

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Hizentra, Immune Globulin Subcutaneous (Human), 20% Liquid
Initial U.S. Approval: 2010

RECENT MAJOR CHANGES

Indications and Usage (1)	XX/2011
Dosage and Administration (2.2, 2.3)	02/2011, XX/2011
Warnings and Precautions (5.2, 5.3, 5.4)	02/2011, XX/2011

INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated for the treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older (1).

DOSAGE AND ADMINISTRATION

For subcutaneous infusion only. Do not inject into a blood vessel.

Start treatment with Hizentra 1 week after the patient's last Immune Globulin Intravenous (Human) (IGIV) infusion, when the patient has received IGIV infusions at regular intervals for at least 3 months.

Dosage (2.2)

- Calculate the initial weekly dose of Hizentra needed to achieve a systemic serum IgG exposure (area under the concentration-time curve [AUC]) not inferior to that of the previous IGIV treatment.

$$\text{Initial dose} = \frac{\text{Previous IGIV dose (in grams)}}{\text{No. of weeks between IGIV doses}} \times 1.53$$

To convert the dose in grams to milliliters (mL), multiply the calculated dose (in grams) by 5.
- Adjust the dose of Hizentra over time based on clinical response and serum IgG trough levels.
 Measure the serum IgG trough level during IGIV therapy prior to switching to Hizentra and again after 2 to 3 months of treatment with Hizentra. Adjust the dose to achieve a serum IgG trough level that is approximately 290 mg/dL higher than the last trough level during prior IGIV therapy.

Administration (2.3)

- Infusion sites – Abdomen, thigh, upper arm, and/or lateral hip. Use up to 4 injection sites simultaneously, with at least 2 inches between sites.
- Infusion volume – For the first infusion, up to 15 mL per injection site. This may be increased to 20 mL per site after the fourth infusion and to a maximum of 25 mL per site as tolerated.
- Infusion rate – For the first infusion, up to 15 mL/hr per site. This may be increased, to a maximum of 25 mL/hr per site as tolerated. **However, the maximum flow rate is not to exceed a total of 50 mL/hr for all sites combined.**

DOSAGE FORMS AND STRENGTHS
 0.2 g/mL (20%) protein solution for subcutaneous injection (3)

CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immune globulin or components of Hizentra, such as polysorbate 80 (4)
- Hyperprolinemia (Hizentra contains the stabilizer L-proline) (4)
- IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (4)

WARNINGS AND PRECAUTIONS

- IgA-deficient patients with anti-IgA antibodies are at greater risk of severe hypersensitivity and anaphylactic reactions. Discontinue use if hypersensitivity reaction occurs (5.1).
- Thrombotic events have been reported with the use of immune globulin products, including Hizentra (5.2).
- Aseptic meningitis syndrome has been reported to occur with IGIV or IGSC treatment (5.3).
- Monitor patients for reactions reported to occur with IGIV treatment that may occur with IGSC treatment, including renal dysfunction/failure, thrombotic events, hemolysis, and transfusion-related acute lung injury (TRALI) (5.4).
- Products made from human plasma can contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.5).

ADVERSE REACTIONS

The most common adverse reactions, observed in ≥5% of study subjects, were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, rash, pruritus, vomiting, abdominal pain (upper), migraine, and pain (6).

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

The passive transfer of antibodies may:

- Lead to misinterpretation of the results of serological testing (5.6, 7.2).
- Interfere with the response to live virus vaccines (7.1).

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- Pediatric: No pediatric-specific dose requirements are necessary to achieve the desired serum IgG levels (8.4).

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

Revised: Month 2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

2 DOSAGE AND ADMINISTRATION

For subcutaneous infusion only. Do not inject into a blood vessel.

2.1 Preparation and Handling

Hizentra is a clear and pale yellow to light brown solution. Do not use if the solution is cloudy or contains particulates.

- Prior to administration, visually inspect each vial of Hizentra for particulate matter or discoloration, whenever the solution and container permit.
- Do not freeze. Do not use any solution that has been frozen.
- Check the product expiration date on the vial label. Do not use beyond the expiration date.
- Do not mix Hizentra with other products.
- Do not shake the Hizentra vial.
- Use aseptic technique when preparing and administering Hizentra.
- The Hizentra vial is for single-use only. Discard all used administration supplies and any unused product immediately after each infusion in accordance with local requirements.

2.2 Dosage

The dose should be individualized based on the patient's clinical response to Hizentra therapy and serum immunoglobulin G (IgG) trough levels.

Start treatment with Hizentra 1 week after the patient's last Immune Globulin Intravenous (Human) (IGIV) infusion. Before receiving treatment with Hizentra, patients need to have received IGIV treatment at regular intervals for at least 3 months. Before switching to Hizentra, obtain the patient's serum IgG trough level to guide subsequent dose adjustments (*see below under Dose Adjustment*).

Establish the initial weekly dose of Hizentra by converting the monthly IGIV dose into a weekly equivalent and increasing it using a dose adjustment factor. The goal is to

44 achieve a systemic serum IgG exposure (area under the concentration-time curve [AUC])
45 not inferior to that of the previous IGIV treatment (*see Pharmacokinetics [12.3]*).
46

47 **Initial Weekly Dose**

48 To calculate the initial weekly dose of Hizentra, divide the previous IGIV dose in grams
49 by the number of weeks between doses during the patient's IGIV treatment (e.g., 3 or 4);
50 then multiply this by the dose adjustment factor of 1.53.
51

52 Initial Hizentra dose = $\frac{\text{Previous IGIV dose (in grams)}}{\text{Number of weeks between IGIV doses}} \times 1.53$
53

54
55 To convert the Hizentra dose (in grams) to milliliters (mL), multiply the calculated dose
56 (in grams) by 5.
57

58 **Dose Adjustment**

59 Over time, the dose may need to be adjusted to achieve the desired clinical response and
60 serum IgG trough level. To determine if a dose adjustment should be considered,
61 measure the patient's serum IgG trough level 2 to 3 months after switching from IGIV to
62 Hizentra. The target serum IgG trough level on weekly Hizentra treatment is projected to
63 be approximately 290 mg/dL higher than the last trough level during prior IGIV therapy.
64

65 To adjust the dose based on trough levels, calculate the difference (in mg/dL) between
66 the patient's serum IgG trough level and the target IgG trough level. Then find this
67 difference in [Table 1](#) (Column 1) and, based on the patient's body weight, the
68 corresponding amount (in mL) by which to increase (or decrease) the weekly dose. **The**
69 **patient's clinical response should be the primary consideration in dose adjustment.**
70 **Additional dosage increments may be indicated based on the patient's clinical**
71 **response (infection frequency and severity).**

Table 1: Adjustment (\pm mL) of the Weekly Hizentra Dose Based on the Difference (\pm mg/dL) From the Target Serum IgG Trough Level

Difference From Target IgG Trough Level (mg/dL)	Body Weight (kg)												
	10	15	20	30	40	50	60	70	80	90	100	110	120
	Dose Adjustment (mL per Week)*												
100	1	1	2	3	4	5	6	7	8	8	9	10	11
150	1	2	3	4	6	7	8	10	11	13	14	15	17
200	2	3	4	6	8	9	11	13	15	17	19	21	23
250	2	4	5	7	9	12	14	16	19	21	23	26	28
300	3	4	6	8	11	14	17	20	23	25	28	31	34
350	3	5	7	10	13	16	20	23	26	30	33	36	39
400	4	6	8	11	15	19	23	26	30	34	38	41	45
450	4	6	8	13	17	21	25	30	34	38	42	46	51
500	5	7	9	14	19	23	28	33	38	42	47	52	56

* Dose adjustment in mL is based on the slope of the serum IgG trough level response to Hizentra dose increments (5.3 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 trough level is 1000 mg/dL, this results in a difference of 100 mg/dL. Therefore, increase the weekly dose of Hizentra by 7 mL.

