initial trial of
407 GAMMAGARD. The mean age of subjects in the phase 4 study was 17.8 years (range
408 1.7 to 55.3).

409 Efficacy and safety of GAMMAGARD S/D in pediatric patients with chronic ITP has not
410 been established.

411 Efficacy and safety of GAMMAGARD S/D in pediatric patients with Kawasaki disease
412 has been established. Virtually all patients treated for Kawasaki's disease were less than
413 5 years of age, with approximately 20% under the age of 1 year.

414 **8.5 Geriatric Use**

415 Limited information is available for the geriatric use of GAMMAGARD S/D. Clinical
416 studies of GAMMAGARD S/D for the treatment of PI did not include sufficient numbers
417 of subjects aged 65 and over to determine whether they respond differently from younger
418 subjects. Use caution when administering GAMMAGARD S/D to patients age 65 and
419 over who are judged to be at increased risk for developing thromboembolic events or

420 renal insufficiency. Do not exceed recommended dose, and administer GAMMAGARD
421 S/D at the minimum infusion rate practicable (*see BOXED WARNING, WARNINGS AND*
422 *PRECAUTIONS [5.2, 5.4] and DOSAGE AND ADMINISTRATION [2.2]*).

423 **10 OVERDOSAGE**

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

427 **11 DESCRIPTION**

428 GAMMAGARD S/D Immune Globulin Intravenous (Human) [IGIV], IgA less than 1
429 µg/mL in a 5% Solution (IgA < 1 µg/mL), is GAMMAGARD S/D, selected to have an
430 IgA concentration of less than 1 µg/mL of IgA in a 5% solution. GAMMAGARD S/D is
431 a solvent/detergent treated, sterile, freeze-dried preparation of purified immunoglobulin
432 G (IgG) derived from large pools of human plasma. IgG preparations are purified from
433 plasma pools using a modified Cohn-Oncley cold ethanol fractionation process, as well
434 as cation and anion exchange chromatography. The distribution of IgG subclasses
435 present in this product is similar to that in normal plasma. The Fc portion is maintained
436 intact. When reconstituted with the total volume of diluent (Sterile Water for Injection,
437 USP) supplied, reconstituted to 5% solution, the product contains approximately 50
438 mg/mL of protein, of which at least 90% is gamma globulin. GAMMAGARD S/D IgA
439 less than 1 µg/mL contains trace amounts of IgA (< 1 µg/mL in a 5% solution) and IgM
440 is present in trace amounts. GAMMAGARD S/D contains all of the IgG antibody
441 activities which are present in the donor population.

442 The product, after reconstituted to 5% solution, contains a physiological concentration of
443 sodium chloride (approximately 8.5 mg/mL) and has a pH of 6.8 ± 0.4 . Stabilizing agents
444 and additional components are present in the following maximum amounts for a 5%
445 solution: 3 mg/mL Albumin (Human), 22.5 mg/mL glycine, 20 mg/mL glucose, 2 mg/mL
446 polyethylene glycol (PEG), 1 µg/mL tri-n-butyl phosphate, 1 µg/mL octoxynol 9, and
447 100 µg/mL polysorbate 80. GAMMAGARD S/D contains no preservative.

448 To prepare a 10% (100 mg/mL) solution for infusion, add half the volume of diluent, as
449 described in *DOSAGE AND ADMINISTRATION [2.1]*. The content of the stabilizing
450 agents and other components, including IgA, for the 10% solution will be doubled
451 compared to the 5% solution.

452 Screening against potentially infectious agents in the product begins with the donor
 453 selection process and continues throughout plasma collection and plasma preparation.
 454 Each individual plasma donation used in the manufacture of GAMMAGARD S/D is
 455 collected only at FDA approved blood establishments and is tested by FDA licensed
 456 serological tests for Hepatitis B Surface Antigen (HBsAg), and for antibodies to Human
 457 Immunodeficiency Virus (HIV-1/HIV-2) and Hepatitis C Virus (HCV) in accordance
 458 with U.S. regulatory requirements. As an additional safety measure, mini-pools of the
 459 plasma are tested for the presence of HIV-1 and HCV by FDA licensed Nucleic Acid
 460 Testing (NAT) and found negative.

