CSL Behring

“貝靈”瑞利勁人體免疫球蛋白靜脈注射液10%

Privigen®

Human normal immunoglobulin solution for infusion (10 %)

衛部菌疫輸字第 000965 號

警語：
1. 含human immune globulin成分藥品可能發生血栓。
2. 血栓的危險因子包括：高齡、長時間不活動、血液過度凝集的狀態、具靜脈或動脈血栓病史、使用雌激素、裝有留置型的中央靜脈導管、患血液高度黏稠之疾病及具心血管危險因子。
3. 無已知血栓危險因子者亦可能發生血栓。
4. 具血栓風險的病人，應以最低有效劑量及適當的最小輸注速率投予含human immune globulin成分藥品。
5. 投予前應確保病人有足夠的水分。
6. 具血液高度黏稠風險的病人，應監測血栓相關徵兆及症狀並評估血液之黏稠度。

組成

a.主成分

靜脈注射用的人體免疫球蛋白(IVIg)*；為人體血漿蛋白，含有至少98 %的丙種免疫球蛋白(IgG)。

IgG亞型分布（平均值）： IgG_1 69 %；IgG_2 26 %,；IgG_3 3 %；IgG_4 2 %。

IgA最大濃度為25 μg/mL。

*由人類捐贈者的血漿製造

b.賦形劑

L-脯胺酸(L-proline)

注射用水、鹽酸（用於 pH 調節）、氫氧化鈉（用於 pH 調節）

Privigen含有微量的鈉(≤ 1 mmol/L) 。

Privigen不含防腐劑。

Privigen不含醣類的安定劑（例如：蔗糖、麥芽糖）。

藥理治療分類

免疫血清與免疫球蛋白：人體免疫球蛋白，由靜脈注射。

ATC code:

J06BA02

劑型與每單位主成分含量

靜脈輸注溶液。

1 ml溶液含：100 mg人體血漿蛋白，其中IgG至少占98 %（10 %溶液）。

本品澄清略帶乳白色光澤，為無色至淡黃色。Privigen為等張溶液，滲透壓為320 mOsmol/kg。

可立即使用溶液的pH值為4.6到5.0 [4.8]。

適應症

作為替代療法

- 原發性免疫不全症(Primary immunodeficiency syndromes，PID)如：
  - 先天性丙種免疫球蛋白缺乏症(congenital agammaglobulinemia)及丙種免疫球蛋白過低症(hypogammaglobulinemia)
  - 常見變異性免疫不全症(common variable immunodeficiency)
  - 嚴重複合型免疫不全症(severe combined immunodeficiency)
  - Wiskott-Aldrich氏症候群
- 慢性淋巴性白血病引致丙種免疫球蛋白過低與復發性細菌感染，且預防性抗生素治療無效的病人。
- 多發性骨髓瘤穩定期(plateau phase)引致丙種免疫球蛋白過低與復發性細菌感染，且施打肺炎鏈球菌疫苗無效的病人。
- 異體造血幹細胞移植後引致丙種免疫球蛋白過低。
- 先天性愛滋病(AIDS)伴隨復發性細菌感染者。

作為免疫調節

- 免疫性血小板缺乏紫斑症(Immune thrombocytopenic purpura, ITP)，且具高出血風險或用於手術前矯正血小板計數
- 格林-巴利症候群(Guillain-Barré Syndrome)
- 川崎氏症(Kawasaki Disease)（與乙醯水楊酸acetylsalicylic acid一起使用；請參閱“劑量/用法”章節。）
- 慢性脫髓鞘多發性神經炎(Chronic inflammatory demyelinating polyneuropathy, CIDP)，對孩童的使用經驗有限。
- 多灶性運動神經病變(Multifocal Motor Neuropathy, MMN)
- 重症肌無力惡化(Myasthenia Gravis exacerbations, MG)
- 藍伯 - 伊頓肌無力症(Lambert-Eaton Myasthenic Syndrome)
- 僵體徵候群(Stiff Person Syndrome)

劑量／用法

劑量

劑量與給藥次數視適應症而定。

替代療法

免疫不全症治療之替代療法應在有經驗的醫師監督下起始治療與監控。替代療法的劑量，需要依據個別病人的藥物動力學與臨床反應而定。體重不足或超重的病人可能需要根據體重調整劑量。以下提供給藥劑量作為參考。

原發性免疫不全症的替代療法(PID)

此療法的劑量，建議應使血清中IgG最低濃度（trough level，於下次輸注前測得）至少為6 g/L或該族群年齡的正常參考範圍內。

建議起使劑量為0.4 - 0.8 g/kg bw，之後每3 - 4週輸注0.2 - 0.8 g/kg bw（2至8 mL/kg）。如果病人錯過一劑治療，應儘速補接受錯過的治療，並恢復每3 - 4週的定期治療。

劑量可能需要隨時間進行調整以達到期望的臨床反應與血清中IgG最低濃度(trough level)。IgG的最低濃度(trough levels)應結合感染的發生率進行測量和評估。為了降低細菌感染率，可能有必要增加劑量並爭取達到更高的最低濃度。

慢性淋巴性白血病引致丙種免疫球蛋白過低與復發性細菌感染，且預防性抗生素治療無效的病人；多發性骨髓瘤穩定期引致丙種免疫球蛋白過低與復發性細菌感染，且施打肺炎鏈球菌疫苗無效的病人；先天性愛滋病(AIDS)伴隨復發性細菌感染者的替代療法

繼發性免疫缺乏疾病（如治療適應症所定義）

劑量應達到至少6 g/l的最低濃度IgG值（在下一次輸注之前測量）或在該族群年齡的正常參考範圍內。

建議劑量為每3 - 4週0.2 - 0.4 g/kg bw。

異體造血幹細胞移植後引致丙種免疫球蛋白過低的替代療法

建議劑量為每3 - 4週0.2 - 0.4 g/kg bw。血清中IgG最低濃度應維持高於5 g/L。

免疫調節

免疫性血小板缺乏紫斑症(ITP)

建議劑量為第一天施以0.8到1 g/kg bw，在三天內，可再重覆給與一次同樣的劑量，或每日給與0.4 g/kg bw，持續2 - 5天。有復發情形，可重複治療。

針對發生血栓栓塞、溶血、急性腎損傷或體液容積過剩(volume overload)風險較高的病人，在給予高劑量免疫球蛋白治療（如給予1 g/kg/天持續2天）前，應仔細評估相對利益與風險。

格林-巴利症候群(Guillain-Barre Syndrome)（如果復發，可以重複給藥）

0.4 g/kg bw/day，給與約5天。對孩童的使用經驗有限。

川崎氏症(Kawasaki Disease)

應該單次給予總劑量為2.0 g/kg bw。病人應合併接受乙醯水楊酸(acetylsalicylic acid)的治療。

慢性脫髓鞘多發性神經炎(CIDP)

建議起始劑量為2 g/kg bw，並於連續2 - 5天內分次給與。後以1 g/kg bw的維持劑量，每3週於1天或連續2天內分次給予。

每個週期後應評估治療效果；如果六個月後仍未見到治療效果，應停止治療。

如果療程是有效的，長期治療應由醫生根據病人的反應和後續反應審慎處理。劑量和間隔可能必須根據疾病的個體病程進行調整。

對於超過25周的長期治療應視病人對於維持療法的反應而定。需根據個案疾病的進程，調整最低有效維持劑量和給藥方案。

建議劑量匯整於下列表格中：

適應症	劑量	劑量間隔
替代療法 原發性免疫不全症	起始劑量： 0.4 - 0.8 g/kg bw 接續： 0.2 - 0.8 g/kg bw	每3到4週給藥，維持血清中IgG 最低濃度至少6 g/L
繼發性免疫缺乏疾病	0.2 - 0.4 g/kg bw	每3到4週給藥， 維持血清中IgG最低濃度至少6 g/L
先天性愛滋病(AIDS)伴隨復發性細菌感染	0.2 - 0.4 g/kg bw	每3到4週給藥
異體造血幹細胞移植後引發丙種免疫球蛋白過低	0.2 - 0.4 g/kg bw	每3到4週給藥，維持血清中IgG最低濃度高於5 g/L
免疫調節 免疫性血小板缺乏紫斑症	0.8 - 1 g/ kg bw 或 0.4 g/kg bw/day	第1天的劑量；此治療在3天內可重複一次 2到5天
格林-巴利症候群	0.4 g/kg bw/day	5天
川崎氏症	2 g/kg bw	單一劑量給藥，併用acetylsalicylic acid
慢性脫髓鞘多發性神經炎	起始劑量：2 g/kg bw 維持劑量：1 g/kg bw	2-5天內分次給予 每3週1 - 2天內
多灶性運動神經病變	起始劑量：2 g/kg bw 維持劑量：0.4 - 2 g/kg bw	2-5天內分次給予 每2-6週給藥
重症肌無力惡化	prior to surgery or during myasthenic crisis 起始劑量：1-2 g/kg bw 維持劑量：0.4 - 1 g/kg bw	 2-5天內分次給予 每4-6週給藥
藍伯 - 伊頓肌無力症	起始劑量：2 g/kg bw 維持劑量：0.4 - 1 g/kg bw	2-5天內分次給予 每2-6週給藥
僵體徵候群	起始劑量：2 g/kg bw 維持劑量：1-2 g/kg bw	2-5天內分次給予 每4-6週給藥

bw：體重(Body weight)

小兒對本品之使用

在一個研究原發性免疫不全症的第三期樞紐試驗(pivotal study)(n = 80)，其中有19名3到11歲的病人，15名12歲到18歲（包含）接受治療的病人。

另一個在研究原發性免疫不全症病人的延伸試驗中(n = 55)，其中有13名3到11歲的病人，以及11位12歲到18歲（包含）接受治療的病人。在一個有57名慢性免疫性血小板缺乏紫斑症病人的臨床研究中，其中有2名（15及16歲）病童接受治療。在這三個研究中，沒有針對孩童做劑量上的調整。

