

1 **CSL Behring**

2

3

4 **Name of the medicinal product**

5 Privigen™

6 Human normal immunoglobulin

7 Solution for infusion (10%)

8 For intravenous use only

9

10

11 **Composition**

12 *a. Active substance*

13 Human immunoglobulin for intravenous use (IVIg)\*.

14 Human plasma protein containing at least 98% immunoglobulin G (IgG).

15

16 Distribution of the IgG subclasses (average values): IgG<sub>1</sub> 69%, IgG<sub>2</sub> 26%, IgG<sub>3</sub> 3%,

17 IgG<sub>4</sub> 2%.

18

19 The maximum IgA content is 25 micrograms/ml.

20

21 \*Produced from the plasma of human donors.

22

23 *b. Excipients*

24 L-proline, water for injections.

25

26 Privigen contains trace amounts of sodium ( $\leq 1$  mmol/l).

27

28 Privigen contains no preservatives.

29

30 Privigen contains no carbohydrate stabiliser (e.g. sucrose, maltose).

31

32 *Pharmacotherapeutic group*

33 Immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular

34 administration.

35 ATC code:

36 J06BA02

37

38

39 **Pharmaceutical form and active substance content per unit**

40 Solution for intravenous infusion.

41

42 1 ml of solution contains: 100 mg human plasma protein with an IgG content of at least 98%

43 (10% solution).

44

45 The solution is clear to slightly opalescent and colourless to pale yellow. Privigen is isotonic,

46 with an osmolality of 320 mOsmol/kg.

47

48 The pH value of the ready-to-use solution is 4.6 to 5.0 [4.8].

49

50 Therapeutic indications

51 Replacement therapy in

51 · *Primary immunodeficiency syndromes (PID) such as:*

52 – congenital agammaglobulinaemia and hypogammaglobulinaemia

53 – common variable immunodeficiency

54 – severe combined immunodeficiency

55 – Wiskott-Aldrich syndrome

- Secondary immunodeficiencies (SID) in patients with severe or recurrent infections, ineffective antimicrobial treatment, and either a confirmed inadequate increase of antibodies from vaccinations (PSAF\*) or serum IgG levels of <4g/L.

*PSAF (proven specific antibody failure) = absence of at least a two-fold rise in the IgG antibody concentration against pneumococcal polysaccharide and polypeptide antigen vaccines.*

64 Immunomodulation

- 65 · *Immune thrombocytopenic purpura (ITP) in children or adults at high risk of bleeding*
- 66 *or prior to surgical interventions to correct the platelet count*
- 67 · *Guillain-Barré syndrome*
- 68 · *Kawasaki disease*
- 69 · *Chronic inflammatory demyelinating polyneuropathy (CIDP)*
  - *Multifocal motor neuropathy (MMN)*

71

72 Allogeneic bone marrow transplantation

73

74

75 **Dosage/Administration**

76 ***Dosage***

77 The dosage and dosage regimen is dependent on the indication. In replacement therapy the  
78 dosage may need to be individualised for each patient depending on the clinical response.

79 The following dosage regimens are given as a guideline.

80

81 Replacement therapy in primary immunodeficiency syndromes

82 The dosage regimen should achieve a trough IgG level (measured before the next infusion) of  
83 at least 5 to 6 g/l. Three to 6 months are required after the initiation of therapy for  
84 equilibration to occur. The recommended starting dose is 0.4 to 0.8 g/kg body weight (bw)  
85 followed by at least 0.2 g/kg bw every 3 to 4 weeks.

86 The dose required to achieve a trough level of 5 to 6 g/l is of the order of 0.2 to  
87 0.8 g/kg bw/month. The dosage interval when steady state has been reached varies from 3 to  
88 4 weeks. Trough levels should be measured in order to adjust the dose and dosage interval.

89

90 Secondary immunodeficiencies (SIDs)

91 The recommended dose is 0.2 to 0.4 g/kg bw every 3 to 4 weeks.

92 IgG trough levels should be measured and assessed in conjunction with the incidence of infection  
The dose should be adapted as necessary to achieve optimum protection against infections.

93 A dose increase may be required in patients with persistent infection; a dose reduction may be  
considered if the patient remains infection-free. .

94

95 Immune thrombocytopenic purpura

96 For the treatment of an acute episode, 0.8 to 1 g/kg bw on day one, which may be repeated

97 once within 3 days, or 0.4 g/kg bw daily for 2 to 5 days. The treatment can be repeated if  
98 relapse occurs (see also section “Properties/Effects”).

99

100 Guillain-Barré syndrome

101 0.4 g/kg bw/day over 5 days. Experience in children is limited.

102

103 Kawasaki disease

104 1.6 to 2.0 g/kg bw should be administered in divided doses over 2 to 5 days or 2.0 g/kg bw as

105 a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

106

107 Chronic inflammatory demyelinating polyneuropathy (CIDP)

108 The recommended starting dose is 2 g/kg bw divided over 2 to 5 consecutive days followed  
109 by maintenance doses of 1 g/kg bw given on one day or divided over 2 consecutive days  
110 every 3 weeks.