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

Dosage requirements for patients switching to Hizentra from another IGSC product: If a patient on Hizentra does not maintain an adequate clinical response or a serum IgG trough level equivalent to that of the previous IGSC treatment, the physician may want to adjust the dose. For such patients, [Table 1](#) also provides guidance for dose adjustment if their desired IGSC trough level is known.

90

91 **Measles Exposure**

92 If a patient is at risk of measles exposure (i.e., due to an outbreak in the US or travel to
93 endemic areas outside of the US), the weekly Hizentra dose should be a minimum of
94 200 mg/kg body weight for two consecutive weeks. If a patient has been exposed to
95 measles, ensure this minimum dose is administered as soon as possible after exposure.

96

97 **2.3 Administration**

98 **Hizentra is for subcutaneous infusion only. Do not inject into a blood vessel.**

99

100 Hizentra is intended for weekly subcutaneous administration using an infusion pump.
101 Infuse Hizentra in the abdomen, thigh, upper arm, and/or lateral hip.

102

- 103 • Injection sites – A Hizentra dose may be infused into multiple injection sites. Do
104 not use more than 4 sites simultaneously. However, if more injection sites are
105 needed for the full weekly dose, they can be used consecutively. Injection sites
106 should be at least 2 inches apart. Change the actual site of injection with each
107 weekly administration.
- 108 • Volume – For the first infusion of Hizentra, do not exceed a volume of 15 mL per
109 injection site. The volume may be increased to 20 mL per site after the fourth
110 infusion and to a maximum of 25 mL per site as tolerated.
- 111 • Rate – For the first infusion of Hizentra, the maximum recommended flow rate is
112 15 mL per hour per site. For subsequent infusions, the flow rate may be increased
113 to a maximum of 25 mL per hour per site as tolerated. **However, the maximum
114 flow rate is not to exceed a total of 50 mL per hour for all sites combined at
115 any time.**

116

117 Follow the steps below and use aseptic technique to administer Hizentra.

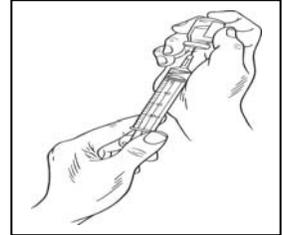
118

- 119 1. **Assemble supplies** – Gather the Hizentra vial(s), disposable supplies (not
120 provided with Hizentra), and other items (infusion pump, sharps or other
121 container, patient's treatment diary/log book) needed for the infusion.
 - 122 2. **Clean surface** – Thoroughly clean a flat surface using an alcohol wipe.
 - 123 3. **Wash hands** – Thoroughly wash and dry hands. The use of gloves when
124 preparing and administering Hizentra is optional.
 - 125 4. **Check vials** – Carefully inspect each vial of Hizentra. Do not use the vial if the
126 liquid looks cloudy, contains particles, or has changed color, if the protective cap
127 is missing, or if the expiration date on the label has passed.
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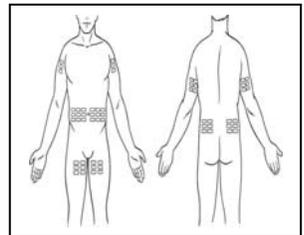
5. Transfer Hizentra from vial(s) to syringe

- Remove the protective cap from the vial to expose the central portion of the rubber stopper of the Hizentra vial.
- Clean the stopper with an alcohol wipe and allow it to dry.
- Attach a sterile transfer needle to a sterile syringe. Pull back on the plunger of the syringe to draw air into the syringe that is equal to the amount of Hizentra to be withdrawn.
- Insert the transfer needle into the center of the vial stopper and, to avoid foaming, inject the air into headspace of the vial (not into the liquid).
- Withdraw the desired volume of Hizentra.



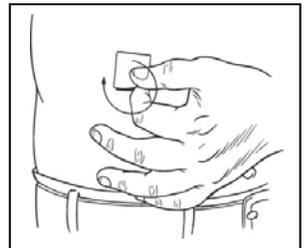
When using multiple vials to achieve the desired dose, repeat this step.

6. Prepare infusion pump and tubing – Follow the manufacturer’s instructions for preparing the pump, using subcutaneous administration sets and tubing, as needed. Be sure to prime the tubing with Hizentra to ensure that no air is left in the tubing.



7. Prepare injection site(s)

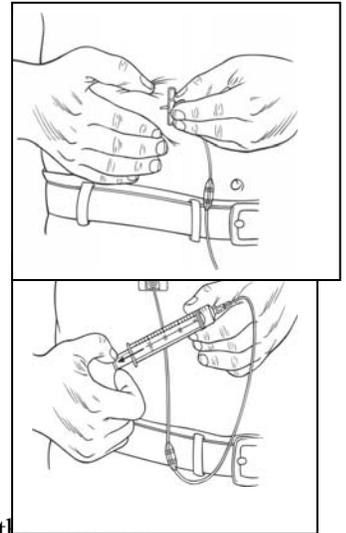
- The number and location of injection sites depends on the volume of the total dose. Infuse Hizentra into a maximum of 4 sites simultaneously; each injection site should be at least 2 inches apart.
- Using an antiseptic skin preparation, clean each site beginning at the center and working outward in a circular motion. Allow each site to dry before proceeding.



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8. Insert needle(s)

- Grasp the skin between 2 fingers and insert the needle into the subcutaneous tissue.
- If necessary, use sterile gauze and tape or transparent dressing to hold the needle in place.
- Before starting the infusion, attach a sterile syringe to the end of the primed administration tubing and gently pull back on the plunger to make sure no blood is flowing back into the tubing. If blood is present, remove and discard the needle and tubing. Repeat the process beginning with step 6 (priming) using a new needle, new infusion tubing, and a different injection site.



9. Start infusion – Follow the manufacturer’s instructions to turn on the infusion pump.

10. Record treatment – Remove the peel-off portion of the label from each vial used, and affix it to the patient’s treatment diary/log book.

11. Clean up – After administration is complete, turn off the infusion pump. Take off the tape or dressing and remove the needle set from the infusion site(s). Disconnect the tubing from the pump. Immediately discard any unused product and all used disposable supplies in accordance with local requirements. Clean and store the pump according to the manufacturer’s instructions.

For self-administration, provide the patient with instructions and training for subcutaneous infusion in the home or other appropriate setting.

3 DOSAGE FORMS AND STRENGTHS

Hizentra is a 0.2 g/mL (20%) protein solution for subcutaneous injection.

4 CONTRAINDICATIONS

Hizentra is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of Hizentra, such as polysorbate 80.

Hizentra is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (see [Description \[11\]](#)).

203 Hizentra is contraindicated in IgA-deficient patients with antibodies against IgA and a
204 history of hypersensitivity (*see Description [11]*).

205
206

207 **5 WARNINGS AND PRECAUTIONS**

208

209 **5.1 Hypersensitivity**

210 Severe hypersensitivity reactions may occur to human immune globulin or components
211 of Hizentra, such as polysorbate 80. In case of hypersensitivity, discontinue the Hizentra
212 infusion immediately and institute appropriate treatment.

213

214 Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic
215 reactions (including anaphylaxis and shock) after administration of blood components
216 containing IgA. Patients with known antibodies to IgA may have a greater risk of
217 developing potentially severe hypersensitivity and anaphylactic reactions with
218 administration of Hizentra. Hizentra contains ≤ 50 mcg/mL IgA (*see Description [11]*).