有文獻指出靜脈輸注免疫球蛋白對患有CIDP的兒童有效。然而目前尚未有與Privigen相關可用數據。

肝功能不全

沒有證據表明需要調整劑量。

腎功能不全

無須劑量調整除非有臨床根據，請參閱“警語與使用注意事項”章節。

老年

無須劑量調整除非有臨床根據，請參閱“警語與使用注意事項”章節。

給藥方式

Privigen應以靜脈輸注。

輸注速率

本產品初始輸注速率應為0.3 mL/kg bw/hr (0.5 mg/kg bw/min)（注射約30分鐘）。若耐受性良好，輸注速率可以逐漸增加。針對原發性免疫不全症(PID)病人，輸注速率可以逐漸增加至4.8 mL/kg bw/hr (8 mg/kg bw/min)。若病人對4.8 mL/kg bw/hr輸注速率耐受性良好，輸注速率可進一步逐漸增加至7.2 mL/kg bw/hr (12 mg/kg bw/min)。針對免疫性血小板缺乏紫斑症病人，輸注速率可以逐漸增加至2.4mL/kg bw/hr (4 mg/kg bw/min)。

在慢性脫髓鞘多發性神經炎(CIDP) 病人中，初始輸注速率建議為0.3 mL/kg bw/hr (0.5 mg/kg bw/min) 。若病人耐受性良好，輸注速率可逐漸增加至4.8 mL/kg bw/hr (8 mg/kg bw/min)。

禁忌症

對其主成分或是賦型劑過敏者（人類免疫球蛋白）（請見章節“組成”）。

患有選擇性IgA缺乏症的病人，如果使用含IgA的產品會產生IgA的抗體，則可能導致過敏反應。

第一型或第二型高脯胺酸血症(hyperprolinemia)病人。

警語與使用注意事項

可追溯性

為了提高生物藥品的可追溯性，應清楚記錄所施用產品的名稱和批號。

部分的嚴重不良反應可能與輸注速率有關。應確實遵循“劑量／用法：給藥方式”章節所建議的輸注速率，並在輸注期間及輸注後必須密切謹慎地觀察病人，監視是否有任何症狀。

不良反應可能較常發生在：

- 高輸注速率的個案，
- 丙種免疫球蛋白過低症(hypogammamaglobulinemia)或丙種免疫球蛋白缺乏症(agammaglobulinemia)的病人，無論有無IgA缺乏症，
- 初次接受人體免疫球蛋白治療的病人。或在較罕見的案例，如轉換自另一種人體免疫球蛋白產品時，或距離上次輸注的間隔時間過久時。

潛在的併發症通常可以避免，只要確保病人：

- 經由緩慢的初始輸注速率(0.3 ml/kg bw/hr)較不會對人體免疫球蛋白敏感；
- 輸注過程中，密集監測是否有任何症狀。特別是下列病人：未使用過人體免疫球蛋白者、轉換自其他IVIg產品者或距離上次輸注已間隔很久者，應在第一次輸注期間以及第一次輸注後一小時做緊密的觀察，以觀察可能潛在之不良反應。所有其他病人都應在施打後觀察至少20分鐘。

萬一有不良反應，應該減緩輸注速率或是停止輸注。

視不良反應的情況與嚴重度進行必要的治療。

不良反應頻率增加可能與較高的劑量有關。因此，應找出個別病人之最低有效劑量且制定仔細且規律的監測程序。

所有病人施與IVIg時需要：

- 於輸注前補充適當的水分
- 監測尿液流出量
- 監測血中肌酸酐(creatinine)濃度
- 避免同時使用環利尿劑(loop diuretics)（請見“交互作用”）

糖尿病人者如需要稀釋Privigen以降低人體免疫球蛋白濃度，應考慮所建議稀釋液中所含的葡萄糖。

血栓：使用含human immune globulin成分藥品治療可能發生血栓。

危險因子包括：高齡、長時間不活動、血液過度凝集的狀態、具靜脈或動脈血栓病史、使用雌激素、裝有留置型的中央靜脈導管、患血液高度黏稠之疾病及具心血管危險因子。

無已知危險因子者亦可能發生血栓。

具血液高度黏稠風險的病人，包括：具冷凝球蛋白、空腹乳糜微粒血症／顯著的高三酸甘油酯或單株伽瑪球蛋白症者，應考慮進行最低有效劑量及適當的最小輸注速率投予本品。

投予前應確保病人有足夠的水分。

具血液高度黏稠風險的病人，應監測血栓相關徵兆及症狀並評估血液之黏稠度。

過敏

真正的過敏反應相當罕見，通常出現在帶有抗IgA抗體的病人。

IVIg不適用於僅有IgA缺乏的選擇性IgA缺乏症病人。

若發生休克，必須進行標準的休克治療程序。

在一些罕見的案例中，人體免疫球蛋白會使得血壓下降並有類過敏性反應(anaphylactoid reaction)，即使是先前對人體免疫球蛋白治療耐受性良好的病人。

溶血性貧血

IVIg產品可能含有血型抗體（例如A型抗體及B型抗體），這可作為溶血素(haemolysins)，引起體內紅血球(RBC)被免疫球蛋白包覆，導致直接抗球蛋白陽性反應(positive direct antiglobulin reaction, Coombs' test)，進而導致極為罕見的溶血現象。由於紅血球隔離作用(sequestration)的增加，IVIg療法後可能產生溶血性貧血。Privigen製程中包含免疫親合層析步驟(IAC) ，可特別減少A型與B型抗體(isoagglutinins A and B)。

免疫親合層析步驟(IAC)製造之Privigen其臨床試驗數據顯示溶血性貧血在統計學上顯著減少（請見“不良反應”和“特性/效果”章節）。

有數個與溶血有關的腎功能損傷／腎衰竭的獨立個案曾發生過，或一些因血管內瀰漫性凝血反應(DIC)導致死亡的案例。

以下為與發生溶血相關危險因子：高劑量（無論是單一劑量給藥或是幾天內分次給藥）；血型A型、B型與AB型（無血型O型）和處於潛在性的發炎反應。對於接受高劑量來治療非原發性免疫不全症(non-PID)的A型、B型與AB型（無血型O型）病人，建議皆須提高警覺。

原發性免疫不全症病人鮮少在替代療法中出現溶血。

接受IVIg的病人需觀察其溶血臨床徵兆和症狀，若在IVIg輸注期間或是輸注後出現溶血性的徵兆和/或症狀，治療醫師應考慮停用IVIg治療（參見“不良反應”章節）。

無菌性腦膜炎症候群(AMS)

無菌性腦膜炎症候群曾被報告與IVIg治療有關。 此症候群通常都在IVIg治療後數個小時至兩天內出現。腦脊髓液分析常常會出現細胞增多現象(pleocytosis)，每立方毫米(mm^3)可多達數千個（且以顆粒性細胞為主），蛋白質濃度也會增加至數百毫克/分升 (mg/dL)。

AMS的發生通常與高劑量(2 g/kg bw)的IVIg治療有關。

表現出此類症狀和徵象的病人應接受徹底的神經系統檢查，包括腦脊液檢查，以排除腦膜炎的其他原因。

停用IVIg治療後，AMS會在幾天內緩解且無後遺症。

血栓栓塞

臨床證據顯示施打IVIg與血栓栓塞事件有關，如心肌梗塞、腦血管疾病（包含中風）、肺栓塞、深層靜脈阻塞。一般認為，這是因為注入了大量的免疫球蛋白，而相對增加了具風險病人血液的黏稠度。因此對肥胖以及帶有血栓危險因子的病人（如：年紀較大、高血壓、糖尿病、有血管疾病或是血栓之病史、後天性或遺傳性好發血栓疾病的病人、長時間不能動的病人、嚴重低血容量病人、有使血液黏稠度增高疾病的病人），開立處方或是輸注IVIg時須特別注意。

對於有血栓栓塞不良反應風險的病人，根據臨床判斷應以最低劑量及輸注速率輸注IVIg產品。

急性腎衰竭

在接受IVIg治療病人中，有被報告出現急性腎衰竭的案例。大部分的個案之危險因子已被確認，如之前已患有腎功能不足、糖尿病、低血容量、過重、併用具腎毒性的藥物或是年齡超過65歲。

應在輸注IVIg之前評估腎臟指數，尤其是被判斷為可能發生急性腎衰竭的風險高病人，並在適當的時間間隔再次評估。

在腎功能損傷與急性腎衰竭的案例中，雖然被指出與許多種核准上市的IVIg產品有關，然而，其中大多數是和採用賦形劑如蔗糖、葡萄糖和麥芽糖等含有蔗糖作為安定劑的產品有關。因此，對於具有風險的病人，應考慮使用不含蔗糖的IVIg產品。Privigen不含蔗糖、麥芽糖或葡萄糖。

急性腎衰竭也可能由Privigen引起之溶血反應所導致。應確認病人在輸注Privigen前並無體液缺乏且應評估腎功能，包括在開始輸注前及輸注後於適當的時間間隔後檢測血尿素氮(BUN)和血清肌酸酐(creatinine)。

在易發展成急性腎衰竭的高風險病人，必須定時監測腎功能及尿液量。若出現腎功能損傷，應考慮停用IVIg。

對於具有腎功能損傷或急性腎衰竭風險的病人，根據臨床判斷應以最低劑量及輸注速率輸注IVIg產品。

輸血相關急性肺損傷(TRALI)

在接受IVIg的病人中，曾有一些急性非心源性肺水腫的報告[輸血相關急性肺損傷(TRALI)]。

TRALI的特徵在於嚴重缺氧、呼吸困難、呼吸窘迫、發紺、發燒和低血壓。TRALI的症狀通常在輸血期間或輸注的6小時內發生，通常在1 - 2小時之內。

因此，必須對IVIg接受者進行監測是否發生肺部不良反應，如果發生肺部不良反應，必須立即停止IVIg輸注。TRALI是一種可能危及生命的疾病，需要立即進行重症監護病房管理。

具傳播性感染物質

Privigen由人體血漿製備而成。用以避免因使用人體血液或是血漿製備而成的醫療產品而導致感染的標準預防措施包含：篩選捐血者、以特定感染標記篩檢單一捐血者及混合血漿(plasma pools)及採用有效去活化/去除病毒的製造步驟（參見“特性／效果”章節）。儘管如此，施與人體血液或是血漿製成之醫療產品時，還是無法完全排除會有傳染感染源的可能性。這也包括未知或是新興的病毒或是其他病原體。

對有套膜的病毒，如人類免疫不全病毒(HIV)、B型肝炎(HBV)和C型肝炎(HCV)，以及其他不具套膜的病毒，如A型肝炎(HAV)、微小病毒B19型(parvovirus B19)，採取這些措施被視為是有效的。