111 The long-term therapy over 25 weeks depends on the patient's response to the maintenance  
112 therapy. The lowest effective maintenance dose and the dosage regimen are to adjust  
113 according to the individual course of the disease.

115 Multifocal motor neuropathy (MMN)

116 Starting dose: 2 g/kg bw over 2 to 5 consecutive days  
117 Maintenance dose: 1 g/kg bw every 2 to 4 weeks or 2 g/kg bw every 4 to 8 weeks. Treatment  
should be discontinued if the therapeutic response seen after 6 months is insufficient. If  
treatment is effective, the physician should evaluate the necessity of long-term treatment based  
on the patient's response. The dosage and the intervals may have to be adapted according to the  
individual course of disease

118 Allogeneic bone marrow transplantation

119 Human immunoglobulin therapy can be used as part of the conditioning regimen and after  
120 transplantation. To treat infections and prevent graft-versus-host disease, the dosage should be  
121 individually adjusted.

122 The starting dosage is usually 0.5 g/kg bw/week, commencing seven days before the  
123 transplant. The treatment is continued for up to 3 months after the transplant. If the lack of  
124 antibody production persists, a dosage of 0.5 g/kg bw/month is recommended until IgG  
125 antibody levels return to normal.

123

124

125 The dosages recommendations are summarised in the following table:

126

Indications	Dose	Intervals between injections
<u>Replacement therapy in</u>  <i>primary immunodeficiency syndromes</i>       <i>secondary immunodeficiency syndromes</i>	starting dose: 0.4-0.8 g/kg bw  thereafter: 0.2-0.8 g/kg bw    0.2-0.4 g/kg bw	every 3-4 weeks to obtain IgG trough levels of at least 5-6 g/l       every 3-4 weeks to obtain IgG trough levels of at least 5-6 g/l
<u>Immunomodulation</u>  <i>Immune thrombocytopenic purpura</i>	0.8-1 g/kg bw       or  0.4 g/kg bw/day	on the first day; the therapy may be repeated once within 3 days       over 2-5 days

*Guillain-Barré syndrome*

0.4 g/kg bw/day

over 5 days

*Kawasaki disease*

1.6-2 g/kg bw

divided into several doses given over 2-5 days in conjunction with acetylsalicylic acid

or

2 g/kg bw

as a single dose in conjunction with acetylsalicylic acid

*Chronic inflammatory demyelinating polyneuropathy (CIDP)*

starting dose:

2 g/kg bw

in divided doses over 2-5 days

maintenance dose:

1 g/kg bw

every 3 weeks over 1-2 days

<u>Allogeneic bone marrow transplantation</u> – treatment of infections and prevention of graft-versus-host disease  – persistent lack of antibody production	0.5 g/kg bw    0.5 g/kg bw	weekly, from day 7 before up to 3 months after the transplant   monthly, until antibody levels return to normal
Multifocal motor neuropathy (MMN)	Starting dose: 2g/kg bw  Maintenance dose: 1g/kg bw or  2g/kg bw	Over 2 to 5 consecutive days  Every 2 to 4 weeks  Every 4 to 8 weeks over 2 to 5 days

127 bw = body weight

128

129 Use of the product in paediatric population

130 In the phase III pivotal study on patients with primary immunodeficiency diseases (n = 80),

131 19 patients between 3 and 11 years of age and 15 patients from 12 up to and including 18

132 years of age were treated. In an extension study of patients with primary immunodeficiency

133 diseases (n = 55), 13 patients between 3 and 11 years of age and 11 between 12 and including

134 18 years of age were treated.

135 In the clinical study on 57 patients with chronic immune thrombocytopenic purpura 2

136 paediatric patients (15 and 16 years of age) were treated. No dose adjustment for children was

137 required in these three studies.

138 Literature reports indicate that intravenous immunoglobulins are effective in children with

139 CIDP. However, no data is available on Privigen in this respect.

140

141 ***Method of administration***

142 Privigen should be infused intravenously.

143

144 **Rate of infusion**

145 The product should initially be infused at a rate of 0.3 ml/kg bw/hr (for approximately 30

146 min). If well tolerated, the infusion rate can be gradually increased to 4.8 ml/kg bw/hr. In

147 patients with immunodeficiency syndrome who have tolerated substitution treatment with

148 Privigen well, the infusion rate may be gradually increased to a maximal value of 7.2 ml/kg

149 bw/hr.

150

151

152 **Contraindications**

153 Hypersensitivity to the active substance or the excipient (see section “Composition”).

154 Hypersensitivity to human immunoglobulins, especially in patients with IgA deficiency where  
155 the patient has anti-IgA antibodies.

156 Hyperprolinaemia. Hyperprolinaemia is a very rare disease, which affects only a few families  
157 worldwide.

158

159

## 160 **Warnings and precautions for use**

161

162 Certain severe adverse reactions may be related to the rate of infusion. The recommended  
163 infusion rate given under section “Dosage/Administration: *Method of administration*” must be  
164 closely followed. Patients must be closely monitored and carefully-observed for any  
167 symptoms (see sections “Warnings and precautions” and “Undesirable effects”).