219

220 **5.2 Thrombotic Events**

221 Thrombotic events have been reported with the use of immune globulin products¹⁻³,
222 including Hizentra. Patients at increased risk may include those with a history of
223 atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac
224 output, hypercoagulable disorders, prolonged periods of immobilization, Factor V
225 Leiden, known or suspected hyperviscosity, and/or those who use estrogen-containing
226 products. Because of the potentially increased risk of thrombosis, consider baseline
227 assessment of blood viscosity in patients at risk for hyperviscosity, including those with
228 cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or
229 monoclonal gammopathies. For patients judged to be at risk of developing thrombotic
230 events, administer Hizentra at the minimum rate practicable.

231

232 **5.3 Aseptic Meningitis Syndrome (AMS)**

233 AMS has been reported with use of IGIV⁴ or IGSC. The syndrome usually begins within
234 several hours to 2 days following immune globulin treatment. AMS is characterized by
235 the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever,
236 photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF)
237 studies frequently show pleocytosis up to several thousand cells per cubic millimeter,
238 predominantly from the granulocytic series, and elevated protein levels up to several
239 hundred mg/dL. AMS may occur more frequently in association with high doses
240 (≥ 2 g/kg) and/or rapid infusion of immune globulin product.

241

242 Patients exhibiting such signs and symptoms should receive a thorough neurological
243 examination, including CSF studies, to rule out other causes of meningitis.
244 Discontinuation of immune globulin treatment has resulted in remission of AMS within
245 several days without sequelae.

246

247 | **5.4 Reactions Reported to Occur With IGIV Treatment**

248 | The following reactions have been reported to occur with IGIV treatment and may occur
249 | with IGSC treatment.

250

251 | **Renal Dysfunction/Failure**

252 | Renal dysfunction/failure, osmotic nephropathy, and death may occur with use of human
253 | immune globulin products. Ensure that patients are not volume depleted and assess renal
254 | function, including measurement of blood urea nitrogen (BUN) and serum creatinine,
255 | before the initial infusion of Hizentra and at appropriate intervals thereafter.

256

257 | Periodic monitoring of renal function and urine output is particularly important in
258 | patients judged to have a potential increased risk of developing acute renal failure.⁵ If
259 | renal function deteriorates, consider discontinuing Hizentra. For patients judged to be at
260 | risk of developing renal dysfunction because of pre-existing renal insufficiency or
261 | predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia,
262 | those who are overweight or use concomitant nephrotoxic medicinal products, or those
263 | who are over 65 years of age), administer Hizentra at the minimum rate practicable.

264

265 | **Hemolysis**

266 | Hizentra can contain blood group antibodies that may act as hemolysins and induce *in*
267 | *vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct
268 | antiglobulin (Coombs') test result and hemolysis.⁶⁻⁸ Delayed hemolytic anemia can
269 | develop subsequent to immune globulin therapy due to enhanced RBC sequestration, and
270 | acute hemolysis, consistent with intravascular hemolysis, has been reported.⁹

271

272 | Monitor recipients of Hizentra for clinical signs and symptoms of hemolysis. If these are
273 | present after a Hizentra infusion, perform appropriate confirmatory laboratory testing. If
274 | transfusion is indicated for patients who develop hemolysis with clinically compromising
275 | anemia after receiving Hizentra, perform adequate cross-matching to avoid exacerbating
276 | on-going hemolysis.

277

278 | **Transfusion-Related Acute Lung Injury (TRALI)**

279 | Noncardiogenic pulmonary edema may occur in patients administered human immune
280 | globulin products.¹⁰ TRALI is characterized by severe respiratory distress, pulmonary
281 | edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs
282 | within 1 to 6 hours following transfusion. Patients with TRALI may be managed using
283 | oxygen therapy with adequate ventilatory support.

284

285 | Monitor Hizentra recipients for pulmonary adverse reactions. If TRALI is suspected,
286 | perform appropriate tests for the presence of anti-neutrophil antibodies in both the
287 | product and patient's serum.

288

289 5.5 Transmissible Infectious Agents

290 Because Hizentra is made from human plasma, it may carry a risk of transmitting
291 infectious agents (e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease [CJD]
292 agent). The risk of infectious agent transmission has been reduced by screening plasma
293 donors for prior exposure to certain viruses, testing for the presence of certain current
294 virus infections, and including virus inactivation/removal steps in the manufacturing
295 process for Hizentra.

296

297 Report all infections thought to be possibly transmitted by Hizentra to CSL Behring
298 Pharmacovigilance at 1-866-915-6958.

299

300 5.6 Laboratory Tests

301 Various passively transferred antibodies in immunoglobulin preparations may lead to
302 misinterpretation of the results of serological testing.

303

304

305 6 ADVERSE REACTIONS

306

307 The most common adverse reactions (ARs), observed in $\geq 5\%$ of study subjects receiving
308 Hizentra, were local reactions (e.g., swelling, redness, heat, pain, and itching at the
309 injection site), headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough,
310 rash, pruritus, vomiting, abdominal pain (upper), migraine, and pain.

311

312 6.1 Clinical Trials Experience

313 Because clinical studies are conducted under widely varying conditions, AR rates
314 observed in clinical studies of a product cannot be directly compared to rates in the
315 clinical studies of another product and may not reflect the rates observed in clinical
316 practice.

317

318 US Study

319 The safety of Hizentra was evaluated in a clinical study in the US for 15 months (3-
320 month wash-in/wash-out period followed by a 12-month efficacy period) in subjects with
321 PI who had been treated previously with IGIV every 3 or 4 weeks. The safety analyses
322 included 49 subjects in the intention-to-treat (ITT) population. The ITT population
323 consisted of all subjects who received at least one dose of Hizentra (*see Clinical Studies*
324 *[14]*).

325

326 Subjects were treated with Hizentra at weekly median doses ranging from 66 to
327 331 mg/kg body weight (mean: 181.4 mg/kg) during the wash-in/wash-out period and
328 from 72 to 379 mg/kg (mean: 213.2 mg/kg) during the efficacy period. The 49 subjects
329 received a total of 2264 weekly infusions of Hizentra.

330
331 Table 2 summarizes the most frequent adverse reactions (ARs) (experienced by at least
332 2 subjects) occurring during or within 72 hours after the end of an infusion. Local
333 reactions were assessed by the investigators 15 to 45 minutes post-infusion and by the
334 subjects 24 hours post-infusion. The investigators then evaluated the ARs arising from
335 the subject assessments. Local reactions were the most frequent ARs observed, with
336 injection-site reactions (e.g., swelling, redness, heat, pain, and itching at the site of
337 injection) comprising 98% of local reactions.

338
339 **Table 2: Incidence of Subjects With Adverse Reactions (ARs)* (Experienced by 2 or**
340 **More Subjects) and Rate per Infusion (ITT Population), US Study**
341

AR (≥2 Subjects)	ARs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=49)	Number (Rate†) of ARs (n=2264 Infusions)
Local reactions‡	49 (100)	1322 (0.584)
Other ARs:		
Headache	12 (24.5)	32 (0.014)
Diarrhea	5 (10.2)	6 (0.003)
Fatigue	4 (8.2)	4 (0.002)
Back pain	4 (8.2)	5 (0.002)
Nausea	4 (8.2)	4 (0.002)
Pain in extremity	4 (8.2)	6 (0.003)
Cough	4 (8.2)	4 (0.002)
Vomiting	3 (6.1)	3 (0.001)
Abdominal pain, upper	3 (6.1)	3 (0.001)
Migraine	3 (6.1)	4 (0.002)
Pain	3 (6.1)	4 (0.002)
Arthralgia	2 (4.1)	3 (0.001)
Contusion	2 (4.1)	3 (0.001)
Rash	2 (4.1)	3 (0.001)
Urticaria	2 (4.1)	2 (< 0.001)

342 * Excluding infections.

