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$_1$ 67.8%；IgG$_2$ 28.7%,；IgG$_3$ 2.3%；IgG$_4$ 1.2%。

IgA最大濃度為25 µg/mL。

*由捐贈者的血漿製造

b. 賦形劑

L-脯胺酸(L-proline)、注射用水

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患者。
- 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患者。
- 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。

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)
- 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。

劑量／用法

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

劑量

劑量與給藥次數視適應症而定。替代療法的劑量，需要依據個別患者的藥物動力學與臨床反應而定。

以下提供給藥劑量作為參考。

Packmittelnr. / packaging code number

原發性免疫不全症的替代療法

建議劑量為每3-4週0.2-0.8 g/kg bw (2至8 mL/kg)。如果患者錯過一劑治療，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)。目前並無隨機具對照組的臨床試驗結果可用來決定此類患者最佳的血清中IgG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患者；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患者；先天性愛滋病(AIDS)伴隨復發性細菌感染者的替代療法

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。

免疫性血小板缺乏紫斑症(ITP)

建議劑量為連續2天1 g/kg bw (總劑量為2 g/kg bw)。

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

格林-巴利症候群(Guillain-Barre Syndrome)

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)

應以分次劑量方式給與2到5天，總劑量為1.6到2.0 g/kg bw。或是，單次劑量2.0 g/kg bw。患者應合併接受乙醯柳酸(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。

對於超過24周的長期治療應視患者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	0.2-0.8 g/kg bw	每3到4週給藥
繼發性免疫缺乏疾病	0.2-0.4 g/kg bw	每3到4週給藥
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濃度高於5 g/L
免疫調節 免疫性血小板缺乏紫斑症	1 g/kg bw	連續2天給藥
格林-巴利症候群	0.4 g/kg bw/day	5天
川崎氏症	1.6-2 g/kg bw 或是 2 g/kg bw	總劑量，在2到5天內分次給藥，併用acetylsalicylic acid 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

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歲的患者，15名12歲到18歲(包含)接受治療的患者。

另一個在研究原發性免疫不全症患者的延伸試驗中(n=55)，其中有13名3到11歲的患者，以及11位12歲到18歲(包含)接受治療的患者。在一個有57名慢性免疫性血小板缺乏紫斑症患者的臨床研究中，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。

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)患者，輸注速率可以逐漸增加至4.8 mL/kg bw/hr (8 mg/kg bw/min)。若患者對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患者，輸注速率可以逐漸增加至2.4 mL/kg bw/hr (4 mg/kg bw/min)。

禁忌症

對其主成分或是賦型劑過敏者(請見章節"組成")。

對人體免疫球蛋白過敏者，特別是在具有抗IgA抗體的之IgA缺乏症患者。

患有高脯胺酸血症(hyperprolinemia)患者。

警語與使用注意事項

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患者，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)的患者，無論有無IgA缺乏症，
- 初次接受人體免疫球蛋白治療的患者。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，只要確保病患：

- 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。特別是下列患者：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。所有其他患者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。

若發生休克，必須進行標準的休克治療程序。

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

所有患者施與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)

糖尿病患者如需要稀釋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抗體的患者。

IVIg不適用於僅有IgA缺乏的選擇性IgA缺乏症患者。

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患者。

溶血性貧血

IVIg產品可能含有血型抗體，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。

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)患者，建議皆須提高警覺。

原發性免疫不全症患者鮮少在替代療法中出現溶血。

接受IVIg的患者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。而停用IVIg治療後，AMS會在幾天內緩解且無後遺症。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)的IVIg治療有關。

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患者血液的黏稠度。因此對肥胖以及帶有血栓危險因子的患者(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患者、長時間不能動的患者、嚴重低血容量患者、有使血液黏稠度增高疾病的患者)，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患者，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治療患者中，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。

若出現腎功能損傷，應考慮停用IVIg。

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，對於具有風險的患者，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。

具有急性腎衰竭風險的患者，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)

在使用IVIg產品治療後，包含Privigen，可能非常罕見地發生非心因性肺水腫。

TRALI的症狀有嚴重呼吸窘迫、肺水腫、低血氧症、左心室功能正常及發燒。症狀通常在治療後1到6小時出現。

請監控患者肺部的不良反應。TRALI可以藉由使用適當的呼吸支持進行氧氣治療加以控制。

安全資訊：可經輸注傳染物質

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之醫療產品時，還是無法完全排除會有傳染病感染源的可能性。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。

強烈建議在每次對患者施與Privigen時，記錄產品的名稱與批號以保留患者與產品批次間的連結。

鈉含量

Privigen基本上無鈉(Privigen為低鈉濃度≤1 mmol/L)。

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患者，應確認其抗體濃度。

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，於妊娠晚期時將增加通過率。

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

駕駛或是操作機械的能力可能會受到一些與Privigen有關的不良反應影響。如果患者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