168 Certain adverse reactions may occur more frequently:

- 169 – in case of high rate of infusion,
- 170 – in patients with hypogammaglobulinaemia or agammaglobulinaemia, with or without  
171 IgA deficiency,
- 172 – in patients who receive human normal immunoglobulin for the first time or, in rare  
173 cases, when the human normal immunoglobulin product is switched or when there has  
174 been a long interval since the previous infusion.

174

175 Potential complications can often be avoided by ensuring that patients:

- 176 – are not sensitive to human normal immunoglobulin by initially infusing the product  
177 slowly (0.3 ml/kg bw/hr);
- 178 – are carefully monitored for any symptoms throughout the infusion period. In particular,  
179 patients, naive to human normal immunoglobulin, switched from an alternative IVIg  
180 product or when there has been a long interval since the previous infusion, should be

181 monitored during the first infusion and for the first hour after the first infusion, in order  
182 to detect potential adverse signs. All other patients should be observed for at least 20  
183 minutes after administration.

184

185 In case of adverse reaction, either the rate of administration must be reduced or the infusion  
186 stopped . (see sections “Warnings and precautions” and “Undesirable effects”). The treatment  
required depends on the nature and severity of the adverse reaction.

187 In case of shock, standard medical treatment for shock should be implemented.

188

189 Higher doses may be associated with increased rates of adverse effects. Therefore, the lowest  
190 effective dose should be sought in individual patients and careful monitoring routine is to  
191 establish.

192

193 In all patients, IVIg administration requires adequate hydration prior to the initiation of the  
194 infusion.

195

#### 196 Hypersensitivity

197 True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

198 IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the  
199 only abnormality of concern.

200

201 Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactoid  
202 reaction, even in patients who had tolerated previous treatment with human normal  
203 immunoglobulin.

204

#### 205 Haemolytic anaemia

206 IVIg products can contain blood group antibodies (e.g. anti-A and anti-B) which may act as  
207 haemolysins and induce in vivo coating of red blood cells (RBC) with immunoglobulin,  
208 causing a positive direct antiglobulin reaction (Coombs` test) and, rarely, haemolysis.

209 Haemolytic anaemia (see sections “Undesirable effects” and “Properties/Effects”) . can develop  
subsequent to IVIg therapy due to enhanced RBC

210 sequestration. The Privigen manufacturing process includes an immunoaffinity

211 chromatography (IAC) step that specifically reduces blood group A and B antibodies

212 (isoagglutinins A and B). Clinical data with Privigen manufactured with the IAC show

213 statistically significant reductions of haemolytic anaemia (see section “Undesirable effects”).  
214

215 Isolated cases of haemolysis-related renal dysfunction/renal failure or disseminated  
216 intravascular coagulation in some cases leading to death have occurred.

217 The following risk factors are associated with the development of haemolysis: high doses,  
218 whether given as a single administration or divided over several days; blood group A, B and  
219 AB (non-0 blood group) and underlying inflammatory state. As this event was commonly  
220 reported in patients with blood group A, B or AB (non-0 blood group) receiving high doses  
221 for non-PID indications, increased vigilance is recommended.

222 Haemolysis has rarely been reported in patients given replacement therapy for PID.

223 IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. If signs  
224 and/or symptoms of haemolysis develop during or after IVIg infusion, discontinuation of IVIg  
225 treatment should be considered by the treating physician (see also section “Undesirable  
226 effects”).

227

#### 228 Aseptic meningitis syndrome (AMS)

229 Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment (see  
section “Undesirable effects”).

230 The syndrome usually begins within several hours to 2 days following IVIg treatment. Patients  
should be informed of the early symptoms such as severe headache, nuchal rigidity, drowsiness,  
fever, photophobia, nausea and vomiting. Patients exhibiting such symptoms should receive a  
thorough neurological examination, including cerebrospinal fluid studies, to rule out other causes of  
meningitis. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several  
thousand cells per mm<sup>3</sup> (predominantly from the granulocytic series) and elevated protein levels up  
to several hundred mg/dl.

231 AMS may occur more frequently in association with high-dose ( $\geq 2$  g/kg) IVIg treatment and/or  
rapid infusion (see section “Dosage/Administration” and “Warnings and precautions”).  
Discontinuing treatment led to remission of the AMS within a few days, without sequelae. Patients  
with a recurrence of AMS in association with IVIg treatment should be monitored for the  
emergence or worsening of symptoms potentially progressing to brain oedema (cerebral oedema).

#### 237 Thromboembolism

238 There is clinical evidence of an association between IVIg administration and thromboembolic  
239 events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary  
240 embolism and deep vein thromboses which is assumed to be related to a relative increase in  
241 blood viscosity through the high influx of immunoglobulins in at-risk patients. Therefore  
242 caution should be exercised in prescribing and infusing IVIg in obese patients and in patients  
243 with pre-existing risk factors for thrombotic events (such as advanced age, hypertension,  
244 diabetes mellitus, a history of vascular disease or thrombotic episodes, acquired or inherited  
245 thrombophilic disorders, prolonged periods of immobilisation, severe hypovolaemia, diseases

246 which increase blood viscosity).

247

248 In patients at risk for thromboembolic reactions, IVIg products should be administered at the

249 minimum rate of infusion and minimum dose practicable based on clinical judgement.