343 † Rate of ARs per infusion.

344 ‡ Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the
345 injection site.

346
347 The ratio of infusions with ARs, including local reactions, to all infusions was 1303 to
348 2264 (57.6%). Excluding local reactions, the corresponding ratio was 56 to 2264 (2.5%).
349

350 **Table 3** summarizes injection-site reactions based on investigator assessments 15 to
351 45 minutes after the end of the 683 infusions administered during regularly scheduled
352 visits (every 4 weeks).
353

354 **Table 3: Investigator Assessments* of Injection-Site Reactions by Infusion, US**
355 **Study**
356

Injection-Site Reaction	Number [†] (Rate [‡]) of Reactions (n=683 Infusions [§])
Edema/induration	467 (0.68)
Erythema	346 (0.51)
Local heat	108 (0.16)
Local pain	88 (0.13)
Itching	64 (0.09)

357 * 15 to 45 minutes after the end of infusions administered at regularly scheduled visits (every 4 weeks).

358 † For multiple injection sites, every site was judged, but only the site with the strongest reaction was recorded.

359 ‡ Rate of injection-site reactions per infusion.

360 § Number of infusions administered during regularly scheduled visits.

361
362 Most local reactions were either mild (93.4%) or moderate (6.3%) in intensity.
363

364 No deaths or serious ARs occurred during the study. Two subjects withdrew from the
365 study due to ARs. One subject experienced a severe injection-site reaction one day after
366 the third weekly infusion, and the other subject experienced moderate myositis. Both
367 reactions were judged to be “at least possibly related” to the administration of Hizentra.
368

369 **European Study**

370 In a clinical study conducted in Europe, the safety of Hizentra was evaluated for 10
371 months (3-month wash-in/wash-out period followed by a 7-month efficacy period) in
372 51 subjects with PI who had been treated previously with IGIV every 3 or 4 weeks or
373 with IGSC weekly.
374

375 Subjects were treated with Hizentra at weekly median doses ranging from 59 to
376 267 mg/kg body weight (mean: 118.8 mg/kg) during the wash-in/wash-out period and
377 from 59 to 243 mg/kg (mean: 120.1 mg/kg) during the efficacy period. The 51 subjects
378 received a total of 1831 infusions of Hizentra.

379
380 Table 4 summarizes the most frequent ARs (experienced by at least 2 subjects) occurring
381 during or within 72 hours after the end of an infusion. Local reactions were assessed by
382 the subjects between 24 and 72 hours post-infusion. The investigators then evaluated the
383 ARs arising from the subject assessments.

384
385 **Table 4: Incidence of Subjects With Adverse Reactions (ARs)* (Experienced by 2 or**
386 **More Subjects) and Rate per Infusion, European Study**
387

AR (≥2 Subjects)	ARs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=51)	Number (Rate)† of ARs (n=1831 Infusions)
Local reactions‡	24 (47.1)	105 (0.057)
Other ARs:		
Headache	9 (17.6)	20 (0.011)
Rash	4 (7.8)	4 (0.002)
Pruritus	4 (7.8)	13 (0.007)
Fatigue	3 (5.9)	5 (0.003)
Abdominal pain, upper	2 (3.9)	3 (0.002)
Arthralgia	2 (3.9)	2 (0.001)
Erythema	2 (3.9)	4 (0.002)
Abdominal discomfort	2 (3.9)	3 (0.002)
Back pain	2 (3.9)	2 (0.001)
Hematoma	2 (3.9)	3 (0.002)
Hypersensitivity	2 (3.9)	4 (0.002)

388 * Excluding infections.

389 † Rate of ARs per infusion.

390 ‡ Includes infusion-related reaction; infusion-site mass; infusion/injection-site erythema, hematoma, induration,
391 inflammation, edema, pain, pruritus, rash, reaction, swelling; injection-site extravasation, nodule; puncture-site
392 reaction.

393
394 The proportion of subjects reporting local reactions decreased over time from
395 approximately 20% following the first infusion to <5% by the end of the study.

396
397 Three subjects withdrew from the study due to ARs of mild to moderate intensity. One
398 subject experienced injection-site pain and injection-site pruritus; the second subject
399 experienced injection-site reaction, fatigue, and feeling cold; and the third subject
400 experienced injection-site reaction and hypersensitivity. All reactions were judged by the
401 investigator to be “at least possibly related” to the administration of Hizentra.

402

403 **6.2 Postmarketing Experience**

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

407

408 **Hizentra**

409 The following adverse reactions have been identified during postmarketing use of
410 Hizentra. This list does not include reactions already reported in clinical studies with
411 Hizentra (see [Adverse Reactions \[6.1\]](#)).

412 • *Infusion reactions:* Allergic-anaphylactic reactions (including swollen face or tongue
413 and pharyngeal edema), pyrexia, chills, dizziness, hypertension/changes in blood
414 pressure, malaise.

415 • *Cardiovascular:* Thromboembolic events, chest discomfort (including chest pain)

416 • *Respiratory:* Dyspnea

417

418 **General**

419 The following adverse reactions have been reported during postmarketing use of immune
420 globulin products¹¹:

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

425 • *Renal:* Acute renal dysfunction/failure, osmotic nephropathy

426 • *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI,
427 cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm

428 • *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse,
429 hypotension

430 • *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis
431 syndrome

432 • *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema
433 multiforme, dermatitis (e.g., bullous dermatitis)

434 • *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin
435 (Coombs') test

436 • *Gastrointestinal:* Hepatic dysfunction, abdominal pain

437 • *General/Body as a Whole:* Pyrexia, rigors

438

439 To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring
440 Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or
441 www.fda.gov/medwatch.

442

443

444 **7 DRUG INTERACTIONS**

445

446 **7.1 Live Virus Vaccines**

447 The passive transfer of antibodies with immunoglobulin administration may interfere
448 with the response to live virus vaccines such as measles, mumps, rubella, and varicella
449 (*see Patient Counseling Information [17]*).

450

451 **7.2 Serological Testing**

452 Various passively transferred antibodies in immunoglobulin preparations may lead to
453 misinterpretation of the results of serological testing.

454

455

456 **8 USE IN SPECIFIC POPULATIONS**

457

458 **8.1 Pregnancy**

459 Pregnancy Category C. Animal reproduction studies have not been conducted with
460 Hizentra. It is not known whether Hizentra can cause fetal harm when administered to a
461 pregnant woman or can affect reproduction capacity. Hizentra should be given to
462 pregnant women only if clearly needed.

463

464 **8.3 Nursing Mothers**

465 Hizentra has not been evaluated in nursing mothers.

466

467 **8.4 Pediatric Use**

468 The safety and effectiveness of Hizentra have been established in the pediatric age groups
469 2 to 16, as supported by evidence from adequate and well-controlled studies. Hizentra
470 was evaluated in 10 pediatric subjects with PI (3 children and 7 adolescents) in a study
471 conducted in the US (*see Clinical Studies [14]*) and in 23 pediatric subjects with PI
472 (18 children and 5 adolescents) in Europe. There were no differences in the safety and
473 efficacy profiles as compared with adult subjects. No pediatric-specific dose
474 requirements were necessary to achieve the desired serum IgG levels.