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，包含Privigen，很少會引起血壓驟降，在一些獨立案例會產生過敏性休克，即使患者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，包含Privigen，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患者。極少的人，在接受高劑量的IVIg，包含Privigen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"安全資訊：可經輸注傳染物質"章節 。

不良反應列表

五項Privigen的臨床研究中，兩項是在患有PID，兩項是在患有ITP的患者中執行，一項是在CIDP患者中執行。在PID樞紐試驗中，共有80名患者接受Privigen治療。其中，72名患者完成為期12個月的治療。PID延伸試驗中，共有55名患者接受Privigen治療。兩項ITP研究中各有57名患者接受Privigen治療。CIDP研究則有28名患者接受Privigen治療。

在這五項臨床研究中，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五項研究中的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。

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 MedDRA Preferred Term	藥物不良反應頻率分類
感染與寄生蟲感染	無菌性腦膜炎	不常見
血液與淋巴系統疾病	貧血、白血球減少、溶血(包含溶血性貧血)、紅血球大小不等症(包含小紅血球增多症)	常見
	血小板增多症	不常見
	血栓栓塞事件	不常見
免疫系統的異常	過敏	常見
	過敏性休克	未知
神經系統疾病	頭痛(包含靜脈竇頭痛、偏頭痛、頭部不適)	非常常見
	暈眩(包含眩暈)	常見
	嗜睡、顫抖、感覺遲鈍	不常見
心臟疾病	心悸(包含心搏過速)	常見
血管疾病	高血壓(包含血壓增加、處置性高血壓、舒張壓增加)、面色潮紅(包含熱潮紅、充血、夜間盜汗)、低血壓(包含血壓降低)	常見
	周邊血管疾病(包含血管炎)	不常見
	輸血相關急性肺損傷	未知
呼吸、胸腔和縱膈疾病	呼吸困難(包含胸痛、口咽部水疱、呼吸疼痛、喉嚨緊縮、胸口不適)	常見
腸胃道疾病	噁心、嘔吐、腹瀉	非常常見
	腹痛(包含上腹痛、胃不適、下腹痛、腹部壓痛)	常見
肝膽疾病	高膽紅素血症(包含結合性膽紅素增加、非結合性膽紅素增加、血中膽紅素增加)	常見
皮膚與皮下組織疾病	皮膚不適(包含紅疹、搔癢、蕁麻疹)	非常常見
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

腎與泌尿系統疾病	蛋白尿(包含血中肌酸酐增加)	不常見
	急性腎衰竭	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、體溫升高、發熱)、類流感症狀(包含鼻咽炎、流感、咽喉疼痛、口咽起泡、咽喉緊縮)	非常常見
	疲勞、衰弱(包含肌肉無力)、注射(輸注)部位疼痛	常見
檢驗	Coombs' direct tests呈陽性反應(Coombs' tests呈陽性反應)、紅血球素減少(包含血球容積比減少、血紅素結合素減少)、ALT增加、血中乳酸脫氫酶增加、AST增加	常見

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"警語與注意事項" 章節。

小兒族群

在Privigen包含兒童患者的臨床研究中，兒童患者在不良反應的性質和發生頻率及嚴重性與成人患者沒有差異。然而上市後經驗觀察到在所有溶血事件當中，兒童患者的比例略高於成人患者。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，特別是具有風險的患者，包含年長者或是患有腎功能損傷的患者。

特性／效果

作用機制/藥效學

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pH4下培養。接下來的純化步驟有深層過濾法、色層分析法，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)與具有廣效功能性完整抗體來抵禦感染物。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。

Privigen包含存在於常態群體中的丙種免疫球蛋白(IgG)抗體，其由不少於1000名捐贈者的血漿所備製。IgG亞型分布粗略與天然人體血漿相符，適量的Privigen能夠將IgG濃度恢復至正常範圍。

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)與美國(PID研究)執行的五項前瞻性、開放設計、單一組別、多中心研究所探討。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)。

在PID樞紐試驗中，共收納了80位年齡介於3到69歲患有PID患者(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/每患者每年(97.5%信賴區間上限為0.182)。在PID延伸試驗中，共收納了55名患者(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名則是新收納的患者)。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/每患者每年，97.5%信賴區間上限為0.098)。

由57名年齡介於15至69歲且患有慢性ITP的患者參與ITP研究。其初始血小板數量小於20×10^9/l。施與Privigen 1 mg/kg (bw)之劑量連續兩天後，80.7%的患者在七天內血小板數量增加至大於50×10^9/l。43%患者在施打後一天、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。對此治療有反應的患者，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歲患者的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 x 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 x 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 x 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 x 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。