250

251 Acute renal failure

252 Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most

253 cases risk factors have been identified e.g. pre-existing renal insufficiency, diabetes mellitus,

254 hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

255

256 In case of renal impairment, IVIg discontinuation should be considered.

257 While these reports of renal dysfunction and acute renal failure have been associated with the  
258 use of many of the licensed IVIg products containing various excipients such as sucrose,  
259 glucose and maltose those containing sucrose as a stabiliser accounted for a disproportionate  
260 share of the total number. In patients at risk, the use of IVIg products that do not contain  
261 sucrose should therefore be considered. Privigen does not contain sucrose, maltose or glucose.  
262

263 In patients at risk of acute renal failure, IVIg products should be administered at the minimum  
264 rate of infusion and minimum dose practicable based on clinical judgement.  
265

#### 266 Transfusion-related acute lung injury (TRALI)

267 Noncardiogenic pulmonary edema may very rarely occur following treatment with IVIg  
268 products. TRALI is characterized by severe respiratory distress, pulmonary edema,  
269 hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1  
270 to 6 hours following treatment.

271 Monitor patients for pulmonary adverse reactions. TRALI may be managed using oxygen  
272 therapy with adequate ventilatory support.  
273

#### 274 Pathogen safety

275 Privigen is made from human plasma. Standard measures to prevent infections resulting from  
276 the use of medicinal products prepared from human blood or plasma include selection of  
277 donors, screening of individual donations and plasma pools for specific markers of infection  
278 and the inclusion of effective manufacturing steps for the inactivation/removal of viruses (see  
279 also section “Properties/Effects”). Despite this, when medicinal products prepared from  
280 human blood or plasma are administered, the possibility of transmitting infective agents  
281 cannot be totally excluded. This also applies to unknown or emerging viruses and other  
282 pathogens.

283

284 The measures taken are considered effective for enveloped viruses such as human  
285 immunodeficiency (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), and for the  
286 non-enveloped viruses such as hepatitis A (HAV) and parvovirus B19.

287

288 There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19  
289 transmission with immunoglobulins, and it is also assumed that the antibody content makes an  
290 important contribution to the viral safety.

291

292 It is recommended that every time Privigen is administered to a patient, the name and batch  
293 number of the product are recorded in order to maintain a link between the patient and the  
294 batch of the product.

295

#### 296 Sodium content

297 Privigen is essentially sodium-free (Privigen has a low sodium content of  $\leq 1$  mmol/l).

298

#### 299 **Paediatric population**

300 Although limited data is available, it is expected that the same warnings, precautions and risk  
301 factors apply to the paediatric population.

302

303

#### 304 **Interactions**

305

##### 306 *Live attenuated virus vaccines*

307 After treatment with immunoglobulins, the efficacy of live attenuated vaccines, such as  
308 measles, mumps, rubella and chickenpox vaccines, may be impaired for a period of at least 6  
309 weeks and up to 3 months. An interval of 3 months should elapse before vaccination with live  
310 attenuated vaccines. In the case of measles vaccinations, the decrease in efficacy may persist  
311 for up to a year. Patients given measles vaccine should therefore have their antibody status  
312 checked.

313

##### 314 *Paediatric population*

315 Although limited data is available, it is expected that the same interactions may occur in the  
316 paediatric population.

317

318

319 **Pregnancy, breast-feeding and fertility**

320 *Pregnancy*

321 Controlled clinical data on the use of Privigen in pregnant women are not available. Caution  
322 should therefore be exercised with regard to administration during pregnancy. IVIg products  
323 have been shown to cross the placenta, increasingly during the third trimester.

324

325 Extensive clinical experience of immunoglobulins suggests that no harmful effects on the  
326 course of the pregnancy, or on the foetus and the newborn child are to be expected.

327

328 Experimental studies of the excipient L-proline carried out in animals found no direct or  
329 indirect toxicity affecting pregnancy, embryonal or foetal development.

330

331 ***Breast-feeding***

332 Immunoglobulins are excreted into the milk and may contribute to protecting the neonate  
333 from pathogens which have a mucosal portal of entry.

334

335 ***Fertility***

336 Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to  
337 be expected.

338

339

340 **Effect on driving and the operation of machines**

341 The ability to drive and operate machines may be impaired by some adverse reactions  
342 associated with Privigen. Patients who experience adverse reactions during treatment should  
343 wait for these to resolve before driving or operating machines.

344

345

346 **Undesirable effects**

347 Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions,  
348 nausea, arthralgia, low blood pressure, and moderate back pain may occur occasionally in  
349 connection with intravenous administration of human immunoglobulin.

350

351 Rarely human immunoglobulin may cause hypersensitivity reactions with a sudden fall in  
352 blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no  
353 hypersensitivity to previous administration (see section “Warnings and precautions”).

355 Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have  
356 been observed with human normal immunoglobulin (see section “Warnings and precautions”).

358 Reversible haemolytic reactions have been observed in patients, especially those with blood  
359 groups A, B, and AB (non-0-blood groups) in immunomodulatory treatment. Rarely,  
360 haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see  
361 section “Warnings and precautions”).

362

363 Increase in serum creatinine levels and/or acute renal failure have been observed (see section  
364 “Warnings and precautions”).