475

476 Safety and effectiveness of Hizentra in pediatric patients below the age of 2 have not
477 been established.

478

479 **8.5 Geriatric Use**

480 Of the 49 subjects evaluated in the US clinical study of Hizentra, 6 subjects were 65
481 years of age or older. No overall differences in safety or efficacy were observed between
482 these subjects and younger subjects. The clinical study of Hizentra in Europe did not
483 include subjects over the age of 65.

484

485

486 **11 DESCRIPTION**

487

488 Hizentra, Immune Globulin Subcutaneous (Human), 20% Liquid, is a ready-to-use,
489 sterile 20% (0.2 g/mL) protein liquid preparation of polyvalent human immunoglobulin G
490 (IgG) for subcutaneous administration. Hizentra is manufactured from large pools of
491 human plasma by a combination of cold alcohol fractionation, octanoic acid
492 fractionation, and anion exchange chromatography. The IgG proteins are not subjected to
493 heating or to chemical or enzymatic modification. The Fc and Fab functions of the IgG
494 molecule are retained. Fab functions tested include antigen binding capacities, and Fc
495 functions tested include complement activation and Fc-receptor-mediated leukocyte
496 activation (determined with complexed IgG).

497

498 Hizentra has a purity of $\geq 98\%$ IgG and a pH of 4.6 to 5.2. Hizentra contains
499 approximately 250 (range: 210 to 290 mmol/L) L-proline (a nonessential amino acid) as a
500 stabilizer, 10 to 30 mg/L polysorbate 80, and trace amounts of sodium. Hizentra contains
501 ≤ 50 mcg/mL IgA. Hizentra contains no carbohydrate stabilizers (e.g., sucrose, maltose)
502 and no preservative.

503

504 Plasma units used in the manufacture of Hizentra are tested using FDA-licensed
505 serological assays for hepatitis B surface antigen and antibodies to human
506 immunodeficiency virus (HIV)-1/2 and hepatitis C virus (HCV) as well as FDA-licensed
507 Nucleic Acid Testing (NAT) for HIV-1 and HCV. All plasma units have been found to
508 be nonreactive (negative) in these tests. For hepatitis B virus (HBV), an investigational
509 NAT procedure is used and the plasma units found to be negative; however, the
510 significance of a negative result has not been established. In addition, the plasma has
511 been tested for B19 virus (B19V) DNA by NAT. Only plasma that passes virus
512 screening is used for production, and the limit for B19V in the fractionation pool is set
513 not to exceed 10^4 IU of B19V DNA per mL.

514

515 The manufacturing process for Hizentra includes three steps to reduce the risk of virus
516 transmission. Two of these are dedicated virus clearance steps: pH 4 incubation to
517 inactivate enveloped viruses; and virus filtration to remove, by size exclusion, both
518 enveloped and non-enveloped viruses as small as approximately 20 nanometers. In
519 addition, a depth filtration step contributes to the virus reduction capacity.¹²

520
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527

These steps have been independently validated in a series of *in vitro* experiments for their capacity to inactivate and/or remove both enveloped and non-enveloped viruses. Table 5 shows the virus clearance during the manufacturing process for Hizentra, expressed as the mean log₁₀ reduction factor (LRF).

Table 5: Virus Inactivation/Removal in Hizentra*

	HIV-1	PRV	BVDV	WNV	EMCV	MVM
Virus Property						
Genome	RNA	DNA	RNA	RNA	RNA	DNA
Envelope	Yes	Yes	Yes	Yes	No	No
Size (nm)	80-100	120-200	50-70	50-70	25-30	18-24
Manufacturing Step	Mean LRF					
pH 4 incubation	≥5.4	≥5.9	4.6	≥7.8	nt	nt
Depth filtration	≥5.3	≥6.3	2.1	3.0	4.2	2.3
Virus filtration	≥5.3	≥5.5	≥5.1	≥5.9	≥5.4	≥5.5
Overall Reduction (Log₁₀ Units)	≥16.0	≥17.7	≥11.8	≥16.7	≥9.6	≥7.8

528 HIV-1, human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; PRV, pseudorabies virus, a nonspecific
529 model for large enveloped DNA viruses (e.g., herpes virus); BVDV, bovine viral diarrhea virus, a model for hepatitis C
530 virus; WNV, West Nile virus; EMCV, encephalomyocarditis virus, a model for hepatitis A virus; MVM, minute virus
531 of mice, a model for a small highly resistant non-enveloped DNA virus (e.g., parvovirus); LRF, log₁₀ reduction factor;
532 nt, not tested; na, not applicable.
533 * The virus clearance of human parvovirus B19 was investigated experimentally at the pH 4 incubation step. The
534 estimated LRF obtained was ≥5.3.

535
536 The manufacturing process was also investigated for its capacity to decrease the
537 infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE),
538 considered a model for CJD and its variant (vCJD).¹² Several of the production steps
539 have been shown to decrease infectivity of an experimental TSE model agent. TSE
540 reduction steps include octanoic acid fractionation (≥6.4 log₁₀), depth filtration
541 (2.6 log₁₀), and virus filtration (≥5.8 log₁₀). These studies provide reasonable assurance
542 that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be
543 removed.

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12 CLINICAL PHARMACOLOGY

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12.1 Mechanism of Action

Hizentra supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The mechanism of action in PI has not been fully elucidated.

553
554
555
556

12.3 Pharmacokinetics

The pharmacokinetics (PK) of Hizentra was evaluated in a PK substudy of subjects with PI participating in the 15-month efficacy and safety study (see *Clinical Studies [14]*). All PK subjects were treated previously with Privigen®, Immune Globulin Intravenous

557 (Human), 10% Liquid and were switched to weekly subcutaneous treatment with
558 Hizentra. After a 3-month wash-in/wash-out period, doses were adjusted individually
559 with the goal of providing a systemic serum IgG exposure (area under the IgG serum
560 concentration vs time curve; AUC) not inferior to that of the previous weekly-equivalent
561 IGIV dose. Table 6 summarizes PK parameters for subjects in the substudy following
562 treatment with Hizentra and IGIV.

563

564 **Table 6: Pharmacokinetics Parameters of Hizentra and IGIV, US Study**

565

	Hizentra	IGIV* (Privigen®)
Number of subjects	18	18
Dose*		
Mean	228 mg/kg bw	152 mg/kg bw
Range	141-381 mg/kg bw	86-254 mg/kg bw
IgG peak levels		
Mean	1616 mg/dL	2564 mg/dL
Range	1090-2825 mg/dL	2046-3456 mg/dL
IgG trough levels		
Mean	1448 mg/dL	1127 mg/dL
Range	952-2623 mg/dL	702-1810 mg/dL
AUC†		
Mean	10560 day x mg/dL	10320 day x mg/dL
Range	7210-18670 day x mg/dL	8051-15530 day x mg/dL

566 bw, body weight.

567 * For IGIV: weekly-equivalent dose.

568 † Standardized to a 7-day period.

569

570 For the 19 subjects completing the wash-in/wash-out period, the average dose adjustment
571 for Hizentra was 153% (range: 126% to 187%) of the previous weekly-equivalent IGIV
572 dose. After 12 weeks of treatment with Hizentra at this individually adjusted dose, the
573 final steady-state AUC determinations were made in 18 of the 19 subjects. The
574 geometric mean ratio of the steady-state AUCs, standardized to a weekly treatment
575 period, for Hizentra vs IGIV treatment was 1.002 (range: 0.77 to 1.20) with a 90%
576 confidence limit of 0.951 to 1.055 for the 18 subjects.