461 The manufacturing process includes treatment with an organic solvent/detergent mixture,
 462 composed of tri-n-butyl phosphate, octoxynol 9 and polysorbate 80. The
 463 GAMMAGARD S/D manufacturing process provides a significant viral reduction in *in*
 464 *vitro* viral reduction studies. These studies, summarized in Table 6 demonstrate virus
 465 clearance during GAMMAGARD S/D manufacturing infectious using human
 466 immunodeficiency virus, Type 1 (HIV-1); as the relevant virus for HIV-1 and HIV-2,
 467 bovine viral diarrhea virus (BVD); a model virus for enveloped RNA viruses such as
 468 hepatitis C virus (HCV), pseudorabies virus (PRV), a generic model virus for enveloped
 469 DNA viruses such as hepatitis B virus (HBV); hepatitis A virus (HAV); and mice minute
 470 virus (MMV), a model for small non-enveloped DNA viruses such as human parvovirus
 471 B19 (B19V).³ These reductions are achieved through a combination of process chemistry,
 472 partitioning and/or inactivation during cold ethanol fractionation and the
 473 solvent/detergent treatment.

Table 6.
***In Vitro* Virus Clearance During GAMMAGARD S/D Manufacturing**

Process Step Evaluated	Virus Clearance (log ₁₀)				
	Enveloped Viruses			Non- Enveloped Viruses	
	BVD	HIV-1	PRV	HAV	MMV
Step 1: Processing of Cryo-Poor Plasma to Fraction I+II+III Precipitate	0.6*	5.6	1.0*	0.5*	NT
Step 2 - 3	2.6*	> 5.7	> 5.2	> 5.2	> 5.3
Step 4: Solvent/Detergent Treatment	>4.9	>3.7	>4.1	NA	NA
Cumulative Reduction of Virus (log ₁₀)	> 7.5	>15.0	> 9.3	> 5.2	> 5.3

474 * These values are not included in the computation of the cumulative reduction of virus since the
 475 virus clearance is within the variability limit of the assay (≤1.0).

476 NA Not Applicable. Solvent/detergent treatment does not affect non- enveloped viruses.

477 NT Not Tested.

478

479 **12 CLINICAL PHARMACOLOGY**

480 **12.1 Mechanism of Action**

481 GAMMAGARD S/D, Immune Globulin Intravenous (Human), supplies a broad spectrum
482 of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral
483 agents. GAMMAGARD S/D also contains a spectrum of antibodies capable of reacting
484 with cells such as erythrocytes. The role of these antibodies and the mechanisms of
485 action of IgG in GAMMAGARD S/D have not been fully elucidated.

486

487 **12.3 Pharmacokinetics**

488 Following infusion, IGIV products show a biphasic decay curve. The initial (α) phase is
489 characterized by an immediate post-infusion peak in serum IgG and is followed by rapid
490 decay due to equilibration between the plasma and extravascular fluid compartments.

491 The second (β) phase is characterized by a slower and constant rate of decay. As a class,
492 IgG survives longer *in vivo* than other serum proteins. Peak levels of IgG reached within
493 30 minutes after an intravenous infusion of GAMMAGARD S/D. In previous studies,
494 where radio-labeled IgG was injected to subjects, the IgG half-life was 21 to 25 days in
495 healthy individuals or 17.7 to 37.6 days in immunodeficient patients. The half-life of IgG
496 can vary considerably from person to person, however. In particular, high serum
497 concentrations of IgG and hypermetabolism associated with fever and infection have
498 been seen to coincide with a shortened half-life of IgG.