365 Very rarely: transfusion related acute lung injury and thromboembolic reactions such as  
366 myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis have occurred  
(see section “Warnings and precautions”).

368 ***Tabulated list of adverse reactions***

369 Seven clinical studies were performed with Privigen, which included patients with PID, ITP  
370 and CIDP patients respectively. In the PID pivotal study, 80 patients were enrolled and  
371 treated with Privigen. Of these, 72 completed the 12 months of treatment. In the PID  
372 extension study, 55 patients were enrolled and treated with Privigen. Another clinical study  
373 included 11 PID patients in Japan. Two ITP studies were performed with 57 patients each.  
374 Two CIDP studies were performed with 28 and 207 patients, respectively.

375

376 Most adverse drug reactions (ADRs) observed in the seven clinical studies were mild to  
377 moderate in nature.

378

379 The following table shows an overview of the ADRs in the seven studies, categorized  
380 according to MedDRA System Organ Class (SOC and Preferred Term Level (PT)) and  
381 frequency. Frequencies per infusion were evaluated according to the adverse reaction and frequency.

382 Frequency convention: Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq$   
383  $1/1,000$  to  $< 1/100$ ). For

384 spontaneous post-marketing ADRs, the reporting frequency is categorized as unknown.

385

386 Within each frequency grouping, undesirable effects are presented in order of decreasing  
frequency.

<b>MedDRA System Organ Class</b>	<b>Adverse Reaction/ MedDRA Term</b>	<b>ADR frequency category</b>
Blood and lymphatic system disorders	Anaemia, haemolysis (including haemolytic anaemia)*, leukopenia	Common
	Anisocytosis (including microcytosis), thrombocytosis	Uncommon
	Decreased neutrophil count	Unknown

Immune system disorders	Hypersensitivity	Common
	Anaphylactic shock	Unknown
Nervous system disorders	Headaches (including sinus headache, migraine, head discomfort, tension headache)	Very common
	Dizziness (including vertigo)	Common
	Somnolence, tremor, aseptic meningitis (AMS), dysaesthesia	Uncommon
Cardiac disorders	Palpitations, tachycardia	Uncommon
Vascular disorders	Hypertension, flushing (including hot flush, hyperaemia), hypotension	Common
	Thromboembolic events, vasculitis (including peripheral vascular disorder)	Uncommon
	Transfusion related acute lung injury	Unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea (including chest pain, chest discomfort, painful respiration)	Common
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain	Common
Hepatobiliary disorders	Hyperbilirubinaemia	Common
Skin and subcutaneous tissue disorders	Skin disorder (including rash, pruritus, urticaria, maculo-papular rash, erythema, skin exfoliation)	Common
Musculoskeletal and connective tissue disorders	Myalgia (including muscle spasms, musculoskeletal stiffness,	Common

	muscuskeletal pain)	
Renal and urinary disorders	Proteinuria, increased blood creatinine	Uncommon
	Acute renal failure	Unknown

General disorders and administration site conditions	Pain (including back pain, pain in extremity, arthralgia, neck pain, facial pain), pyrexia (including chills), influenza like illness (including nasopharyngitis, pharyngolaryngeal pain, oropharyngeal blistering, throat tightness)	Very Common
	Fatigue, asthenia (including muscular weakness)	Common
	Injection site pain (including infusion site discomfort)	Uncommon
Investigations	Decreased haemoglobin (including decreased red blood cell count, decreased haematocrit), Coombs' (direct) test positive, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood lactate dehydrogenase	Common

388

389 \* The frequency is calculated based on studies completed prior to implementation of the Immuno-Affinity  
390 Chromatography isoagglutinin reduction step (IAC) into Privigen production. In a Post-Authorization Safety  
391 Study (PASS) assessing: “Privigen® Use and Haemolytic Anaemia in Adults and Children and the Privigen®  
392 Safety Profile in Children with CIDP – An Observational Hospital-Based Cohort Study in the US”, data of 7,759  
393 patients who received Privigen identifying 4 haemolytic anaemia cases after IAC versus 9,439 patients who  
394 received Privigen identifying 47 haemolytic anaemia cases prior to IAC (baseline) showed a 89% statistically  
395 significant reduction in the overall rate of probable haemolytic anaemia based on an incidence rate ratio of 0.11  
396 adjusted for in-/outpatient setting, age, sex, Privigen dose and indication for Privigen use (one-sided p-value  
397 <0.01).

398

399 Paediatric Population

400 In Privigen clinical studies with paediatric patients, the frequency, nature and severity of  
401 adverse reactions did not differ between children and adults. In postmarketing reports it is  
402 observed that the proportion of haemolysis cases to all case reports occurring in children is

403 slightly higher than in adults. Please refer to section "Warnings and precautions" for details  
404 on risk factors and monitoring recommendations.

405

#### 406 ***Reporting of suspected adverse reactions***

407 Reporting suspected adverse reactions after authorisation of the medicinal product is  
408 important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

409 Healthcare professionals are asked to report any suspected adverse reactions.

410

#### 411 **Overdose**

412 Overdose can lead to fluid volume overload and hyperviscosity, particularly in patients at  
413 risk, including elderly patients or patients with cardiac or renal impairment.