臨床經驗相信，人體免疫球蛋白不會傳播A型肝炎或微小病毒B19型的感染，而抗體被認為是具病毒安全性的重要原因。

鈉含量

該藥用產品每100毫升中含有少於2.3毫克的鈉，相當於WHO建議成人每天最多攝入2克鈉的0.12 %。

小兒族群

雖可用數據有限，仍預期相同警語、注意事項及危險因子適用於小兒族群。

於上市後經驗中觀察到高劑量IVIg使用在兒童上，特別是川崎氏症，相較於其它使用在兒童上的IVIg適應症在溶血反應有關的通報比率上有增加。

交互作用

活性減毒疫苗(Live attenuated virus vaccines)

於施予免疫球蛋白後六週至三個月內，施打活性減毒疫苗（如麻疹、腮腺炎、德國麻疹和水痘疫苗）的效果會變差。施打本產品到施打活性減毒疫苗之前，需要間隔三個月。如果是麻疹疫苗，其效力降低的影響會持續至一年。因此接受麻疹疫苗的病人，應確認其抗體濃度。

利尿劑

避免同時使用loop利尿劑。

小兒族群

雖可用數據有限，仍預期相同交互作用可能發生於小兒族群。

懷孕、授乳與生殖

懷孕

未有懷孕女性使用Privigen的臨床條件控制研究數據，因此對懷孕及授乳婦女投藥時要注意。IVIg產品已經被證實可以通過胎盤，於第三孕程將增加通過率。

臨床經驗顯示使用免疫球蛋白，對懷孕過程、或是胎兒及新生兒並無出現有害的影響。

試驗型研究發現，接受賦型劑L-Proline的動物關於懷孕、胚胎或是胎兒發展，都未發現直接或是間接性的毒性。

授乳

免疫球蛋白會被分泌到乳汁中，而有可能保護新生兒遠離經黏膜侵入之病原菌。

生殖

免疫球蛋白的臨床經驗並未顯示對生殖出現有害的影響。

對駕駛與操作機械的影響

Privigen對駕駛和使用機器的能力有輕度影響，例如:頭暈（請參閱“不良反應”章節）。

如果病人在治療過程中出現不良反應，在駕駛或操作機械前應等待這些不良反應獲得解決。

不良反應

與靜脈施打人體免疫球蛋白相關之不良反應像是冷顫、頭痛、暈眩、發燒、嘔吐、過敏反應、噁心、關節疼痛、低血壓、中等程度的下背痛偶爾會發生。

人體免疫球蛋白很少會引起血壓驟降，在一些獨立案例曾產生過敏性休克，即使病人在先前的治療沒有出現過敏反應也有可能發生。

使用人體免疫球蛋白有觀察到可逆性無菌性腦膜炎個案與罕見案例出現暫時性皮膚反應。

曾觀察到可逆性溶血反應，特別是血型A、B、AB型（無血型O型），接受免疫調節治療的病人。極少的人，在接受高劑量的IVIg後，會產生需要接受輸血的溶血性貧血。（參見“警語與注意事項”章節）亦可能觀察到血清肌酸酐增加與/或急性腎衰竭的情況。

極罕見但發生過的案例有：輸血相關急性肺損傷(TRALI)和血栓栓塞事件，如心肌梗塞、中風、肺栓塞與深層靜脈阻塞。

對於可經由輸注傳染物質的安全資訊，請參見“具傳播性感染物質” 章節 。

不良反應列表

七項Privigen的臨床研究中，分別於患有PID、ITP與CIDP的病人執行。在PID樞紐試驗中，共有80名病人接受Privigen治療，其中有72名病人完成為期12個月的治療。PID延伸試驗中，共有55名病人接受Privigen治療。另一項臨床研究包括日本的11名PID病人。兩項ITP研究中各有57名病人接受Privigen治療。兩項CIDP研究中則分別有28名及207名病人接受Privigen治療。

在這七項臨床研究中，大部分藥物不良反應(ADRs)為輕微至中度。

以下表格呈現歸納這七項研究中的ADRs，根據國際通用醫學術語辭典器官系統分類（MedDRA System Organ Class, SOC及首選語等級(Preferred Term Level (PT)）及頻率來分類。不良反應的頻率是根據以下的常規做評估：非常常見（≧1/10）、常見（≧1/100 至 <1/10）、不常見（≧1/1,000 至 < 1/100）。

對於自發性的上市後ADRs，通報頻率分類為未知。

在各個分組下，依照不良反應的頻率遞減列出。

MedDRA System Organ Class	不良反應	每個病人的頻率	每次輸注頻率
感染與寄生蟲感染	無菌性腦膜炎	不常見	罕見
血液與淋巴系統疾病	貧血、溶血（包含溶血性貧血）[β]、白血球減少	常見	不常見
	紅血球大小不等症（包含小紅血球增多症）	不常見	不常見
	血小板增多症		罕見
	嗜中性白血球數量下降	未知	未知
免疫系統異常	過敏	常見	不常見
	過敏性休克	未知	未知
神經系統疾病	頭痛（包含靜脈竇頭痛、偏頭痛、頭部不適、緊張性頭痛）	非常常見	非常常見
	暈眩（包含眩暈）	常見	不常見
	嗜睡	不常見	不常見
	顫抖		罕見
心臟疾病	心悸、心搏過速	不常見	罕見
血管疾病	高血壓、面色潮紅（包含熱潮紅、充血）	常見	不常見
	低血壓		罕見
	血栓栓塞性事件、血管炎（包含周邊血管疾病）	不常見	罕見
	輸血相關急性肺損傷	未知	未知
呼吸、胸腔和縱膈疾病	呼吸困難（包含胸痛、胸口不適、呼吸疼痛）	常見	不常見
腸胃道疾病	噁心、嘔吐、腹瀉	常見	常見
	腹痛		不常見
肝膽疾病	高膽紅素血症	常見	罕見
皮膚與皮下組織疾病	皮膚不適（包含紅疹、搔癢、蕁麻疹、斑性丘狀發疹、紅斑、皮膚脫落）	常見	常見
肌肉骨骼與結締組織疾病	肌痛（包含肌肉痙攣、肌肉骨骼僵硬、肌肉骨骼疼痛）	常見	不常見
腎與泌尿系統疾病	蛋白尿、血中肌酸酐增加	不常見	罕見
	急性腎衰竭	未知	未知
全身不適與注射部位狀況	疼痛（包含背痛、肢體疼痛、關節痛、頸部疼痛、臉部疼痛）、發熱（包含發冷）、類流感症狀（包含鼻咽炎、咽喉疼痛、口咽起泡、咽喉緊縮）	非常常見	常見
	疲勞	常見	常見
	衰弱（包含肌肉無力）		不常見
	注射部位疼痛（包括輸液部位不適）	不常見	罕見
檢驗	紅血球素減少（包含紅血球數量減少、血球容積比減少）、Coombs' (direct) test呈陽性反應、ALT增加、AST增加、血中乳酸脫氫酶增加	常見	不常見

[β]頻率是根據將免疫親和色譜法異凝集素還原步驟(IAC)應用於Privigen生產之前，所完成的研究計算得出的。在上市後安全性研究(PASS)中：“在成人和兒童，Privigen的使用和溶血性貧血，以及CIDP兒童的Privigen安全性概況–一項在美國以醫院為主的觀察性世代研究”，評估了7759位接受Privigen的病人，在生產過程加入IAC後，確認了4例溶血性貧血病例的數據；以及9,439位接受Privigen的病人，在生產過程加入IAC之前（基線），確認了47例溶血性貧血病例的數據；根據0.11的發生率比率（根據住院/門診情況、年齡、性別、Privigen劑量和使用Privigen的適應症（單側p值< 0.01），結果顯示，溶血性貧血的總體發生率，具有統計學意義地降低了89 %。溶血性貧血的可能病例(probable cases)，乃由針對溶血性貧血的國際疾病分類(ICD) - 9或ICD - 10醫院出院代碼而定義。溶血性貧血的疑似病例(possible cases)，為透過ICD - 9或ICD - 10出院代碼所確定、或通過對醫院收費說明複查的未明確輸血反應，並與溶血性貧血檢查作業中的血紅蛋白測試、直接抗球蛋白測試，或是間接抗球蛋白測試具時間關聯性。

與可經輸注傳染物質的安全性資料及危險因子的額外資訊，參見 “警語與使用注意事項” 章節。

小兒族群

在Privigen包含兒童病人的臨床研究中，兒童病人在不良反應的性質和發生頻率及嚴重性與成人病人沒有差異。然而上市後經驗觀察到在所有溶血事件當中，兒童病人的比例略高於成人病人。有關危險因子及監測之詳細建議，請見“警語與注意事項”章節。

疑似不良反應通報

在藥品上市後，通報疑似的不良反應是很重要的。

其可以持續監控藥品的利益/風險平衡。醫療專業人員需要報告每一件疑似的不良反應。

過量

過量會導致體液容積超載與高黏稠度，特別是具有風險的病人，包含年長者或是患有心臟功能或腎功能損傷的病人。

特性／效果

作用機制/藥效學

Privigen由1,000名或以上之人類捐贈者之血漿所製備。製造Privigen過程包含以下步驟：IgG血漿分餾過程中的乙醇沉澱作用，接著是octanoic acid分餾，在pH 4下培養。接下來的純化步驟有深層過濾法、色層分析法、可特別減少A型與B型抗體(isoagglutinins A and B)之免疫親合層析(IAC)，以及可以除去20 nm大小微粒的過濾方式。

Privigen主要含有丙種免疫球蛋白(IgG)，IgG存在於正常的人類族群，且具有廣效功能性完整抗體來抵禦感染物。在替代療法中，適量的Privigen能夠將IgG濃度恢復至正常範圍從而有助於抵抗感染。

IgG亞型分布粗略與天然人體血漿相符。IgG分子的Fc與Fab功能區被保留。Fab區段與抗原接合的能力是經生化與生物方法證明；Fc功能區由補體活化以及Fc受體調節的白血球活化作檢測。抑制免疫複合體誘發補體活化的功能被保留在Privigen（“清除” (scavenging)，IVIgs抗發炎反應的功能）。Privigen不會使得非特異性補體系統或是prekallikrein被活化。

除替代療法外，用於其他適應症的機轉尚未完全了解，但具有免疫調節的效果。

臨床療效

關於Privigen安全性與療效，是在歐洲（ITP、PID及CIDP研究），日本（PID和CIDP研究）， 與美國（PID和CIDP研究）執行的七項前瞻性、開放設計、單一組別、多中心研究所探討。上市後安全性研究(PASS)中收集了更多的安全性數據，是一項在美國進行，在具有多種免疫學狀況病人的觀察性多中心試驗。進一步安全性與療效資料則是根據另一項於美國執行的前瞻性、開放設計、單一組別、多中心研究（PID延伸試驗）。