499 The pharmacokinetics of GAMMAGARD S/D was evaluated in 15 subjects with PI, 10
500 of them were previously treated. In the previously treated subjects, the half-life of
501 GAMMAGARD S/D is approximately 37.7 ± 15 days compared to 34.1 ± 15.7 days for
502 GAMMAGARD. The half lives of the IgG subclasses were similar, ranging from $28.1 \pm$
503 11.2 days for IgG₄ to 42.3 ± 26.6 days for IgG₁. The half life of pneumococcal antibody
504 in these subjects was 41.4 ± 28.5 days. Pharmacokinetics did not differ between the
505 previously licensed IGIV and GAMMAGARD S/D formulations administered to the
506 previously treated patients. The pharmacokinetics of the GAMMAGARD S/D
507 formulation in previously untreated patients was not significantly different from the
508 results obtained in previously treated patients. The mean trough IgG concentration in the
509 previously untreated patients was 1186 ± 614 mg/dL and the peak post infusion
510 concentration was 1859 ± 872 mg/dL. The mean dose was 460 ± 194 mg/kg.

511 **14 CLINICAL STUDIES**

512 Clinical studies were conducted with lots of GAMMAGARD S/D containing
513 IgA < 2.2 µg/mL. No clinical studies have been specifically conducted using only lots
514 with IgA content of < 1 µg/mL.

515 **14.1 Primary Immunodeficiency (PI)**

516 Intravenous use of GAMMAGARD was initially evaluated in a study of 17 subjects with
517 PI. Twelve (71%) were adults and 5 (29%) were children 16 years or younger. Six
518 subjects received a series of 5 infusions at 4 week intervals, with the starting infusion
519 does of 100 mg/kg and then increased to 200, 300, and 400 mg/kg at rates of 0.1 to 0.2
520 mg/kg/hr. Five of the 6 subjects completed the 5 infusions and received another 6
521 monthly infusions with the following doses each administered twice: 200-400 mg/kg at
522 0.1 to 0.2 g/kg/hr, 400 mg/kg at 0.1 to 0.4 g/kg/hr and 400-800 mg/kg at 0.1 to 0.4 g/
523 kg/hr. Then all of the 17 subjects received GAMMAGARD at 400 mg/kg every 4 weeks
524 at a rate of 0.1 to 0.4 g/kg/hr. Fifteen of the subjects were treated for 56 to 77 weeks in
525 this study. There were no instances of pneumonia or other infections that would qualify
526 as an acute bacterial infection. The overall rate of non-serious bacterial infections was
527 4.4 per subject per year.

528 In a study of 15 subjects with PI to compare the pharmacokinetics of GAMMAGARD
529 S/D with GAMMAGARD, the subjects received a total of 28 infusions, half with
530 GAMMAGARD S/D and half with GAMMAGARD. Five systemic AEs reported during
531 the study and 2 occurred with GAMMAGARD S/D treatment. The study then enrolled
532 additional 38 patients with the diagnosis of PI (8), ITP (13), CVID (5), CLL (2) and other
533 miscellaneous diseases (3) to evaluate acute tolerability and the viral safety of
534 GAMMAGARD S/D.

535 The mean age of the subjects was 12 years old (range 0.7 to 57.2 years), 17 were males
536 and 21 were females. The subjects received an average of 10 (range 1-22) infusions over
537 an average of 7.7 months (range 0.3-11 months). A total of 394 infusions were
538 administered and all were completed. The average dose was 460 mg/kg (range: 188-1110
539 mg/kg). Incidence of infections was not recorded, though one subject had a recurrence of
540 chronic cellulitis. Adverse events and viral safety data were analyzed (see *ADVERSE*
541 *REACTIONS [6]*).