414

415

#### 416 **Properties/Effects**

417

#### 418 **Mechanism of Action/Pharmacodynamics**

419 Privigen is prepared from plasma from 1000 or more human donors. The manufacturing  
420 process for Privigen includes the following steps: ethanol precipitation of the IgG plasma

421 fraction, followed by octanoic acid fractionation and incubation at pH 4. Subsequent

422 purification steps comprise depth filtration, chromatography, immunoaffinity chromatography

423 to specifically reduce blood group A and B antibodies (isoagglutinins A and B), see sections "Undesirable  
424 effects and "Clinical efficacy" and a filtration step that can remove particles to a size of 20 nm.

424 Privigen contains mainly (IgG) that are present in the normal human population and that show

425 a broad spectrum of functionally intact antibodies against infectious agents. In the

426 replacement therapy adequate doses of Privigen may restore abnormally low IgG levels to the

427 normal range and thus help against infections.

428 The IgG subclass distribution in Privigen corresponds roughly to that of native human plasma.

429 Both the Fc and the Fab functions of the IgG molecules are preserved. The ability of the Fab  
430 parts to bind antigens was demonstrated with biochemical and biological methods. The Fc  
431 function was tested with complement activation and with Fc receptor-mediated leukocyte  
432 activation. The inhibition of immune complex-induced complement activation (“scavenging”,  
433 an anti-inflammatory function of IVIGs) is preserved in Privigen. Privigen does not lead to  
434 non-specific activation of the complement system or of prekallikrein.  
436

437 The mechanism of action in indications other than replacement therapy is not fully elucidated,  
438 but includes immunomodulatory effects.  
439

#### 440 **Clinical Efficacy**

441 The safety and efficacy of Privigen was investigated in 7 prospective, open, single-arm,  
442 multicentre studies carried out in Europe (ITP, PID and CIDP studies), Japan (PID and CIDP  
443 study), and in the US (PID and CIDP study). Further data on safety and efficacy were  
444 collected in a prospective, open, single-arm, multicentre extension study with PID patients  
445 performed in the US.

446

#### 447 PID

448 In the pivotal study, 80 patients between 3 and 69 years of age with PID were given a  
449 Privigen infusion at a median dose of 200-888 mg/kg bw every 3 to 4 weeks for at most 1  
450 year. With this treatment, constant IgG trough levels were achieved over the whole of the  
451 treatment period, the mean concentrations being 8.84 g/l to 10.27 g/l. The incidence of acute,  
452 severe bacterial infections (aSBI) was 0.08 per patient per year (the upper 97.5% confidence  
453 limit was 0.182).

454 As in the pivotal study, Privigen dosages were administered in the PID extension study to a  
455 total of 55 patients (of which 45 had already been treated in the pivotal study and 10 were  
456 newly recruited patients). The results of the pivotal study were confirmed for the average IgG  
457 trough levels (9.31 g/l to 11.15 g/l) and the rate of aSBI (0.018 per patient per year with an  
458 upper 97.5 % confidence interval of 0.098).

459

#### 460 ITP

461 57 patients aged between 15 and 69 years with chronic ITP took part in the ITP study. Their  
462 platelet count at the start was  $20 \times 10^9/l$ . After administration of Privigen at a dose 1 g/kg bw

463 on two consecutive days, the platelet count rose to at least  $50 \times 10^9/l$  within 7 days of the first  
464 infusion in 80.7% of the patients. In 43% of the patients, this increase occurred after just one  
465 day, before the second infusion. The mean time until this platelet count was reached was 2.5  
466 days. In patients who responded to the treatment, the platelet count remained  $\geq 50 \times 10^9/l$  for a  
467 mean period of 15.4 days.

468

469 In the second ITP study on patients aged between 18 and 65 years, in 42 subjects (74%) the  
470 platelet count increased at least once to  $\geq 50 \times 10^9/l$  within 6 days after the first infusion,  
471 which was well within the expected range and similar to response rates were reported for

472 other IVIGs in this indication (70%). A second dose in subjects with platelet counts  $\geq 50 \times 10^9/l$   
473 after the first dose provided a relevant additional benefit in terms of higher and longer-lasting  
474 increases in platelet counts compared to a single dose. In subjects with platelet counts  $< 50 \times$   
475  $10^9/l$  on day 3 receiving a mandatory second infusion, the lowest median platelet count  
476 ( $8.0 \times 10^9/l$ ) was observed already at the baseline. In this group, only 30% of subjects were  
477 observed with platelet response after the mandatory second dose. Consequently, it was more  
478 difficult to increase platelet counts with one infusion in these subjects.

479

#### 480 CIDP

481 In the first CIDP study, a prospective multicenter open label trial PRIMA (Privigen impact  
482 on mobility and autonomy study), 28 patients with CIDP (13 subjects with and 15 without  
483 IVIg pre-treatment) were treated with a loading dose of 2 g/kg bw given over 2-5 days  
484 followed by 6 maintenance doses of 1 g/kg bw given over 1-2 days every 3 weeks. Previously  
485 treated patients were withdrawn from IVIg before treatment with Privigen until the  
486 deterioration of clinical symptoms was confirmed on the basis of the INCAT scale  
487 (Inflammatory Neuropathy Cause and Treatment). On the adjusted 10 point INCAT scale a  
488 clinically meaningful improvement of at least 1-point from baseline to treatment week 25 was  
489 observed in 17 / 28 patients (60.7%, 95% confidence interval 42.41, 76.4). Nine patients  
490 responded already after receiving the initial induction dose to the treatment at week 4 and 16  
491 by week 10.