577

578 With Hizentra, peak serum levels are lower (1616 vs 2564 mg/dL) than those achieved
579 with IGIV while trough levels are generally higher (1448 vs 1127 mg/dL). In contrast to
580 IGIV administered every 3 to 4 weeks, weekly subcutaneous administration results in
581 relatively stable steady-state serum IgG levels.^{13,14} After the subjects had reached steady-
582 state with weekly administration of Hizentra, peak serum IgG levels were observed after
583 a mean of 2.9 days (range: 0 to 7 days) in 18 subjects.

584

585

586 **13 NONCLINICAL TOXICOLOGY**

587

588 **13.2 Animal Toxicology and/or Pharmacology**

589 Long- and short-term memory loss was seen in juvenile rats in a study modeling
590 hyperprolinemia. In this study, rats received daily subcutaneous injections with L-proline
591 from day 6 to day 28 of life.¹⁵ The daily amounts of L-proline used in this study were
592 more than 60 times higher than the L-proline dose that would result from the
593 administration of 400 mg/kg body weight of Hizentra once weekly. In unpublished
594 studies using the same animal model (i.e., rats) dosed with the same amount of L-proline
595 with a dosing interval relevant to IGSC treatment (i.e., on 5 consecutive days on days 9 to
596 13, or once weekly on days 9, 16, and 23), no effects on learning and memory were
597 observed. The clinical relevance of these studies is not known.

598

599

600 **14 CLINICAL STUDIES**

601

602 **14.1 US Study**

603 A prospective, open-label, multicenter, single-arm, clinical study conducted in the US
604 evaluated the efficacy, tolerability, and safety of Hizentra in 49 adult and pediatric
605 subjects with PI. Subjects previously receiving monthly treatment with IGIV were
606 switched to weekly subcutaneous administration of Hizentra for 15 months. Following a
607 3-month wash-in/wash-out period, subjects received a dose adjustment to achieve an
608 equivalent AUC to their previous IGIV dose (*see Pharmacokinetics [12.3]*) and
609 continued treatment for a 12-month efficacy period. The efficacy analyses included
610 38 subjects in the modified intention-to-treat (MITT) population. The MITT population
611 consisted of subjects who completed the wash-in/wash-out period and received at least
612 one infusion of Hizentra during the efficacy period.

613

614 Although 5% of the administered doses could not be verified, the weekly median doses of
615 Hizentra ranged from 72 to 379 mg/kg body weight during the efficacy period. The mean
616 dose was 213.2 mg/kg, which was 149% of the previous IGIV dose.

617

618 In the study, the number of injection sites per infusion ranged from 1 to 12. In 73% of
619 infusions, the number of injection sites was 4 or fewer. Up to 4 simultaneous injection
620 sites were permitted using 2 pumps; however, more than 4 sites could be used
621 consecutively during one infusion. The infusion flow rate did not exceed 50 mL per hour
622 for all injection sites combined. During the efficacy period, the median duration of a
623 weekly infusion ranged from 1.6 to 2.0 hours.

624

625 The study evaluated the annual rate of serious bacterial infections (SBIs), defined as
626 bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial
627 meningitis, and visceral abscess. The study also evaluated the annual rate of any
628 infections, the use of antibiotics for infection (prophylaxis or treatment), the days out of

629 work/school/kindergarten/day care or unable to perform normal activities due to
630 infections, hospitalizations due to infections, and serum IgG trough levels.

631
632 **Table 7** summarizes the efficacy results for subjects in the efficacy period (MITT
633 population) of the study. No subjects experienced an SBI in this study.

634
635 **Table 7: Summary of Efficacy Results (MITT Population)**
636

Number of subjects (efficacy period)	38
Total number of subject days	12,697
Infections	
Annual rate of SBIs*	0 SBIs per subject year [†]
Annual rate of any infections	2.76 infections/subject year [‡]
Antibiotic use for infection (prophylaxis or treatment)	
Number of subjects (%)	27 (71.1)
Annual rate	48.5 days/subject year
Total number of subject days	12,605
Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections	
Number of days (%)	71 (0.56)
Annual rate	2.06 days/subject year
Hospitalizations due to infections	
Number of days (%)	7 (0.06) [§]
Annual rate	0.2 days/subject year

637 * Defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and
638 visceral abscess.

639 [†] Upper 99% confidence limit: 0.132.

640 [‡] 95% confidence limits: 2.235; 3.370.

641 [§] Based on 1 subject.

642
643 The mean IgG trough levels increased by 24.2%, from 1009 mg/dL prior to the study to
644 1253 mg/dL during the efficacy period.

645 646 **14.2 European Study**

647 In a prospective, open-label, multicenter, single-arm, clinical study conducted in Europe,
648 51 adult and pediatric subjects with PI switched from monthly IGIV (31 subjects) or
649 weekly IGSC (20 subjects) to weekly treatment with Hizentra. For the 46 subjects in the
650 efficacy analysis, the weekly mean dose in the efficacy period was 120.1 mg/kg (range 59
651 to 243 mg/kg), which was 104% of the previous weekly equivalent IGIV or weekly IGSC
652 dose.

653
654 None of the subjects had an SBI during the efficacy period, resulting in an annualized
655 rate of 0 (upper one-sided 99% confidence limit of 0.192) SBIs per subject. The
656 annualized rate of any infections was 5.18 infections per subject for the efficacy period.

657
658

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- 697

698

699 **16 HOW SUPPLIED/STORAGE AND HANDLING**

700

701 **16.1 How Supplied**

702 Hizentra is supplied in a single-use, tamper-evident vial containing 0.2 grams of protein
703 per mL of preservative-free liquid. Each vial label contains a peel-off strip with the vial
704 size and product lot number for use in recording doses in a patient treatment record.

705

706 The components used in the packaging for Hizentra contain no latex.

707

708 The following dosage presentations are available:

709

NDC Number	Fill Size (mL)	Grams Protein
------------	----------------	---------------

44206-451-01	5 mL	1
--------------	------	---

44206-452-02	10 mL	2
--------------	-------	---

44206-454-04	20 mL	4
--------------	-------	---

714

715 **16.2 Storage and Handling**

716 When stored at room temperature (up to 25°C [77°F]), Hizentra is stable for up to
717 30 months, as indicated by the expiration date printed on the outer carton and vial label.
718 DO NOT FREEZE. Do not use product that has been frozen. Do not shake. Keep
719 Hizentra in its original carton to protect it from light.

720

721

722 **17 PATIENT COUNSELING INFORMATION**

723

724 • **Self-administration** – If self-administration is appropriate, ensure that the patient
725 receives instructions and training on subcutaneous administration in the home or
726 other appropriate setting and has demonstrated the ability to perform
727 subcutaneous infusions.

- 728 • Ensure patients understand the importance of adhering to the weekly
729 administration schedule to maintain the steady levels of IgG in their blood.

- 730 • Instruct patients to keep their treatment diary/log book current by recording,
731 after each infusion, the time, date, dose, and any reactions, and by removing
732 the peel-off portion of the label (containing the lot number) from the product
733 vial and placing it in the treatment diary/log book.

- 734 • Tell patients that mild to moderate local (injection-site) reactions (e.g.,
735 swelling and redness) are a common side effect of subcutaneous therapy, but
736 to contact their healthcare professional if a local reaction persists for more
737 than a few days.