542 GAMMAGARD S/D was compared to Gamimune N in a double-blind, cross-over study
543 of 36 PI subjects. The mean age of subjects was 17.8 years (range 1.7 to 55.3 years), 22
544 subjects were male and 14 were female. Eighteen were naïve to IGIV therapy. Each

545 subject received 6 infusions of both products. There were a total of 211 GAMMAGARD
 546 S/D infusions and 210 Gamimune-N infusions. The dose of GAMMAGARD S/D
 547 administered was 300-600 mg/kg every 14 to 28 days for previously untreated subjects
 548 and the same as their pre-study dose and frequency for previously treated subjects. The
 549 infusions were started at 1.0 mL/kg/hr and increased every 30 minutes to a maximum of
 550 4.8 mL/kg/hr as tolerated. The mean dose administered for both products was 440
 551 mg/kg. The mean infusion rate was 2.35 ± 0.54 mL/kg/hr for GAMMAGARD S/D and
 552 2.33 ± 0.71 for Gamimune-N. Two subjects withdrew from the study. One subject was
 553 pregnant, and the other subject was withdrawn by his parents after the 8th infusion for
 554 reasons other than adverse events.

555 The use of GAMMAGARD S/D as a 10% solution and the maximal rate of infusion were
 556 evaluated in a postmarketing study of 27 subjects with PI. Subjects were treated with
 557 GAMMAGARD S/D at 400 mg/kg every 4 weeks for up to 12 months. Each subject
 558 received an initial infusion of GAMMAGARD S/D 5% solution at 4 mL/kg/hr.
 559 Subsequently, the concentration was increased to 7.5% and then to 10% as tolerated.
 560 Therefore, the infusion rate was gradually increased to a maximal 8 mL/kg/hr as
 561 tolerated. There were totally 276 infusions administered and 26 of the 27 subjects were
 562 able to reach the maximum infusion rate and concentration.

563 **14.2 B-cell Chronic Lymphocytic Leukemia (CLL)**

564 The efficacy of GAMMAGARD in reducing bacterial infections of B-cell CLL patients
 565 has been demonstrated in a double-blind, placebo controlled trial of 81 subjects.⁴
 566 Subjects were treated with 400 mg/kg/dose GAMMAGARD or saline solution every 3
 567 weeks for a total of 17 infusions. Forty-one subjects received GAMMAGARD and 40
 568 subjects received saline. The infection outcomes, including the frequency of
 569 bacterial/viral/fungal infections, mean time to first bacterial infections, were compared
 570 between the two groups and are shown in Table 7.

Table 7.
Infection Outcomes of 81 B-Cell CLL Subjects with GAMMAGARD or Placebo

Outcome	GAMMAGARD S/D	Placebo	Significance P value
Number of subjects	41	40	-
Frequency of bacterial infections	56.1%	105%	0.01
Mean time to first bacterial infection	> 365	192	0.026
Total Bacterial Infections	23	42	0.01
Total Viral Infections	40	37	0.65

Fungal or Candida infection	3	2	-
Patients free of any infection	13	11	0.68

571

572 Patients receiving GAMMAGARD had fewer infections with *Streptococcus pneumoniae*
573 and *Haemophilus influenza*, but the incidence of other gram negative infections was
574 similar.

575 **14.3 Idiopathic Thrombocytopenic Purpura (ITP)**

576 The efficacy of GAMMAGARD has been demonstrated in a clinical study involving 16
577 patients: thirteen had chronic ITP (11 adults, 2 children), and 3 had acute ITP (one adult,
578 2 children). All 16 patients (100%) demonstrated a rise in platelet count to a level greater
579 than 40,000/mm³ following the administration of GAMMAGARD. Ten of the 16
580 patients (62.5%) exhibited a platelets rise to greater than 80,000 /mm³. Of these 10
581 patients, 7 had chronic ITP (5 adults, 2 children), and 3 had acute ITP (one adult, 2
582 children).

583 The rise in platelet count to greater than 40,000/mm³ occurred after a single 1 g/kg
584 infusion of GAMMAGARD in 8 patients with chronic ITP (6 adults, 2 children), and in 2
585 patients with acute ITP (one adult, one child). A similar response was observed after two
586 1 g/kg infusions in 3 adult patients with chronic ITP, and one child with acute ITP. The
587 remaining 2 adult patients with chronic ITP received more than two 1 g/kg infusions
588 before achieving a platelet count greater than 40,000/mm³. The rise in platelet count
589 occurred within 5 days. However, this rise was transient and not considered curative.
590 Platelet count rises lasted 2 to 3 weeks, with a range of 12 days to 6 months. It should be
591 noted that childhood ITP may resolve spontaneously without treatment.