PID

在PID樞紐試驗中，共收納了80位年齡介於3到69歲患有PID病人（3 - 11歲：19人；12 - 15歲：12人；≧ 16歲：49人）接受輸注中位數劑量200 - 888 mg/kg bw之Privigen，每三到四週施打一次，為期一年。這樣的治療使得IgG最低血中濃度於整個治療期間皆達到穩定，平均濃度為8.84 - 10.27 g/l。急性嚴重細菌感染發生率(aSBI)為0.08 / 每病人每年（97.5 %信賴區間上限為0.182）。在PID延伸試驗中，共收納了55名病人（3 - 11歲：13人；12 - 15歲：8人；≧16歲：34人）接受Privigen治療（其中45名來自樞紐試驗，10名則是新收納的病人）。延伸試驗結果確認了IgG平均最低血中濃度(9.31 ~ 11.15 g/l)與急性嚴重細菌感染發生率（0.018 / 每病人每年，97.5 %信賴區間上限為0.098）。

ITP

由57名年齡介於15至69歲且患有慢性ITP的病人參與ITP研究。其初始血小板數量小於20×10^9/l。施與Privigen 1 g/kg (bw)之劑量連續兩天後，80.7 %的病人在七天內血小板數量增加至大於50×10^9/l。43 %病人在施打後一天、第二次輸注前，其血小板數量就增加至大於50×10^9/l。血小板達到此數量的中位數時間為2.5天。對此治療有反應的病人，其血小板數量可以維持在≧50×10^9/l的中位數時間長度為15.4天。

在第二項年齡介於18至65歲病人的ITP研究中，42名受試者(74 %)在第一次施打後的6天內血小板數量一次至少增加至≥ 50×10^9/l，此反應於預期的範圍之中且與其他的IVIg產品報導此適應症的反應率類似(70 %)。在第一次施打後血小板數量≥ 50×10^9/l的受試者於施打第二次後相關附加益處比單次施打的血小板數量增加更多且維持更久。血小板數量< 50×10^9/l的受試者於第三天強制接受第二次輸注，觀察到最低的血小板數量的中位數(8×10^9/l)已於baseline。在此組別中，在第二次強制輸注後只有30 %的受試者有觀察到血小板反應。因此，這些受試者更難以在單次輸注中增加血小板的數量。

CIDP

在第一個CIDP研究：前瞻性、多國多中心、開放式試驗 PRIMA (Privigen impact on mobility and autonomy study)中，對於28位CIDP病人（13位病人先前已接受IVIg治療，15位病人未接受過IVIg治療）給予起始劑量2 g/kg bw 2 - 5天，接著每3週於1 - 2天內給與維持劑量1 g/kg bw 共六次。於先前已接受過治療的病人，在使用Privigen治療前，皆須放棄先前治療用的IVIg，直到以INCAT評分（發炎性神經病變病因及治療）確認臨床症狀有惡化。經過25週的治療，觀察到在28名的病人中，有17人在校正後的10分INCAT評分中由baseline具有臨床意義改善至少1分以上（Response rate為60.7 %，95 %信賴區間42.41，76.4）。有9名病人於接受初始劑量治療後於第四週時就已經有臨床反應，到第10週時則有16名。

依醫療研究協會(MRC)分數測定所有病人的肌力改善為6.9分（95 %信賴區間[4.11，9.75]），在先前已接受治療的病人為6.1分（95 %信賴區間[2.72，9.44]、在未接受過治療的病人則為7.7分（95 %信賴區間[2.89，12.44]）。MRC反應率（定義為MRC至少增加3分）為84.8 %，在先前已接受治療的病人（81.5 % [58.95，100.00]）及未接受過治療的病人（86.7 % [69.46，100.00]）反應率差不多。在INCAT定義為無反應的病人，其肌力改善為5.5分（95 %信賴區間[0.6，10.2]），而有反應者則為7.4分（95 %信賴區間[4.0，11.7]）。

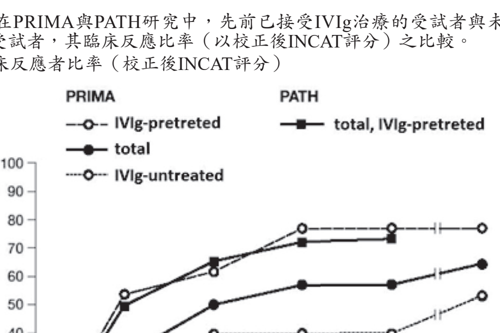
在第二個臨床研究:前瞻性、多國多中心、隨機分配、安慰劑對照試驗PATH (Polyneuropathy and Treatment with Hizentra) 中，對於207位患有CIDP之受試者，在隨機分配前階段給予Privigen治療。所有受試者接受至少8週之IVIg預先治療，且在至12週內斷藥期，藉由臨床上顯著惡化確認IVIg依賴性，接著給予病人Privigen起始劑量2 g/kg bw。其後，每3週至13週給予Privigen維持劑量1 g/kg bw 共四次。

在IVIg斷藥期追蹤臨床惡化程度，主要由減少1分以上之校正後INCAT評分來定義具有CIDP臨床意義的改善。其他測量CIDP改善的方法有R-ODS (Rasch-built Overall Disability Scale) 增加4分以上、平均握力增加8 kPa以上，或MRC總分增加3分以上。總體而言，91 %受試者（188位病人）在第13週達到上述至少一項改善標準。

由校正後INCAT評分觀察，第13週有臨床反應者的比率為72.9 %（207位病人中共151位），其中149位病人在第10週便產生臨床反應。依校正後INCAT評分評估CIDP病人的狀態， 在207位病人中，共有43位病人相較於進入試驗時病情獲得改善。

下圖一顯示在PRIMA與PATH研究中，先前已接受IVIg治療的受試者與未接受過IVIg治療的受試者，其臨床反應比率（以校正後INCAT評分）之比較。

圖一、有臨床反應者比率（校正後INCAT評分）



IVIg: 靜脈注射用的人體免疫球蛋白；Ref Visit: reference visit

在PRIMA研究中，在治療結束時相較於reference visit受試者平均改善1.4分（先前使用過IVIg治療之受試者為1.8分）， 在PATH研究中為1.2分。

在PRIMA研究中，有MRC反應（定義為MRC至少增加3分）的病人比例為85 %（未接受過IVIg治療的病人為87 %、先前已接受IVIg治療的病人為82 %），在PATH研究中為57 %。至達到第一個MRC總分反應的中位數時間在PRIMA研究為6週（未接受過IVIg治療的病人為6週、先前已接受IVIg治療的病人為3週），在PATH研究中為9.3週。MRC總分在PRIMA研究中改善了6.9分（未接受過IVIg治療的病人改善7.7分、先前已接受IVIg治療的病人改善6.1分）， 在PATH研究中改善3.6分。

在PRIMA研究中，受試者慣用手握力改善14.1 kPa（未接受過IVIg治療的病人改善17.0 kPa、先前已接受IVIg治療的病人改善10.8 kPa）。在PATH研究中，受試者慣用手握力改善12.2 kPa。在PRIMA與PATH研究中，非慣用手握力試驗得到了相似的結果。

在PRIMA與PATH研究中，Privigen對於CIDP病人之療效與安全性的結果是相似的。

上市後安全性研究(PASS)

在一項以醫院為主的觀察性世代上市後安全性研究(PASS)中，從2008年1月1日至2019年4月30日，對具有各種免疫學狀況的病人，進行了Privigen治療後發生溶血性貧血的風險評估。溶血性貧血風險在實施風險最小化措施之前（基線）和之後進行了評估，在Privigen製造過程中引入了免疫親和色譜(IAC)步驟。溶血性貧血的疑似病例由針對溶血性貧血的ICD - 9或ICD - 10醫院出院代碼定義。（疑似的溶血性貧血病例包括通過ICD - 9或ICD - 10出院代碼確定，或通過對醫院收費說明進行複查的未明確輸血反應，與之具時間關聯性，在溶血檢查中進行的血紅蛋白、直接抗球蛋白測試或間接抗球蛋白測試）。溶血性貧血發生率具有統計學意義地降低了89 %（基於0.11的發生率；根據住院/門診情況、年齡、性別、Privigen劑量和Privigen使用適應症進行調整；與基線相比，在實施IAC步驟後觀察到單側p值< 0.01）：

	基線	IAC
期間[ϕ]	2008年1月1日至2012年12月31日	2016年10月1日至2019年4月30日
中位數抗A滴定量[£]	1:32	1:8
中位數抗B滴定量[£]	1:16	1:4
可能的溶血性貧血[α]	47	4
病人數(n)	n = 9439	n = 7759
每10.000住院天數可能溶血性貧血[α]風險的粗發病率	0.74 95 % CI[&]: 0.54 - 0.98	0.08 95 % CI: 0.02 - 0.20
發病率可能降低溶血性貧血[α]相對於基準	-	89 %
溶血性貧血與基準的校正後[§]發病率比	-	0.11 95 % CI: 0.04 - 0.31, one-sided p-value: < 0.01

[ϕ] 在2013年10月1日至2015年12月31日期間，排除了具有高度A型抗體效價的人類血漿捐贈者，以作為溶血性貧血的初始風險最小措施，而這樣做也指出了與基準線相比，可以減少38 %可能造成的溶血性貧血發生率，隨後即被Privigen製程中的免疫親和層析法所取代。

[£] 根據Ph.Eur通過直接測試方法測得的異凝集素中位數

[α] 可能的溶血性貧血病例：由溶血性貧血專用的ICD - 9或ICD - 10出院碼及如果Privigen輸注大於1次，則從第一次輸注到最後一次輸注後30天之間發生來定義

[&] 信賴區間

[§] 校正因素：住院/門診情況、年齡、性別、Privigen劑量和Privigen使用指示

IAC實施後與基線相比，溶血性貧血發生率降低，在使用Privigen劑量大於等於0.75 g/kg bw的病人中尤為明顯。

此外，從2008年1月1日至2019年4月30日的整個研究期間，確定有28名小於18歲CIDP兒科病人。在總計486次Privigen給藥中，沒有CIDP兒童病人經歷溶血性貧血、AMS、急性腎功能衰竭、嚴重的過敏反應或血栓栓塞事件。兩名病人經歷中度過敏反應，相當於所有Privigen給藥的0.4 %。