492

493 In a second clinical study, a prospective, multicenter randomized, placebo-controlled PATH  
494 [Polyneuropathy and Treatment with Hizentra] study, 207 subjects with CIDP were treated  
495 with Privigen in the prerandomization phase of the study. Subjects all with IVIg pretreatment  
496 of at least 8 weeks and an IVIg-dependence confirmed by clinically evident deterioration

497 during an IVIg withdrawal phase of up to 12 weeks, received a Privigen loading dose of  
498 2 g/kg bw followed by up to 4 Privigen maintenance doses of 1 g/kg bw every 3 weeks for up  
499 to 13 weeks.

500 Following clinical deterioration during IVIg withdrawal, clinical improvement of CIDP was  
501 primarily defined by a decrease of  $\geq 1$  point at the adjusted INCAT score. Additional  
502 measures of CIDP improvement were an R-ODS increase of  $\geq 4$  points, a mean grip strength  
503 increase of  $\geq 8$  kPa, or an MRC sum score increase of  $\geq 3$  points. Overall, 91 % of subjects  
504 (188 patients) showed improvement in at least one of the criteria above by week 13.

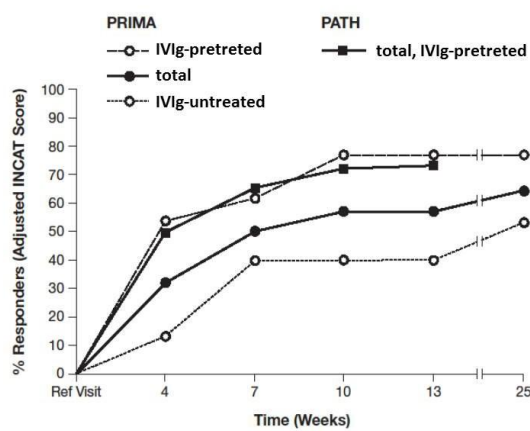
505 By adjusted INCAT score, the responder rate by week 13 was 72.9 % (151 / 207 patients),  
506 with 149 patients responding already by week 10. A total of 43 of the 207 patients achieved a

507 better CIDP status as assessed by the adjusted INCAT score compared to their CIDP status at  
508 study entry.

509 The comparability of the response rates and mean adjusted INCAT scores for the IVIg  
510 pretreated subjects in both PRIMA and PATH study are shown in the Figure 1 below.  
511

512 **Figure 1. Percentage of Responders (Adjusted INCAT Score)**

513



514

515 IVIg: intravenous immunoglobulin; Ref Visit: reference visit

516

517 The mean improvement at the end of the treatment period compared to reference visit was  
518 1.4 points in the PRIMA (1.8 points in IVIg pretreated subjects) and 1.2 points in PATH  
519 study.

520

521 In PRIMA, the percentage of responders in the overall Medical Research Council (MRC)

522 score (defined as an increase by  $\geq 3$  points) was 85 % (87 % in the IVIg-untreated and 82 %  
523 in IVIg-pretreated) and 57 % in PATH. The overall median time to first MRC sum score  
524 response in PRIMA was 6 weeks (6 weeks in the IVIg-untreated and 3 weeks in the IVIg-  
525 pretreated) and 9.3 weeks in PATH. MRC sum score in PRIMA improved by 6.9 points  
526 (7.7 points for IVIg-untreated and 6.1 points for IVIg-pretreated) and by 3.6 points in PATH.  
527 The grip strength of the dominant hand improved by 14.1 kPa (17.0 kPa in IVIg-untreated and  
528 10.8 kPa in IVIg pretreated subjects) in the PRIMA study, while in PATH the grip strength of  
529 the dominant hand improved by 12.2 kPa. For the non-dominant hand similar results were  
530 observed in both studies, PRIMA and PATH.  
531

532 The efficacy and safety profile in the PRIMA and the PATH study in CIDP patients were  
533 overall comparable.

534

### 535 *Paediatric population*

536 No differences were observed in the pharmacodynamic properties and safety profile between  
537 adult and paediatric study patients.

538

### 539 **Pharmacokinetics**

540 Privigen is immediately and completely bioavailable in the recipient's circulation after  
541 intravenous administration. It is distributed relatively quickly between plasma and  
542 extravascular fluid. Equilibrium between the intravascular and extravascular compartments is  
543 reached after approximately 3 to 5 days.

544

545 IgG and IgG complexes are broken down in the cells of the reticuloendothelial system. The half-life  
546 may vary from patient to patient.

547

548 The pharmacokinetic parameters for Privigen were determined in both clinical studies in  
549 patients with primary immunodeficiency syndrome (see section "Properties/Effects"). 25  
550 patients (aged 13 to 69 years) in the pivotal study and 13 patients (aged 9 to 59 years) in an  
551 extension of this study participated in the pharmacokinetic (PK) assessment (see table below).