在CIDP研究中，一多國多中心開放式試驗 PRIMA (Privigen impact on mobility and autonomy study)中，對於 CIDP患者(有或無接受IVIg預先治療)給予起始劑量2 g/kg bw 2-5天，並每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患者，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)確認臨床症狀的惡化程度。經過25週的治療，觀察到在28名的患者中，在校正後的10分INCAT評分中由baseline改善至少1分以上的患者有17人(60.7%，95%信賴區間42.41，76.4)。有9名患者於接受初始劑量治療時就已經有反應，到第10週時則有16名。

依醫療研究協會(MRC)分數測定所有患者的肌力改善為6.9分(95% 信賴區間 [4.11，9.75])，先前已接受過治療的患者改善為6.1分(95% 信賴區間 [2.72，9.44])及從未受過治療的病患為7.7分(95% 信賴區間 [2.89，12.44])。MRC反應率至少增加了3分，約84.8%，類似於治療過的 (81.5% [58.95，100.00])及從未治療的(86.7% [69.46，100.00])。在INCAT定義為無反應者的肌力改善為5.5分(95% 信賴區間 [0.6，10.2])相較於有反應者的7.4分(95% 信賴區間 [4.0，11.7])。

小兒族群

成人與兒童受試者間在藥效學特性沒有觀察到差異。

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。

Privigen的藥物動力學參數是由兩個原發性免疫不全症患者的臨床研究所確立的(參見"特性/效果"章節)。樞紐試驗中25名患者(年紀介於13至69歲)與其延伸試驗的13名患者(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患者的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)

在原發性免疫不全症患者的樞紐試驗中，Privigen半衰期的中位數為36.6天，延伸試驗則是31.1天。半衰期會因患者個體而異，特別是在原發性免疫不全患者。

IgG與IgG複合體會在網狀內皮系統的細胞內被分解。

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兒童患者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，在患者血液中，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。

請存放於兒童不可取得之處。

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體溫。施打Privigen時應使用過濾器的輸注管線。須刺穿塞蓋之中心有標記處的區域。

若需要稀釋，應使用5%葡萄糖溶液作為稀釋液。欲配置50 mg/l (5%)的免疫球蛋白溶液，需將Privigen 100 mg/l (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

2017年8月

注意：Privigen®是CSL Behring AG在許多國家的註冊商標。

CSL Behring

Privigen[TM/®]

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$_1$ 67.8%, IgG$_2$ 28.7%, IgG$_3$ 2.3%, IgG$_4$ 1.2%.

The maximum IgA content is 25 micrograms/ml.

*Produced from the plasma of human donors.

b. Excipients

L-proline, water for injection.

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 mOsm/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*

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*
- *Chronic inflammatory demyelinating polyneuropathy (CIDP), Only limited experience is available in children.*

Dosage/Administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Dosage

The dosage and dosage regimen is dependent on the indication. In replacement therapy the dosage may need to be individualised for each patient depending on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes

The recommended dose is 0.2 to 0.8 g/kg bw (2 to 8 mL/kg), administered 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. No randomized, controlled trial data are available to determine an optimal trough level in patients receiving immune globulin therapy.

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

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.

Immune thrombocytopenic purpura

The recommended dose is 1 g/kg bw (resulting in a total dosage of 2 g/kg) administered daily for 2 consecutive days.

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.

Kawasaki disease

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 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 long-term therapy over 24 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 summarizedin the following table:

Indications	Dose	Intervals between injections
Replacement therapy in *primary immunodeficiency syndromes*	0.2-0.8 g/kg bw	every 3-4 weeks
secondary immunodeficiency syndromes	0.2-0.4 g/kg bw	every 3-4 weeks
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 trough levels should be maintained above 5 g/l.
Immunomodulation *Immune thrombocytopenic purpura*	1 g/kg bw	over 2 consecutive days
Guillain-Barré syndrome	0.4 g/kg bw/day	over 5 days
Kawasaki disease	1.6-2 g/kg bw or 2 g/kg bw	divided into several doses given over 2-5 days in conjunction with acetylsalicylic acid 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

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.

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 bw/min).

Contraindications

Hypersensitivity to the active substance or the excipient (see section "Composition").

Hypersensitivity to human immunoglobulins, especially in patients with IgA deficiency

where the patient has anti-IgA antibodies.

Patients with hyperprolinaemia.

Warnings and precautions for use

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.

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

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 (loop diuretics)

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.

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 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.

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.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. 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) IVIg treatment.

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.

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.

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

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.

In patients at risk of acute renal failure, IVIg products should be administered at the minimum rate of infusion and minimum dose practicable.

Transfusion-related acute lung injury (TRALI)

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

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

Information on safety: in regard to transmissible agents

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.

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

Sodium content

Privigen is essentially sodium-free (Privigen has a low sodium content of ≤ 1 mmol/l).

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.

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

The ability to drive and operate machines may be impaired by some adverse reactions associated with Privigen. 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.