小兒族群

成人與兒童受試者間在藥效學特性和安全性沒有觀察到差異。

藥物動力學

人類正常免疫球蛋白靜脈注射後，其被施以者的血液循環中是立即且完全地生體可用。其相對快速地分佈在血漿與血管外液間，血管內與血管外間室在約3到5天後會達到平衡。

IgG與IgG複合體會在網狀內皮系統的細胞內被分解。半衰期會因病人個體而異。

Privigen的藥物動力學參數是由兩個原發性免疫不全症病人的臨床研究所確立的（參見 “特性/效果” 章節）。樞紐試驗中25名病人（年紀介於13至69歲）與其延伸試驗的13名病人（年紀介於9至59歲）有參與藥物動力學的評估（參見下表）。

患有原發性免疫不全症病人的Privigen藥物動力學參數

參數	樞紐試驗(N = 25) 中位數（範圍）	延伸試驗(N = 13) 中位數（範圍）
C_{max}（最高血中濃度：g/L）	23.4 (10.4 - 34.6)	26.3 (20.9 - 32.9)
C_{min}（最低血中濃度：g/L）	10.2 (5.8 - 14.7)	12.3 (10.4 - 18.8)（每3週給藥） 9.4 (7.3 - 13.2)（每4週給藥）
$t_{1/2}$（半衰期：天）	36.6 (20.6 - 96.9)	31.1 (14.6 - 43.6)

C_{max}，最高血清濃度；C_{min}，最低血清濃度；$t_{½}$，清除半衰期

在原發性免疫不全症病人的樞紐試驗中，Privigen半衰期的中位數為36.6天，延伸試驗則是31.1天。

小兒族群

PID的成人與兒童受試者間在藥物動力學參數沒有觀察到差異。沒有CIDP兒童病人的藥物動力學特性數據。

臨床前期資料

數個臨床前期研究特別探討Privigen的賦形劑L-proline的安全性，L-proline為生理、非必要的胺基酸。於每日給與大鼠1450 mg/kg bw 劑量的L-proline的研究中，並未顯示有任何致畸毒性或是胚胎毒性。致畸毒性研究中，L-proline沒有顯示任何病理上的發現。

一些已發表之高脯胺酸血症(hyperprolinaemia)的研究顯示，長期、高劑量的L-proline對幼鼠腦部發展會有影響。然而，數個與Privigen臨床適應症劑量相關的研究中，並未發現其對腦部發展的影響。更多關於L-proline藥物安全性的研究顯示，幼鼠或是成鼠都沒有出現行為偏差。

免疫球蛋白是天然人體抗體的一部份。因異種的免疫球蛋白與其引起產生的抗體間的交互作用，動物急性與長期毒性試驗及胚胎毒性之數據，並不是有絕對關聯性的。在兔子局部耐受性研究中，Privigen經由靜脈、靜脈旁、動脈內或是皮下注射時，本品耐受性良好。

其他資訊

不相容性

此藥品不可與其他醫療產品混合，也不可以和生理食鹽水混合。然而，可以以5 %葡萄糖溶液稀釋。

對診斷檢查的影響

在輸注免疫球蛋白後，在病人血液中，各種被動輸入的抗體會瞬間增加，導致血清學檢查的偽陽性。

被動輸入對抗紅血球抗原，如A、B和D的抗體，會使得部份針對紅血球抗體血清學檢查（如直接抗球蛋白試驗，direct Coombs' test）之判讀結果不正確。

關於與活性減毒疫苗間的交互作用，請參見“交互作用”章節。

儲存期限與儲存注意事項

Privigen可維持安定直到外盒與小瓶標籤上所載之有效期限到期時。

若超過所載之有效期限(EXP)，請勿使用本產品。

存放請勿超過25 ℃，請勿冷凍。若Privigen被冷凍，請勿使用本產品。請勿晃動本產品。

本品請存放於兒童無法看見及取得處。

保持小瓶存放於外盒內以避免光照。

產品打開後的儲存期限

Privigen是單次使用的。

因溶液不含任何防腐劑， Privigen一旦開封後應立即使用/輸注。

使用指示與處理

Privigen是可立即使用的溶液。使用前，本產品應置於室溫或是等同體溫的環境。

若需要稀釋，應使用5 %葡萄糖溶液作為稀釋液。欲配置50 mg/ml (5 %)的免疫球蛋白溶液，需將Privigen 100 mg/ml (10 %)與等量5 %葡萄糖溶液進行稀釋。Privigen稀釋過程中一定是使用無菌的技術。

Privigen一定不可與生理食鹽水混合，然而，用生理食鹽水潤洗輸注管是允許的。

溶液必須是澄清且略呈乳白色，請勿使用渾濁或是含有顆粒的溶液。

任何未使用的產品或是耗材都應該按照當地要求之衛生法規回收。

包裝

25、50、100、200 毫升玻璃小瓶裝，100支以下盒裝。

小瓶中溶液：

- 2.5 g / 25 mL
- 5 g / 50 mL
- 10 g / 100 mL
- 20 g / 200 mL

製造廠

CSL Behring AG

Wankdorfstrasse 10

3014 Bern, Switzerland

藥商

傑特貝林有限公司

臺北市信義區基隆路1段333號16樓(1612室)

電話：(02)2757-6970

更新日期

2022年2月

CSL Behring

Privigen®

Human normal immunoglobulin Solution for infusion (10 %)

MoHW-Biologics-Import-Reg. No. 000965

Warning:
1. Thrombosis may occur with human immune globulin products.
2. Risk factors of thrombosis include: advanced age, prolonged immobilization, hypercoagulable states, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors.
3. Thrombosis may occur in the absence of known risk factors.
4. For patients at risk of thrombosis, administer drugs containing human immune globulin at the minimum dose and infusion rate practicable.
5. Ensure adequate hydration in patients before administration.
6. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Composition

a. Active substance

Human immunoglobulin for intravenous use (IVIg)*.
Human plasma protein containing at least 98 % immunoglobulin G (IgG).
Distribution of the IgG subclasses (average values): IgG_1 69 %, IgG_2 26 %, IgG_3 3 %, IgG_4 2 %.
The maximum IgA content is 25 micrograms/ml.
* Produced from the plasma of human donors.

b. Excipients

L-proline,
Water for injection, Hydrochloric acid (for pH-adjustment), Sodium hydroxide (for pH adjustment).
Privigen contains trace amounts of sodium (≤ 1 mmol/l).
Privigen contains no preservatives.
Privigen contains no carbohydrate stabiliser (e.g. sucrose, maltose).

Pharmacotherapeutic group

Immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration.
ATC code:
J06BA02

Pharmaceutical form and active substance content per unit

Solution for intravenous infusion.
1 ml of solution contains: 100 mg human plasma protein with an IgG content of at least 98 % (10 % solution).
The solution is clear to slightly opalescent and colourless to pale yellow. Privigen is isotonic, with an osmolality of 320 mOsmol/kg.
The pH value of the ready-to-use solution is 4.6 to 5.0 [4.8].

Therapeutic indications

Replacement therapy in
- Primary immunodeficiency syndromes (PID) such as:
  - congenital agammaglobulinaemia and hypogammaglobulinaemia
  - common variable immunodeficiency
  - severe combined immunodeficiency
  - Wiskott-Aldrich syndrome
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation.
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation.
- Congenital AIDS and recurrent bacterial infections

As Immunomodulation
- Immune thrombocytopenic purpura (ITP) in children or adults at high risk of bleeding or prior to surgical interventions to correct the platelet count
- Guillain-Barré syndrome
- Kawasaki disease (in conjunction with acetylsalicylic acid; see section "Dosage/Administration".)
- Chronic inflammatory demyelinating polyneuropathy (CIDP), Only limited experience is available in children.
- Multifocal Motor Neuropathy (MMN)
- Myasthenia Gravis exacerbations (MG)
- Lambert-Eaton Myasthenic Syndrome
- Stiff Person Syndrome

Dosage/Administration

Dosage

The dosage and dosage regimen is dependent on the indication.

Replacement therapy

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency. In replacement therapy the dosage may need to be individualised for each patient depending on the pharmacokinetic and clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients.
The following dosage regimens are given as a guideline.

Replacement therapy in primary immunodeficiency (PID) syndromes

The dosage regimen is suggested to achieve a trough IgG level (measured before the next infusion) of at least 6 g/L or within the normal reference range for the population age.
The recommended starting dose is 0.4 - 0.8 g/kg bw, and then administered 0.2 to 0.8 g/kg bw (2 to 8 mL/kg) every 3 to 4 weeks. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable.
Adjust the dosage over time to achieve the desired serum IgG trough levels and clinical responses.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Replacement therapy in Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase; multiple myeloma patients who have failed to respond to pneumococcal immunisation; Congenital AIDS and recurrent bacteria infections

Secondary immunodeficiencies (as defined in Therapeutic indications)

The dose regimen should achieve a trough IgG level (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age.
The recommended dosage is 0.2 to 0.4 g/kg bw every 3 to 4 weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation.

The recommended dose is 0.2-0.4 g/kg every three to four weeks. The trough levels should be maintained above 5 g/L.

Immunomodulation

Immune thrombocytopenic purpura (ITP)

The recommended dose is 0.8 to 1 g/kg bw on day one, which may be repeated once within 3 days, or 0.4 g/kg bw daily for 2 to 5 days. The treatment can be repeated if relapse occurs.
Carefully consider the relative risks and benefits before prescribing the high dose regimen (e.g., 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, haemolysis, acute kidney injury, or volume overload.