- 738 • Inform patients of the importance of having an infusion needle long enough to
739 reach the subcutaneous tissue and of changing the actual site of injection with
740 each infusion. Explain that Hizentra is for subcutaneous infusion only, and

- 741 must not be injected into a blood vessel. Make sure patients know how to
742 avoid blood vessels and check if the needle has entered a blood vessel.
- 743 • Inform patients to consider adjusting the injection-site location, volume per
744 site, and rate of infusion based on how infusions are tolerated.
745
 - 746 • **Dose adjustments** – Inform patients that they should be tested regularly to make
747 sure they have the correct levels of Hizentra (IgG) in their blood. These tests may
748 result in adjustments to the Hizentra dose.
749
 - 750 • **Hypersensitivity** – Inform patients of the early signs of hypersensitivity reactions
751 to Hizentra (including hives, generalized urticaria, tightness of the chest,
752 wheezing, hypotension, and anaphylaxis), and advise them to notify their
753 physician if they experience any of these symptoms.
754
 - 755 • **Thrombotic events** – Inform patients of the symptoms of a thrombotic or
756 embolic event, including shortness of breath, pain and swelling of a limb, focal
757 neurological deficits, changes in mental status, chest pain, and other
758 manifestations of thrombotic and embolic events.
759
 - 760 • **AMS** – Inform patients of the signs of AMS, including severe headache, neck
761 stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea,
762 and vomiting, and advise them to notify their physician if they experience any of
763 these symptoms.
764
 - 765 • **Interference with vaccines** – Inform patients that administration of IgG may
766 interfere with the response to live virus vaccines (e.g., measles, mumps, rubella,
767 and varicella) and to notify their immunizing physician of recent therapy with
768 Hizentra.
769
 - 770 • **Reactions reported to occur with immune globulin treatment** – Advise
771 patients to be aware of and immediately report to their physician symptoms of the
772 following potential reactions:
 - 773 • Decreased urine output, sudden weight gain, fluid retention/edema, and/or
774 shortness of breath, which may suggest kidney problems
 - 775 • Fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored
776 urine, which may suggest hemolysis
 - 777 • Severe breathing problems, lightheadedness, drops in blood pressure, and
778 fever, which may suggest TRALI (a condition typically occurring within 1 to
779 6 hours following transfusion)
 - 780
 - 781 • **Transmissible infectious agents** – Inform patients that Hizentra is made from
782 human plasma (part of the blood) and may contain infectious agents that can
783 cause disease (e.g., viruses and, theoretically, the CJD agent). Explain that the
784 risk that Hizentra may transmit an infectious agent has been reduced by screening

785 the plasma donors, by testing the donated plasma for certain virus infections, and
786 by inactivating and/or removing certain viruses during manufacturing.

787
788 The attached Hizentra “Information for Patients” contains more detailed instructions for
789 patients who will be self-administering Hizentra.

790

791

Hizentra

792

Immune Globulin Subcutaneous (Human), 20% Liquid

793

Information for Patients

794
795 This patient package insert summarizes important information about Hizentra. Please
796 read it carefully before using this medicine. This information does not take the place of
797 talking with your healthcare professional, and it does not include all of the important
798 information about Hizentra. If you have any questions after reading this, ask your
799 healthcare professional.

800

What is the most important information I should know about Hizentra?

801
802 Hizentra is supposed to be infused under your skin only. DO NOT inject Hizentra into a
803 blood vessel (vein or artery).

804

What is Hizentra?

805
806 Hizentra (Hi – ZEN – tra) is a prescription medicine used to treat primary immune
807 deficiency (PI). Hizentra is made from human plasma. It contains antibodies, called
808 immunoglobulin G (IgG), that healthy people have to fight germs (bacteria and viruses).

809

810 People with PI get a lot of infections. Hizentra helps lower the number of infections you
811 will get.

812

Who should NOT take Hizentra?

813
814 Do not take Hizentra if you have too much proline in your blood (called
815 “hyperprolinemia”) or if you have had reactions to polysorbate 80.

816

817 Tell your doctor if you have had a serious reaction to other immune globulin medicines
818 or if you have been told that you also have a deficiency of the immunoglobulin called
819 IgA.

820

821 Tell your doctor if you have a history of heart or blood vessel disease or blood clots, have
822 thick blood, or have been immobile for some time. These things may increase your risk
823 of having a blood clot after using Hizentra. Also tell your doctor what drugs you are
824 using, as some drugs, such as those that contain the hormone estrogen (for example, birth
825 control pills), may increase your risk of developing a blood clot.

826

How should I take Hizentra?

827
828 You will take Hizentra through an infusion, only under your skin. Make sure that the
829 infusion is not into a blood vessel. You will place up to 4 needles into different areas of

830 your body each time you use Hizentra. The needles are attached to a pump with an
831 infusion tube. It usually takes about 60 minutes to do one infusion. You will need to
832 have infusions once a week.

833
834 Instructions for using Hizentra are at the end of this patient package insert (see “How do I
835 use Hizentra?”). Do not use Hizentra by yourself until you have been taught how by your
836 doctor or healthcare professional.

837
838 **What should I avoid while taking Hizentra?**

839 Vaccines may not work well for you while you are taking Hizentra. Tell your doctor or
840 healthcare professional that you are taking Hizentra before you get a vaccine.

841
842 Tell your doctor or healthcare professional if you are pregnant or plan to become
843 pregnant, or if you are nursing.

844
845 **What are possible side effects of Hizentra?**

846 The most common side effects with Hizentra are:

- 847
- 848 • Redness, swelling, itching, and/or bruising at the injection site
 - 849 • Headache/migraine
 - 850 • Nausea and/or vomiting
 - 851 • Pain (including pain in the chest, back, joints, arms, legs)
 - 852 • Fatigue
 - 853 • Diarrhea
 - 854 • Stomach ache/bloating
 - 855 • Cough
 - 856 • Rash (including hives)
 - 857 • Itching
 - 858 • Fever and/or chills
 - 859 • Shortness of breath
 - 860 • Dizziness

861
862 Tell your doctor right away or go to the emergency room if you have hives, trouble
863 breathing, wheezing, dizziness, or fainting. These could be signs of a bad allergic
864 reaction.

865
866 Tell your doctor right away if you have any of the following symptoms. They could be
867 signs of a serious problem.

- 868
- 869 • Reduced urination, sudden weight gain, or swelling in your legs. These could be
870 signs of a kidney problem.
 - 871 • Pain, swelling, warmth, redness, or a lump in your legs or arms. These could be
872 signs of a blood clot.

- 873 • Numbness or weakness of an arm or leg or one side of your face. Sudden
874 confusion, or trouble speaking or understanding.
- 875 • Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light.
876 These could be signs of a brain swelling called meningitis.
- 877 • Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a
878 blood problem.
- 879 • Chest pains or trouble breathing.
- 880 • Fever over 100°F. This could be a sign of an infection.

881

882 Tell your doctor about any side effects that concern you. You can ask your doctor to give
883 you more information that is available to healthcare professionals.

884

885 **How do I use Hizentra?**

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

890

891 **Instructions for use**

892 Hizentra comes in single-use vials.

893

894 Keep Hizentra in the storage box at room temperature.

895

896 **Step 1: Assemble supplies**

897 Gather the Hizentra vial(s), the following disposable supplies (not provided with
898 Hizentra), and other items (infusion pump, sharps or other container, treatment diary or
899 log book):

900

- 901 Infusion administration tubing
- 902 Needle or catheter sets (for subcutaneous infusion)
- 903 Y-site connectors (if needed)
- 904 Alcohol wipes
- 905 Antiseptic skin preps
- 906 Syringes
- 907 Transfer needles
- 908 Gauze and tape, or transparent dressing
- 909 Gloves (if recommended by your doctor)

910

911 **Step 2: Clean surface**

912 Thoroughly clean a table or other flat surface using one of the alcohol wipes.

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Step 3: Wash hands

- Thoroughly wash and dry your hands (Figure 1).
- If you have been told to wear gloves when preparing your infusion, put the gloves on.