552

### 553 **Pharmacokinetic parameters of Privigen in patients with primary immunodeficiency** 554 **syndrome**

555

Parameter	Pivotal study (N=25)	Extension study (N=13)

	<b>Median (range)</b>	<b>Median (range)</b>
C <sub>max</sub> (peak level) in g/l	23.4 (10.4-34.6)	26.3 (20.9-32.9)
C <sub>min</sub> (trough level) in g/l	10.2 (5.8-14.7)	9.75 (5.72-18.01)
t <sub>1/2</sub> (half-life) in days	36.6 (20.6-96.6)	31.1 (14.6-43.6)

556 C<sub>max</sub>, maximum serum concentration; C<sub>min</sub>, trough (minimum level) serum concentration; t<sub>1/2</sub>, elimination half-life.

557

558 In the pivotal study the median half-life of Privigen in primary immunodeficiency patients

559 was 36.6 days and 31.1 days in the extension of this study.

560

561 ***Paediatric population***

562 No differences were seen in the pharmacokinetic parameters between adult and paediatric  
563 study patients with PID. There are no data on pharmacokinetic properties in paediatric  
564 patients with CIDP.

565

#### 566 **Preclinical data**

567 The safety of Privigen has been investigated in several preclinical studies with particular  
568 reference to the excipient L-proline. L-proline is a physiological, non-essential amino acid.  
569 Studies in rats given daily L-proline doses of 1450 mg/kg bw did not show any evidence of  
570 teratogenicity or embryotoxicity. Genotoxicity studies of L-proline did not show any  
571 pathological findings.

572

573 Some published studies pertaining to hyperprolinaemia have shown that long-term, high doses  
574 of L-proline have effects on brain development in very young rats. However, in studies where  
575 the dosing was designed to reflect the clinical indications for Privigen, no effects on brain  
576 development were observed. Further safety-pharmacology studies of L-proline in adult and  
577 juvenile rats did not reveal behavioural disorders.

578

579 Immunoglobulins are natural components of the human body. Data from animal testing of  
580 acute and chronic toxicity and embryofetal toxicity of immunoglobulins are inconclusive on  
581 account of interactions between immunoglobulins from heterogeneous species and the  
582 induction of antibodies to heterologous proteins. In local tolerability studies in rabbits in  
583 which Privigen was administered intravenously, paravenously, intra-arterially, and  
584 subcutaneously, the product was well tolerated.

585

586

#### 587 **Other information**

588 ***Incompatibilities***

589 This medicine must not be mixed with other medicinal products nor with physiological saline.

590 However, dilution with 5% glucose solution is permitted.

591

592 ***Influence on diagnostic tests***

593 After infusion of immunoglobulins, the transient increase in the various passively transmitted

594 antibodies in the patient's blood can lead to false-positive results in serological tests.

595

596 The passive transmission of antibodies to erythrocyte antigens, e.g. A, B and D, can lead to  
597 incorrect results in some serological tests for erythrocyte isoantibodies (e.g. Coombs' test),  
598 determinations of the reticulocyte count, and the haptoglobin test.

599

600 For interactions with attenuated live vaccines, see section "Interactions".

601

### 602 ***Shelf life and special precautions for storage***

603 Privigen is stable until the expiry date stated on the vial label and the outer carton after  
604 "EXP". After the imprinted expiry date (EXP) the medicine must not be used.

605 Do not store above 25 °C. Do not freeze. Do not use if Privigen has been frozen. Do not  
606 shake.

607 Keep out of the sight and reach of children.

608 Keep the vial in the outer carton in order to protect from light.

609

### 610 Shelf life of the product after opening:

611 Privigen is intended for single use. Because the solution contains no preservative, Privigen  
612 should be used / infused immediately once opened.

613

### 614 ***Instructions for use and handling***

615 Privigen is a ready-to-use solution. The product should be at room or body temperature before  
616 use. A vented infusion line with integrated filter should be used for the administration of

617 Privigen. Always pierce the stopper at its centre, within the marked area.

618 If dilution is desired, 5% glucose solution should be used. For obtaining an immunoglobulin

619 solution of 50 mg/ml (5%), Privigen 100 mg/ml (10%) should be diluted with an equal

620 volume of the 5% glucose solution. Aseptic technique must be strictly observed during the

621 dilution of Privigen.

622 Privigen must not be mixed with physiological saline. However, after-rinsing of the infusion

623 tubes with physiological saline is permitted.

624 The solution must be clear or slightly opalescent. Do not use solutions that are cloudy or have  
625 particulate matter.

626 Any unused product and waste material should be disposed of in accordance with local  
627 requirements.

628

629

630

631 **Packs**

632 Solution in vials:

633 · 2.5 g / 25 ml

634 · 5 g / 50 ml

635 · 10 g / 100 ml

636 · 20 g / 200 ml

637

638

639 **Manufactured by:**

640 **CSL Behring AG**

641 Bern, Switzerland

642

643 **Date of revision of the text**

644

645 Sep 2025

646

647 Note: Privigen® is a registered trademark of CSL Behring AG in many countries.