Guillain-Barré syndrome

0.4 g/kg bw/day over 5 days. Experience in children is limited. (possible repeat of dosing in case of relapse)

Kawasaki disease

2.0 g/kg bw should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Chronic inflammatory demyelinating polyneuropathy (CIDP)

The recommended starting dose is 2 g/kg bw divided over 2 to 5 consecutive days followed by maintenance doses of 1 g/kg bw given on one day or divided over 2 consecutive days every 3 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective long term treatment should be subject to the physicians discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.
The long-term therapy over 25 weeks depends on the patient`s response to the maintenance therapy. The lowest effective maintenance dose and the dosage regimen are to adjust according to the individual course of the disease.
The dosages recommendations are summarized in the following table:

Indications	Dose	Intervals between injections
Replacement therapy in primary immunodeficiency syndromes	starting dose: 0.4 – 0.8 g/kg bw thereafter: 0.2 – 0.8 g/kg bw	every 3 – 4 weeks to maintain IgG trough levels of at least 6 g/L
secondary immunodeficiency syndromes	0.2 – 0.4 g/kg bw	every 3 – 4 weeks to maintain IgG trough levels of at least 6 g/L
congenital AIDS and recurrent bacterial infections	0.2 – 0.4 g/kg bw	every 3 – 4 weeks
Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation.	0.2 – 0.4 g/kg bw	every 3 – 4 weeks, the IgG trough levels should be maintained above 5 g/L.
Immunomodulation Immune thrombocytopenic purpura	0.8 – 1 g/kg bw or 0.4 g/kg bw/day	on day 1, possibly repeated once within 3 days over 2 – 5 days
Guillain-Barré syndrome	0.4 g/kg bw/day	over 5 days
Kawasaki disease	2 g/kg bw	as a single dose in conjunction with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy (CIDP)	starting dose:2 g/kg bw maintenance dose: 1 g/kg bw	in divided doses over 2 – 5 days every 3 weeks over 1 – 2 days
Multifocal motor neuropathy	starting dose: 2 g/kg bw maintenance dose: 0.4 – 2 g/kg bw	in divided doses over 2 – 5 days every 2 – 6 weeks
Myasthenia gravis exacerbations	prior to surgery or during myasthenic crisis starting dose: 1 – 2 g/kg bw maintenance dose: 0.4 – 1 g/kg bw	in divided doses over 2 – 5 days every 4 – 6 weeks
Lambert-Eaton myasthenic syndrome	starting dose: 2 g/kg bw maintenance: 0.4 – 1 g/kg bw	in divided doses over 2 – 5 days every 2 – 6 weeks
Stiff person syndrome	starting dose: 2 g/kg bw maintenance: 1 – 2 g/kg bw	in divided doses over 2 – 5 days every 4 – 6 week

bw = body weight

Use of the product in paediatric population

In the phase III pivotal study on patients with primary immunodeficiency diseases (n = 80), 19 patients between 3 and 11 years of age and 15 patients from 12 up to and including 18 years of age were treated.
In an extension study of patients with primary immunodeficiency diseases (n = 55), 13 patients between 3 and 11 years of age and 11 between 12 and including 18 years of age were treated.
In the clinical study on 57 patients with chronic immune thrombocytopenic purpura 2 paediatric patients (15 and 16 years of age) were treated. No dose adjustment for children was required in these three studies.
Literature reports indicate that intravenous immunoglobulins are effective in children with CIDP. However, no data is available on Privigen in this respect.
Hepatic impairment
No evidence is available to require a dose adjustment.
Renal impairment
No dose adjustment unless clinically warranted, see section "Warnings and precautions for use".
Elderly
No dose adjustment unless clinically warranted, see section "Warnings and precautions for use".

Method of administration

Privigen should be infused intravenously.

Rate of infusion

The product should initially be infused at a rate of 0.3 mL/kg bw/hr (0.5 mg/kg bw/min) (for approximately 30 min). If well tolerated, the infusion rate can be gradually increased. In patients with primary immunodeficiency syndromes, the infusion rate can be gradually increased to 4.8 mL/kg bw/hr (8 mg/kg bw/min). In patients with immunodeficiency syndrome who have tolerated substitution treatment with the infusion rate of 4.8 mL/kg bw/hr well, the infusion rate may be gradually increased to a maximal value of 7.2 mL/kg bw/hr (12 mg/kg bw/min). In patients with Immune thrombocytopenic purpura, the infusion rate can be gradually increased to 2.4 mL/kg bw/hr (4 mg/kg/min).
In patients with chronic inflammatory demyelinating polyneuropathy (CIDP), the initial infusion rate suggested is 0.3 mL/kg bw/hr (0.5 mg/kg bw/min). If well tolerated, the infusion rate can be gradually increased to 4.8 mL/kg bw/hr (8 mg/kg bw/min).

Contraindications

Hypersensitivity to the active substance (human immunoglobulins) or the excipient (see section "Composition").
Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.
Patients with type I or type II hyperporlinaemia.

Warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate given under section "Dosage/Administration: *Method of administration*" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period and thereafter.
Certain adverse reactions may occur more frequently:
– in case of high rate of infusion,
– in patients with hypogammaglobulinaemia or agammaglobulinaemia, with or without IgA deficiency,
– in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.
Potential complications can often be avoided by ensuring that patients:
– are not sensitive to human normal immunoglobulin by initially infusing the product slowly (0.3 ml/kg bw/hr);
– are carefully monitored for any symptoms throughout the infusion period. In particular, patients, naive to human normal immunoglobulin, switched from an alternative IVIg product or when there has been a long interval since the previous infusion, should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.
In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.
Higher doses may be associated with increased rates of adverse effects. Therefore, the lowest effective dose should be sought in individual patients and careful monitoring routine is to establish.
In all patients, IVIg administration requires:
– adequate hydration prior to the initiation of the infusion.
– monitoring of urine output
– monitoring of serum creatinine levels
– avoidance of concomitant use of loop diuretics (see section "Interactions")
For patients suffering from diabetes mellitus and requiring dilution of Privigen to lower concentrations, the presence of glucose in the recommended diluent should be taken into account.
Thrombosis: Thrombosis may occur following treatment with human immune globulin products.
Risk factors include: advanced age, prolonged immobilization, hypercoagulable states, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors.
Thrombosis may occur in the absence of known risk factors.
Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including cryoglobulinemia, fasting chylomicronemia/significant high triglyceride or monoclonal gammopathy.
For patients at risk of thrombosis, administer this product at the minimum dose and infusion rate practicable.
Ensure adequate hydration in patients before administration.
Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.
IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.
In case of shock, standard medical treatment for shock should be implemented.
Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactoid reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Haemolytic anaemia

IVIg products can contain blood group antibodies (e.g. anti-A and anti-B) which may act as haemolysins and induce in vivo coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs` test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration. The Privigen manufacturing process includes an immunoaffinity chromatography (IAC) step that specifically reduces blood group A and B antibodies (isoagglutinins A and B)
Clinical data with Privigen manufactured with the IAC step show statistically significant reductions of haemolytic anaemia (see section "Undesirable effects" and "Properties/Effects").
Isolated cases of haemolysis-related renal dysfunction/renal failure or disseminated intravascular coagulation in some cases leading to death have occurred.
The following risk factors are associated with the development of haemolysis: high doses, whether given as a single administration or divided over several days; blood group A, B and AB (non-O blood group) and underlying inflammatory state. As this event was commonly reported in patients with blood group A, B or AB (non-O blood group) receiving high doses for non-PID indications, increased vigilance is recommended.
Haemolysis has rarely been reported in patients given replacement therapy for PID.
IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. If signs and/or symptoms of haemolysis develop during or after IVIg infusion, discontinuation of IVIg treatment should be considered by the treating physician (see also section "Undesirable effects").

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment.
The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3 (predominantly from the granulocytic series) and elevated protein levels up to several hundred mg/dL.
AMS may occur more frequently in association with high-dose (2 g/kg bw) IVIg treatment.
Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.
Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Thromboembolism

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

Acute renal failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases risk factors have been identified e.g. pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65.
Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals.
While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose should therefore be considered. Privigen does not contain sucrose, maltose or glucose.
Acute renal failure may also occur as a result of Privigen-induced hemolysis. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.
Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. If renal function deteriorates, consider discontinuing Privigen. In patients at risk of renal dysfunction or acute renal failure, IVIg products should be administered at the minimum rate of infusion and minimum dose practicable based on clinical judgement.

Transfusion-related acute lung injury (TRALI)

In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion Related Acute Lung Injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1 - 2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Transmissible infectious substance.

Privigen is made from human plasma. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include: selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses (see also section "Properties/Effects"). Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
The measures taken are considered effective for enveloped viruses such as human immunodeficiency (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), and for the non-enveloped viruses such as hepatitis A (HAV) and parvovirus B19.
There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins, and it is also assumed that the antibody content makes an important contribution to the viral safety.

Sodium content

This medicinal product contains less than 2.3 mg sodium per 100 ml, equivalent to 0.12 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

Although limited data is available, it is expected that the same warnings, precautions and risk factors apply to the paediatric population. In postmarketing reports it is observed that IVIg high dose indications in children, particularly Kawasaki disease, are associated with an increased reporting rate of haemolytic reactions compared to other IVIg indications in children.

Interactions

Live attenuated virus vaccines

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

Loop diuretics

Avoidance of concomitant use of loop diuretics.

Paediatric population

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

Pregnancy, breast-feeding and fertility

Pregnancy

Controlled clinical data on the use of Privigen in pregnant women are not available. Caution should therefore be exercised with regard to administration during pregnancy women and breast-feeding mothers. IVIg products have been shown to cross the placenta, increasingly during the third trimester.
Extensive clinical experience of immunoglobulins suggests that no harmful effects on the course of the pregnancy, or on the foetus and the newborn child are to be expected.
Experimental studies of the excipient L-proline carried out in animals found no direct or indirect toxicity affecting pregnancy, embryonal or foetal development.

Breast-feeding

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

Fertility

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

Effect on driving and the operation of machines

Privigen has minor influence on the ability to drive and use machines, e.g. dizziness (see section "Undesirable effects"). Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

Undesirable effects

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, and moderate back pain may occur occasionally in connection with intravenous administration of human immunoglobulin.
Rarely human immunoglobulin may cause hypersensitivity reactions with a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.
Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin.
Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB (non-O-blood groups) in immunomodulatory treatment. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see section "Warnings and precautions").
Increase in serum creatinine levels and/or acute renal failure have been observed.
Very rare instances have occurred: transfusion related acute lung injury (TRALI) and thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis.
For safety information with respect to transmissible agents, see Transmissible infectious substance.

Tabulated list of adverse reactions

Seven clinical studies were performed with Privigen, which included patients with PID, ITP and CIDP respectively. In the PID pivotal study 80 patients were enrolled and treated with Privigen. Of these, 72 completed the 12 months of treatment. In the PID extension study, 55 patients were enrolled and treated with Privigen. Another clinical study included 11 PID patients in Japan. Two ITP studies were performed with 57 patients each treated with Privigen. Two CIDP studies were performed with 28 and 207 patients treated with Privigen, respectively.
Most adverse drug reactions (ADRs) observed in the seven clinical studies were mild to moderate in nature.
The following table shows an overview of the ADRs in the seven studies, categorized according to MedDRA System Organ Class (SOC and Preferred Term Level (PT)) and frequency. Frequencies of undesirable effects were evaluated according to the following conventions: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100).
For spontaneous post-marketing ADRs, the reporting frequency is categorized as unknown.
Within each grouping, undesirable effects are presented in order of decreasing frequency.