592 **14.3 Kawasaki Syndrome**

593 The efficacy of GAMMAGARD S/D in reducing the incidence of coronary artery
594 aneurysm in patients with Kawasaki Syndrome has been demonstrated in a clinical study
595 of 44 patients.⁷ The incidence of coronary artery aneurysm in patients with Kawasaki
596 syndrome receiving GAMMAGARD either at a single dose of 1 g/kg (n=22) or at a dose
597 of 400 mg/kg for four consecutive days (n=22), beginning within seven days of onset of
598 fever, was 3/44 (6.8%). This was significantly different (p=0.008) from a comparable
599 group of patients that received aspirin only in previous trials and of whom 42/185
600 (22.7%) experienced coronary artery aneurysms. All patients in the GAMMAGARD trial
601 received concomitant aspirin therapy and none experienced hypersensitivity-type
602 reactions (urticaria, bronchospasm or generalized anaphylaxis).

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646 **16 HOW SUPPLIED/STORAGE AND HANDLING**

647 GAMMAGARD S/D is supplied in single use bottles containing the labeled amount of
 648 functionally active IgG. The following presentation of GAMMAGARD S/D is available:
 649

Grams Protein	NDC
5 g	0944-2655-03
10 g	0944-2655-04

650 Each bottle of GAMMAGARD S/D is furnished with a suitable volume of Sterile Water
 651 for Injection, USP, a transfer device and an administration set which contains an integral
 652 airway and a 15 micron filter.

653 GAMMAGARD S/D is to be stored at a temperature not to exceed 25°C (77°F) for 24
 654 months.

655 **Do not Freeze.**

656 **17 PATIENT COUNSELING INFORMATION**

657 Inform patients to immediately report the following signs and symptoms to their
 658 healthcare provider:

- 659 • Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness
 660 of breath (*see WARNINGS AND PRECAUTIONS [5.2]*).

- 661 • Acute chest pain, shortness of breath, leg pain, and swelling of the legs/feet,
662 numbness in the face or extremities, weakness or paralysis, severe headache,
663 confusion, visual disturbances (*see WARNINGS AND PRECAUTIONS [5.3]*).
- 664 • Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye
665 movements, nausea, and vomiting (*see WARNINGS AND PRECAUTIONS [5.4]*).
- 666 • Increased heart rate, fatigue, yellowing of the skin or eyes, and dark-colored urine
667 (*see WARNINGS AND PRECAUTIONS [5.5]*).
- 668 • Trouble breathing, chest pain, blue lips or extremities, fever (*see WARNINGS AND*
669 *PRECAUTIONS [5.6]*).

670 Inform patients that GAMMAGARD S/D is made from human plasma and may contain
671 infectious agents that can cause disease (e.g., viruses and, theoretically, the vCJD agent).
672 The risk of GAMMAGARD S/D transmitting an infectious agent has been reduced by
673 screening plasma donors for prior exposure, testing donated plasma, and inactivating or
674 removing certain viruses during manufacturing, patients should report any symptoms that
675 concern them might be caused by infections (*see WARNINGS AND PRECAUTIONS*
676 *[5.7]*).

677 Inform patients that GAMMAGARD S/D can interfere with their immune response to
678 live viral vaccines such as measles, mumps and rubella. Inform patients to notify their
679 healthcare professional of this potential interaction when they are receiving vaccinations
680 (*see DRUG INTERACTIONS [7]*).

681 To enroll in the confidential, industry-wide Patient Notification System, call 1-888-
682 UPDATE U (1-888-873-2838)

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684 the U.S. Patent and Trademark Office.

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