Rarely human immunoglobulin including Privigen 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 including Privigen.

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 including Privigen (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 and thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis.

For safety information with respect to transmissible agents, see Information on safety: in regard to transmissible agents.

Tabulated list of adverse reactions

Five clinical studies were performed with Privigen, two included patients with PID, two with patients with ITP and 1 with CIDP patients 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. The two ITP studies were performed with 57 patients each treated with Privigen. The CIDP study was performed with 28 patients treated with Privigen.

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

The following table shows an overview of the ADRs in the five 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 MedDRA Preferred Term	ADR frequency category
Infections and infestations	Aseptic meningitis	Uncommon
Blood and lymphatic system disorders	Anaemia, leukopenia, haemolysis (including haemolytic anaemia), anisocytosis (including microcytosis)	Common
	Thrombocytosis	Uncommon
	Thromboembolic events	Uncommon
Immune system disorders	Hypersensitivity	Common
	Anaphylactic shock	Unknown
Nervous system disorders	Headaches (including sinus headache, migraine, head discomfort)	Very common
	Dizziness (including vertigo)	Common
	Somnolence, tremor, dysaesthesia	Uncommon
Cardiac disorders	Palpitations (including tachycardia)	Common
Vascular disorders	Hypertension (including increased blood pressure, procedural hypertension, increased diastolic blood pressure), flushing (including hot flush, hyperaemia, night sweats), hypotension (including decreased blood pressure)	Common
	Peripheral vascular disorder (including vasculitis)	Uncommon
	Transfusion related acute lung injury	Unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea (including chest pain, oropharyngeal blistering, painful respiration, throat tightness, chest discomfort)	Common
Gastrointestinal disorders	Nausea, vomiting, Diarrhoea	Very Common
	Abdominal pain (including upper abdominal pain, stomach discomfort, lower abdominal pain, abdominal tenderness)	Common
Hepatobiliary disorders	Hyperbilirubinaemia (including increased conjugated bilirubin, increased unconjugated blood bilirubin, increased blood bilirubin)	Common
Skin and subcutaneous tissue disorders	Skin disorder (including rash, pruritus, urticaria)	Very Common
Musculoskeletal and connective tissue disorders	Myalgia (including muscle spasms, musculoskeletal stiffness, muscuskeletal pain)	Common
Renal and urinary disorders	Proteinuria (including 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, increased body temperature, hyperthermia), influenza like illness (including nasopharyngitis, influenza, pharyngolaryngeal pain, oropharyngeal blistering, throat tightness)	Very Common
	Fatigue, asthenia (including muscular weakness), injection (infusion) site pain	Common

Investigations	Coombs` direct test positive (Coombs` test positive), decreased haemoglobin (including decreased haematocrit, decreased haptoglobin), increased alanine aminotransferase, increased blood lactate dehydrogenase, increased aspartate aminotransferase	Common

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 renal impairment.

Properties/Effects

Mechanism of Action/Pharmacodynamics

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, and a filtration step that can remove particles to a size of 20 nm.

Privigen contains mainly immunoglobulin G (IgG) with a broad spectrum of functionally intact antibodies to infectious agents. 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.

Privigen contains the immunoglobulin G antibodies present in the normal population. It is prepared from plasma from not fewer than 1,000 donors. The IgG subclass distribution corresponds roughly to that of native human plasma. Adequate doses of Privigen may restore low IgG levels to the normal range.

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 5 prospective, open, single-arm, multicentre studies carried out in Europe (ITP, PID and CIDP studies) and in the USA (PID study). 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).

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).

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 x 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 x 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 ≥50 x 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 ≥50 × 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 ≥50×10^9/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 × 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.

In the CIDP study, a multicentre open label trial PRIMA (Privigen impact on mobility and autonomy study), patients with CIDP (with or without IVIg pre-treatment) were treated with a starting 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 an improvement of at least 1-point from baseline to treatment week 25 was observed in 17 / 28 patients (60.7%, 95% confidence interval 42.41, 76.4). Nine patients responded already after receiving the initial induction dose to the treatment 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 (81.5% [58.95, 100.00]) and untreated (86.7% [69.46, 100.00]) patients. 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])

Paediatric population

No differences were seen in the pharmacodynamic properties 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.

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)

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. The half-life may vary from patient to patient, especially in patients with Primary immunodeficiency syndromes.

IgG and IgG complexes are broken down in the cells of the reticuloendothelial system.

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.

Keep out of the 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. A vented infusion line with integrated filter should be used for the administration of Privigen. Always pierce the stopper at its centre, within the marked area.

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, 200ml 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

Manufactured by:

CSL Behring AG

Wankdorfstrasse 10

3014 Bern, Switzerland

PHARMACEUTICAL COMPANY

CSL Behring Ltd.

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