MedDRA System Organ Class	Adverse Reaction	Frequency per patient	Frequency per infusion
Infections and infestations	Aseptic meningitis	Uncommon	Rare
Blood and lymphatic system disorders	Anaemia, haemolysis (including haemolytic anaemia) [β], leukopenia	Common	Uncommon
	Anisocytosis (including microcytosis)	Uncommon	Uncommon
	Thrombocytosis		Rare
	Decreased neutrophil count	Unknown	Unknown
Immune system disorders	Hypersensitivity	Common	Uncommon
	Anaphylactic shock	Unknown	Unknown
Nervous system disorders	Headaches (including sinus headache, migraine, head discomfort, tension headache)	Very common	Very common
	Dizziness (including vertigo)	Common	Uncommon
	Somnolence	Uncommon	Uncommon
	Tremor		Rare
Cardiac disorders	Palpitations, tachycardia	Uncommon	Rare
Vascular disorders	Hypertension, flushing (including hot flush, hyperaemia)	Common	Uncommon
	Hypotension		Rare
	Thromboembolic events, vasculitis (including peripheral vascular disorder)	Uncommon	Rare
	Transfusion related acute lung injury	Unknown	Unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea (including chest pain, chest discomfort, painful respiration)	Common	Uncommon
Gastrointestinal disorders	Nausea, vomiting, diarrhoea,	Common	Common
	Abdominal pain		Uncommon
Hepatobiliary disorders	Hyperbilirubinaemia	Common	Rare
Skin and subcutaneous tissue disorders	Skin disorder (including rash, pruritus, urticaria, maculo-papular rash, erythema, skin exfoliation)	Common	Common
Musculoskeletal and connective tissue disorders	Myalgia (including muscle spasms, musculoskeletal stiffness, muscuskeletal pain)	Common	Uncommon
Renal and urinary disorders	Proteinuria, increased blood creatinine	Uncommon	Rare
	Acute renal failure	Unknown	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	Common
	Fatigue	Common	Common
	Asthenia (including muscular weakness)		Uncommon
	Injection site pain (including infusion site discomfort)	Uncommon	Rare
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	Uncommon

[β] The frequency is calculated based on studies completed prior to implementation of the Immunoaffinity Chromatography isoagglutinin reduction step (IAC) into Privigen production. In a Post-Authorization Safety Study (PASS): "Privigen Use and Haemolytic Anaemia in Adults and Children and the Privigen Safety Profile in Children with CIDP – An Observational Hospital-Based Cohort Study in the US", assessing data of 7,759 patients who received Privigen identifying 4 haemolytic anaemia cases after IAC versus 9,439 patients who received Privigen identifying 47 haemolytic anaemia cases prior to IAC (baseline), an 89 % statistically significant reduction in the overall rate of probable haemolytic anaemia was demonstrated based on an incidence rate ratio of 0.11 adjusted for in-/outpatient setting, age, sex, Privigen dose and indication for Privigen use (one-sided p-value < 0.01). Probable cases of haemolytic anaemia were defined by an International Classification of Disease (ICD) - 9 or ICD - 10 hospital discharge code specific for haemolytic anaemia. Possible cases of haemolytic anaemia consisted of an unspecified transfusion reaction identified via ICD - 9 or ICD - 10 discharge codes or via review of hospital charge descriptions in temporal association with a haptoglobin, a direct antiglobulin test or indirect antiglobulin performed in the workup of haemolytic anaemia.

For safety with respect to transmissible agents and additional details on risk factors, see section "Warnings and precautions".

Paediatric Population

In Privigen clinical studies with paediatric patients, the frequency, nature and severity of adverse reactions did not differ between children and adults. In postmarketing reports it is observed that the proportion of haemolysis cases to all case reports occurring in children is slightly higher than in adults. Please refer to section" Warnings and precautions" for details on risk factors and monitoring recommendations.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

Overdose

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

Properties/Effects

Mechanism of Action/Pharmacodynamics

Privigen is prepared from plasma from 1000 or more human donors. The manufacturing process for Privigen includes the following steps: ethanol precipitation of the IgG plasma fraction, followed by octanoic acid fractionation and incubation at pH 4. Subsequent purification steps comprise depth filtration, chromatography, immunoaffinity chromatography to specifically reduce blood group A and B antibodies (isoagglutinins A and B) and a filtration step that can remove particles to a size of 20 nm.
Privigen contains mainly IgG that are present in the normal human population and that show a broad spectrum of functionally intact antibodies against infectious agents. In the replacement therapy adequate doses of Privigen may restore abnormally low IgG levels to the normal range.
The IgG subclass distribution in Privigen corresponds roughly to that of native human plasma. Both the Fc and the Fab functions of the IgG molecules are preserved. The ability of the Fab parts to bind antigens was demonstrated with biochemical and biological methods. The Fc function was tested with complement activation and with Fc receptor-mediated leukocyte activation. The inhibition of immune complex-induced complement activation ("scavenging", an anti-inflammatory function of IVIgs) is preserved in Privigen. Privigen does not lead to non-specific activation of the complement system or of prekallikrein.
The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Clinical Efficacy

The safety and efficacy of Privigen was investigated in 7 prospective, open, single-arm, multicentre studies carried out in Europe (ITP, PID and CIDP studies) , Japan (PID and CIDP studies), and the US (PID and CIDP studies). Additional safety data were collected in a Post-Authorization Safety Study (PASS), an observational multicentre trial in patients with various immunological conditions performed in the US. Further data on safety and efficacy were collected in a prospective, open, single-arm, multicentre extension study with PID patients performed in the USA (PID extension study).

PID

In the PID pivotal study, 80 patients between 3 and 69 years of age with PID (3 - 11 years of age: 19 patients, 12 - 15 years of age: 12 patients, ≥ 16 years of age: 49 patients) were given a Privigen infusion at a median dose of 200 - 888 mg/kg bw every 3 to 4 weeks for at most 1 year. With this treatment, constant IgG trough levels were achieved over the whole of the treatment period, the mean concentrations being 8.84 g/l to 10.27 g/l. The incidence of acute, severe bacterial infections (aSBI) was 0.08 per patient per year (the upper 97.5 % confidence limit was 0.182).
Privigen dosages were administered in the PID extension study to a total of 55 patients (3 - 11 years of age: 13 patients, 12 - 15 years of age: 8 patients, ≥ 16 years of age: 34 patients) (of which 45 had already been treated in the extension study and 10 were newly recruited patients). The results of the pivotal study were confirmed for the average IgG trough levels (9.31 g/l to 11.15 g/l) and the rate of aSBI (0.018 per patient per year with an upper 97.5 % confidence interval of 0.098).

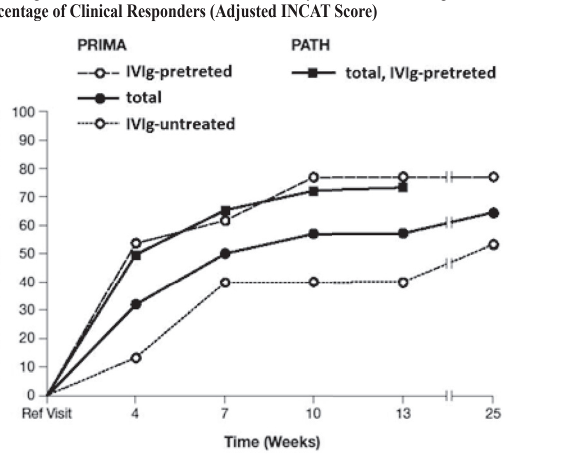
ITP

57 patients aged between 15 and 69 years with chronic ITP took part in the ITP study. Their platelet count at the start was $< 20 \times 10^9$ /l. After administration of Privigen at a dose 1 g/kg bw on two consecutive days, the platelet count rose to at least 50×10^9 /l within 7 days in 80.7 % of the patients. In 43 % of the patients, this increase occurred after just one day, before the second infusion. The mean time until this platelet count was reached was 2.5 days. In patients who responded to the treatment, the platelet count remained $\geq 50 \times 10^9$ /l for a mean period of 15.4 days.
In the second ITP study on patients aged between 18 and 65 years, in 42 subjects (74 %) the platelet count increased at least once to $\geq 50 \times 10^9$ /l within 6 days after the first infusion, which was well within the expected range and similar to response rates were reported for other IVIGs in this indication (70 %). A second dose in subjects with platelet counts $\geq 50 \times 10^9$ /l after the first dose provided a relevant additional benefit in terms of higher and longer-lasting increases in platelet counts compared to a single dose. In subjects with platelet counts $< 50 \times 10^9$ /l on day 3 receiving a mandatory second infusion, the lowest median platelet count (8.0×10^9 /l) was observed already at the baseline. In this group, only 30 % of subjects were observed with platelet response after the mandatory second dose. Consequently, it was more difficult to increase platelet counts with one infusion in these subjects.

CIDP

In the first CIDP study: prospective, multicenter, open label trial PRIMA (Privigen impact on mobility and autonomy study), 28 patients with CIDP (13 subjects with and 15 without IVIg treatment) were treated with a loading dose of 2 g/kg bw given over 2 - 5 days followed by 6 maintenance doses of 1 g/kg bw given over 1 - 2 days every 3 weeks. Previously treated patients were withdrawn from IVIg before treatment with Privigen until the deterioration of clinical symptoms was confirmed on the basis of the INCAT scale (Inflammatory Neuropathy Cause and Treatment). On the adjusted 10 point INCAT scale a clinically meaningful improvement of at least 1-point from baseline to treatment week 25 was observed in 17 / 28 patients (Response rate is 60.7 %, 95 % confidence interval 42.41, 76.4). Nine patients responded clinically already after receiving the initial induction dose to the treatment at week 4 and 16 by week 10.
Muscle strength as measured by the MRC (Medical Research Council) Score improved in all patients by 6.9 points (95 % confidence interval [4.11, 9.75], in previously treated patients by 6.1 points (95 % confidence interval [2.72, 9.44] and in untreated patients by 7.7 points (95 % confidence interval [2.89, 12.44]). The MRC responder rate, an increase of at least 3 points, was 84.8 % which was similar in previously treated patients (81.5 % [58.95, 100.00]) and untreated patients (86.7 % [69.46, 100.00]). In patients defined as INCAT non responders, muscle strength improved by 5.5 points (95 % confidence interval [0.6, 10.2]) as compared to INCAT responders (7.4 points (95 % confidence interval [4.0, 11.7])
In a second clinical study: prospective, multicenter randomized, placebo-controlled PATH (Polyneuropathy and Treatment with Hizentra) study, 207 subjects with CIDP were treated with Privigen before the randomization phase of the study. Subjects all with IVIg pretreatment of at least 8 weeks and an IVIg-dependence confirmed by clinically evident deterioration during an IVIg withdrawal phase of up to 12 weeks, received a Privigen loading dose of 2 g/kg bw followed by up to 4 Privigen maintenance doses of 1 g/kg bw every 3 weeks for up to 13 weeks.
Following clinical deterioration during IVIg withdrawal, clinical improvement of CIDP was primarily defined by a decrease of ≥ 1 point at the adjusted INCAT score. Additional measures of CIDP improvement were an R-ODS (Rasch-built Overall Disability Scale) increase of ≥ 4 points, a mean grip strength increase of ≥ 8 kPa, or an MRC sum score increase of ≥ 3 points. Overall, 91 % of subjects (188 patients) showed improvement in at least one of the criteria above at week 13.
By adjusted INCAT score, the clinical responder rate at week 13 was 72.9 % (151 / 207 patients), with 149 patients responding clinically alreadyat week 10. A total of 43 of the 207 patients achieved a better CIDP status as assessed by the adjusted INCAT score compared to their CIDP status at study entry.
The comparability of the clinical response rates (graded with adjusted INCAT scores) for the subjects with or without IVIg treatment in both PRIMA and PATH study are shown in the Figure 1 below.