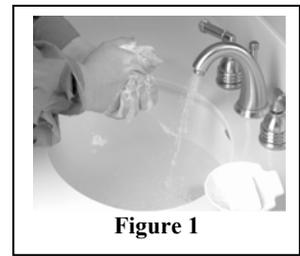


Figure 1

Step 4: Check vials

Carefully look at the liquid in each vial of Hizentra (Figure 2). It should look clear and be pale yellow to light brown. Check for particles or color changes. **Do not use the vial if:**



Figure 2

- The liquid looks cloudy, contains particles, or has changed color.
- The protective cap is missing.
- The expiration date on the label has passed.

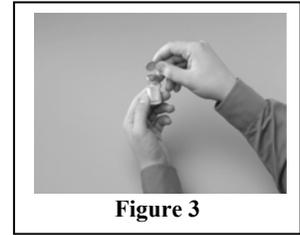


Figure 3

Step 5: Transfer Hizentra from vial(s) to syringe

- Take the protective cap off the vial (Figure 3).
- Clean the vial stopper with an alcohol wipe (Figure 4). Let the stopper dry.

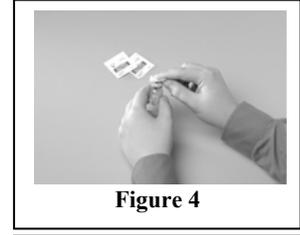


Figure 4

- Attach a sterile transfer needle to a sterile syringe (Figure 5).
- Pull out the plunger of the syringe to fill the syringe with air. The amount of air should be the same as the amount of Hizentra you will transfer from the vial.
- Put the Hizentra vial on a flat surface. Keeping the vial upright, insert the transfer needle into the center of the rubber stopper.
- Check that the tip of the needle is not in the liquid. Then, push the plunger of the syringe down. This will inject the air from the syringe into the airspace of the vial.
- Leaving the needle in the stopper, carefully turn the vial upside down (Figure 6).
- Slowly pull back on the plunger of the syringe to fill the syringe with Hizentra.

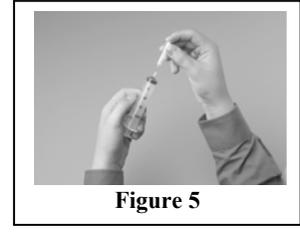


Figure 5

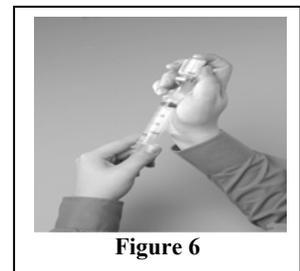


Figure 6

- 958 • Take the filled syringe and needle out of the stopper. Take off the
959 needle and throw it away in the sharps container.

960
961 When using multiple vials to achieve the desired dose, repeat this step.

962
963 **Step 6: Prepare infusion pump and tubing**

964 Prepare the infusion pump (following the manufacturer’s instructions) and
965 prime (fill) the infusion tubing. To prime the tubing, connect the syringe
966 filled with Hizentra to the infusion tubing and gently push on the syringe
967 plunger to fill the tubing with Hizentra (Figure 7).



Figure 7

968
969 **Step 7: Prepare injection site(s)**

- 970 • Select an area on your abdomen, thigh, upper arm, or side of upper
971 leg/hip for the infusion (Figure 8).
972 • Use a different site from the last time you infused Hizentra. New sites
973 should be at least 1 inch from a previous site.
974 • Never infuse into areas where the skin is tender, bruised, red, or hard.
975 Avoid infusing into scars or stretch marks.
976 • If you are using more than one injection site, be sure each site is at
977 least 2 inches apart.
978 • During an infusion, do not use more than 4 injection sites at the same
979 time.
980 • Clean the skin at each site with an antiseptic skin prep (Figure 9). Let
981 the skin dry.

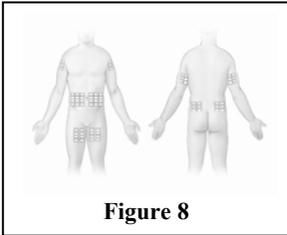


Figure 8

982
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984 **Step 8: Insert needle(s)**

- 985 • With two fingers, pinch together the skin around the injection site.
986 Insert the needle under the skin (Figure 10).

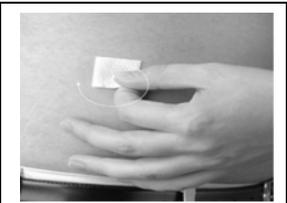


Figure 9

- 987
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990
991 • Put sterile gauze and tape or a transparent dressing over the injection
992 site (Figure 11). This will keep the needle from coming out.



Figure 10

- 993
994 • Make sure you are not injecting Hizentra into a blood vessel. To test
995 for this, attach a sterile syringe to the end of the infusion tubing. Pull
996 the plunger back gently (Figure 12). If you see any blood flowing
997 back into the tubing, take the needle out of the injection site. Throw
998 away the tubing and needle. Start the infusion over at a different site
999 with new infusion tubing and a new needle.

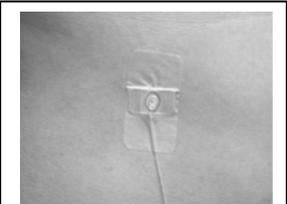


Figure 11

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1001



Figure 12

1002 **Step 9: Start infusion**

1003 Follow the manufacturer's instructions to turn on the infusion pump
 1004 (Figure 13).

1005
 1006

1007 **Step 10: Record treatment** (Figure 14)

1008 Peel off the removable part of the label of the Hizentra vial. Put this
 1009 label in your treatment diary or log book with the date and time of the
 1010 infusion. Also include the exact amount of Hizentra that you infused.

1011
 1012

1012 **Step 11: Clean up**

- 1013 • When all the Hizentra has been infused, turn off the pump.
 1014 • Take off the dressing and take the needle out of the injection site.
 1015 Disconnect the tubing from the pump.
 1016 • Throw away any Hizentra that is leftover in the single-use vial, along
 1017 with the used disposable supplies, in the sharps container (Figure 15).
 1018 • Clean and store the infusion pump, following the manufacturer's
 1019 instructions.

1020

1021 Be sure to tell your doctor about any problems you have doing your
 1022 infusions. Your doctor may ask to see your treatment diary or log book,
 1023 so be sure to take it with you each time you visit the doctor's office.

1024

1025 Call your doctor for medical advice about side effects. You can also
 1026 report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

1027

1028 Manufactured by:

1029 **CSL Behring AG**

1030 Bern, Switzerland

1031 US License No. 1766

1032

1033 Distributed by:

1034 **CSL Behring LLC**

1035 Kankakee, IL 60901 USA

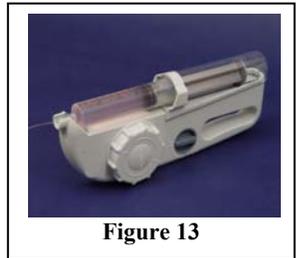


Figure 13

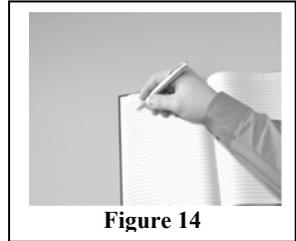


Figure 14

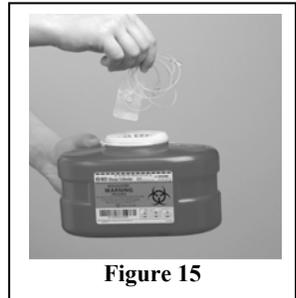


Figure 15