Figure 1. Percentage of Clinical Responders (Adjusted INCAT Score)



IVIg: intravenous immunoglobulin; Ref Visit: reference visit

The mean improvement at the end of the treatment period compared to reference visit was 1.4 points in the PRIMA (1.8 points in IVIg treated subjects) and 1.2 points in PATH study.
In PRIMA, the percentage of responders in the overall Medical Research Council (MRC) (defined as at least an increase by ≥ 3 points) was 85 % (87 % in the IVIg-untreated and 82 % in IVIg-treated) and 57 % in PATH. The median time to first MRC sum score response in PRIMA was 6 weeks (6 weeks in the IVIg-untreated and 3 weeks in the IVIg-treated) and 9.3 weeks in PATH. MRC sum score in PRIMA improved by 6.9 points (7.7 points for IVIg-untreated and 6.1 points for IVIg-treated) and by 3.6 points in PATH.
The grip strength of the dominant hand improved by 14.1 kPa (17.0 kPa in IVIg-untreated and 10.8 kPa in IVIg treated subjects) in the PRIMA study, while in PATH the grip strength of the dominant hand improved by 12.2 kPa. For the non-dominant hand similar results were observed in both studies, PRIMA and PATH.
The efficacy and safety results in the PRIMA and the PATH study in CIDP patients were overall comparable.

Post-Authorisation Safety Study (PASS)

In an observational hospital-based cohort Post-Authorisation Safety Study (PASS), the risk of haemolytic anaemia following Privigen therapy was evaluated in patients with various immunological conditions from 1 January 2008 to 30 April 2019. The risk of haemolytic anaemia was assessed prior (baseline) and after the implementation of a risk minimisation measure, the introduction of the Immunoaffinity Chromatography (IAC) step in the Privigen manufacturing process. Probable cases of haemolytic anaemia were defined by an ICD - 9 or ICD - 10 hospital discharge code specific for haemolytic anaemia. (Possible cases of haemolytic anaemia consisted of an unspecified transfusion reaction identified via ICD - 9 or ICD - 10 discharge codes or via review of hospital charge descriptions in temporal association with a haptoglobin, a direct antiglobulin test or indirect antiglobulin performed in the workup of haemolytic anaemia).
A statistically significant rate reduction of 89 % of haemolytic anaemia (based on an incidence rate ratio of 0.11; adjusted for in-/outpatient setting, age, sex, Privigen dose and indication for Privigen use; one-sided p-value < 0.01) was observed after implementation of the IAC step compared to baseline:

	Baseline	IAC
Period[ϕ]	1. January 2008- 31. December 2012	1. October 2016- 30. April 2019
Median anti-A titers[£]	1:32	1:8
Median anti-B titers[£]	1:16	1:4
Probable haemolytic anaemia[α] cases	47	4
Patient number (n)	n = 9439	n = 7759
Crude incidence rate of probable haemolytic anaemia[α] per 10.000 patient-days at risk	0.74 95 % CI[&]: 0.54-0.98	0.08 95 % CI: 0.02-0.20
Incidence rate reduction of probable haemolytic anaemia [α] versus baseline	-	89 %
Adjusted[§] incidence rate ratio for haemolytic anaemia versus baseline	-	0.11 95 % CI: 0.04 - 0.31, one-sided p-value: < 0.01

[ϕ] The exclusion of human blood plasma donors with high anti-A titres performed between 1. October 2013 and 31. December 2015 as the initial risk minimisation measure for haemolytic anaemia indicated a 38 % reduction in probable haemolytic anaemia incidence versus baseline and was subsequently replaced by the IAC step in the Privigen manufacturing process, as provided above.
[£] Median isoagglutinin titers measured by direct testing method according to Ph.Eur
[α] Probable haemolytic anaemia case: defined by an ICD - 9 or ICD - 10 hospital discharge code specific for haemolytic anaemia and the occurrence during the time interval from the first infusion up to 30 days after the last infusion, if > 1 Privigen infusions were administered
[&] Confidence interval
[§] Adjusted for: in-/outpatient setting, age, sex, Privigen dose and indication for Privigen use

The reduction in probable haemolytic anaemia incidence rate after IAC implementation versus baseline was especially pronounced in patients treated with Privigen doses ≥ 0.75 g/kg bw.
Additionally, 28 paediatric patients with CIDP < 18 years of age were identified throughout the entire study period from 1 January 2008 to 30 April 2019. No paediatric patients with CIDP given a total of 486 Privigen administrations experienced haemolytic anaemia, AMS, acute renal failure, severe anaphylactic reaction or a thromboembolic event. Two patients experienced a moderate anaphylactic reaction, equating to 0.4 % of all Privigen administrations.

Paediatric population

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

Pharmacokinetics

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively quickly between plasma and extravascular fluid. Equilibrium between the intravascular and extravascular compartments is reached after approximately 3 to 5 days.
IgG and IgG complexes are broken down in the cells of the reticuloendothelial system. The half-life may vary from patient to patient.
The pharmacokinetic parameters for Privigen were determined in both clinical studies in patients with primary immunodeficiency syndrome (see section "Properties/Effects"). 25 patients (aged 13 to 69 years) in the pivotal study and 13 patients (aged 9 to 59 years) in an extension of this study participated in the pharmacokinetic (PK) assessment (see table below).

Pharmacokinetic parameters of Privigen in patients with primary immunodeficiency syndrome

Parameter	Pivotal study (N = 25) Median (range)	Extension study (N = 13) Median (range)
C_{max} (peak level) in g/l	23.4 (10.4 - 34.6)	26.3 (20.9 - 32.9)
C_{min} (trough level) in g/l	10.2 (5.8 - 14.7)	12.3 (10.4 - 18.8) (3-week schedule) 9.4 (7.3 - 13.2) (4-week schedule)
$t_{½}$ (half-life) in days	36.6 (20.6 - 96.6)	31.1 (14.6 - 43.6)

C_{max}, maximum serum concentration; C_{min}, trough (minimum level) serum concentration; $t_{½}$, elimination half-life.

In the pivotal study the median half-life of Privigen in primary immunodeficiency patients was 36.6 days and 31.1 days in the extension of this study.

Paediatric population

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

Preclinical data

The safety of Privigen has been investigated in several preclinical studies with particular reference to the excipient L-proline. L-proline is a physiological, non-essential amino acid. Studies in rats given daily L-proline doses of 1450 mg/kg bw did not show any evidence of teratogenicity or embryotoxicity. Genotoxicity studies of L-proline did not show any pathological findings.
Some published studies pertaining to hyperprolinaemia have shown that long-term, high doses of L-proline have effects on brain development in very young rats. However, in studies where the dosing was designed to reflect the clinical indications for Privigen, no effects on brain development were observed. Further safety-pharmacology studies of L-proline in adult and juvenile rats did not reveal behavioural disorders.
Immunoglobulins are natural components of the human body. Data from animal testing of acute and chronic toxicity and embryofoetal toxicity of immunoglobulins are inconclusive on account of interactions between immunoglobulins from heterogeneous species and the induction of antibodies to heterologous proteins. In local tolerability studies in rabbits in which Privigen was administered intravenously, paravenously, intra-arterially, and subcutaneously, the product was well tolerated.

Other information

Incompatibilities

This medicine must not be mixed with other medicinal products nor with physiological saline. However, dilution with 5 % glucose solution is permitted.

Influence on diagnostic tests

After infusion of immunoglobulins, the transient increase in the various passively transmitted antibodies in the patient's blood can lead to false-positive results in serological tests.
The passive transmission of antibodies to erythrocyte antigens, e.g. A, B and D, can lead to incorrect results in some serological tests for erythrocyte isoantibodies (e.g. DAT, direct Coombs' test), determinations of the reticulocyte count, and the haptoglobin test.
For interactions with attenuated live vaccines, see section "Interactions".

Shelf life and special precautions for storage

Privigen is stable until the expiry date stated on the vial label and the outer carton after "EXP". After the imprinted expiry date (EXP) the medicine must not be used.
– Do not store above 25 °C. Do not freeze. Do not use if Privigen has been frozen. Do not shake.
Keep out of the sight and reach of children.
Keep the vial in the outer carton in order to protect from light.

Shelf life of the product after opening:

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

Instructions for use and handling

Privigen is a ready-to-use solution. The product should be at room or body temperature before use.
If dilution is desired, 5 % glucose solution should be used. For obtaining an immunoglobulin solution of 50 mg/ml (5 %), Privigen 100 mg/ml (10 %) should be diluted with an equal volume of the 5 % glucose solution. Aseptic technique must be strictly observed during the dilution of Privigen.
Privigen must not be mixed with physiological saline. However, after-rinsing of the infusion tubes with physiological saline is permitted.
The solution must be clear or slightly opalescent. Do not use solutions that are cloudy or have particulate matter.
Any unused product and waste material should be disposed of in accordance with local requirements.

Packs

25, 50, 100, 200 ml glass vials. Under 100 vials per box.
Solution in vials:
- 2.5 g / 25 ml
- 5 g / 50 ml
- 10 g / 100 ml
- 20 g / 200 ml

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