23 April 2026
EMADOC-1700519818-3007695
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Privigen

International non-proprietary name: Human normal immunoglobulin

Procedure No. EMA/VR/0000304719

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

CDC	Centers for Disease Control
ERA	Environmental risk assessment
EUR	European Region
IG	Immunoglobulin G
IM	intramuscular
IVIG	intravenous immunoglobulin G
MMR	measles, mumps, rubella
SmPC	Summary of Product Characteristics
US	United States
WHO	World Health Organization

Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, CSL Behring GmbH submitted to the European Medicines Agency on 10 October 2025 an application for a group of variations.

The following variations were requested in the group:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II
B.II.d.1.c	B.II.d.1.c Addition of a new specification parameter to the specification with its corresponding test method	Variation type IB

A grouped application consisting of:

C.I.6: Extension of indication to include treatment of patients with measles pre/post-exposure prophylaxis in whom active immunisation is contraindicated or not advised, for Privigen, in alignment with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/2007 Rev.6); As a consequence, sections 2, 4.1, 4.2 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP version 9 has also been submitted.

B.II.d.1.c: To add anti-measles as immunological requirement to the specifications of the finished product with its corresponding test method.

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Information on paediatric requirements

Not applicable

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	10 October 2025
Start of procedure:	01 November 2025
CHMP Rapporteur's preliminary assessment report circulated on:	18 December 2025
PRAC Rapporteur's preliminary assessment report circulated on:	22 December 2025
PRAC members comments	09 January 2026
Updated PRAC Rapporteur Assessment Report	09 January 2026
PRAC Outcome	15 January 2026
CHMP members comments	22 January 2026
CHMP Rapporteur's updated assessment report circulated on:	23 January 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	29 January 2026
MAH's responses submitted to the CHMP on:	19 February 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 March 2026
PRAC Rapporteur's preliminary assessment report circulated on:	25 March 2026
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC RMP advice and assessment overview adopted by PRAC	10 April 2026
CHMP members comments	N/A
CHMP Rapporteur's updated assessment report circulated on:	N/A
CHMP opinion:	23 April 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Measles is a preventable, highly contagious, acute febrile viral illness. Following exposure, approximately 90% of susceptible individuals will develop measles. The period of contagiousness is estimated to be from 5 days before the appearance of the rash to 4 days afterward. The illness is airborne and is readily transmitted in public spaces, even in the absence of physical person-to-person contact. One or more complications occur in approximately 30% of measles cases (Gastanaduy et al, 2021). Complications of measles can be debilitating and have serious consequences such as secondary infections of diarrhoea and pneumonia, measles encephalitis, and other neurological syndromes such as acute disseminated encephalomyelitis or subacute sclerosing panencephalitis, including death. The risk of complications is increased in resource-limited settings, where the case fatality rate is 4% to 10%. It remains an important cause of global mortality and morbidity and accounts for about 100,000 deaths annually despite the availability of an effective vaccine (Kondamudi and Waymack, 2023).

State the claimed therapeutic indication

The proposed indication was:

Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunisation is contraindicated or not advised.

Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles of pre-/post-exposure prophylaxis and active immunisation.

Epidemiology and risk factors

The epidemiology of measles is variable across the globe and is related to immunisation levels achieved in a particular region. Before implementing widespread vaccination programmes, measles accounted for an estimated 2.6 million deaths. Outbreaks of measles have occurred in resource-rich settings where vaccination uptake has declined, allowing for transmission of imported measles virus from unvaccinated and infected travellers (Paules, 2019; Mahase, 2023; Minta, 2023) and the World Health Organization (WHO) reported that approximately 134,200 deaths (15 deaths/hour) occurred in 2015 due to measles. According to the Centers for Disease Control and Prevention (CDC), there were 372 cases in 2018 and 764 cases through May of 2019 in the USA.

In 2010, all 53 countries in the WHO European Region (EUR) confirmed their commitment to eliminate measles as a priority in the European Vaccine Action Plan 2015- 2020 (Zimmerman, 2019). Between 2009 and 2017, efforts to improve vaccination coverage were successful, with 90% of individuals in the region receiving a second vaccine dose. As a result, by the end of 2017, 70% of EUR countries were verified to have eliminated endemic measles. However, in 2018, there was a subsequent increase in measles (89.5 cases per million population) due to large outbreaks in several European countries including some countries that had achieved elimination (Zimmerman, 2019). In 2018, more than 82,000 cases were reported in Europe. Eleven countries (Albania, France, Georgia, Greece, Israel, Italy, Kyrgyzstan, Romania, Russia, Serbia, and Ukraine) reported

more than 1000 infections. The largest number occurred in Ukraine (more than 53,000 cases). Between 1 February 2024 and 31 January 2025 of the 32,265 cases with known age, 14,556 (45.1%) were in children under 5 years of age; and 8,721 (27.0%) cases were aged 15 years or older. The highest notification rates were observed in infants under 1 year of age (1052.2 cases per million) and children aged 1 to 4 years (617.1 cases per million). Of 29,481 cases (100.0% of all cases) with a known age and vaccination status, 25,503 (86.5%) were unvaccinated, 2,583 (8.8%) were vaccinated with 1 dose of a measles containing vaccine, 1,304 (4.4%) were vaccinated with 2 or more doses, and 52 (0.2%) were vaccinated with an unknown number of doses. Nineteen deaths (case fatality rate: 0.1) attributable to measles were reported to the European Centre for Disease Prevention and Control during the 12-month period by Romania (18) and Ireland (1) (ECDC Monthly Report, 2025). The increase in cases has been primarily attributed to lack of vaccination of susceptible populations (Hahne, 2010; van den Hof, 2002; CDC, 2011).

Individuals at risk for measles include children prior to being vaccinated, those who have not been vaccinated for medical or other reasons, those who have not received a second (booster) dose of measles vaccine, and those for whom the vaccine failed to elicit a protective immune response (a very small fraction of those immunized with 2 doses of vaccine). Travel to areas where measles is endemic or contact with ill persons arriving from these countries increases the risk of exposure to measles (Sotir, 2016). Individuals without antibodies if exposed to measles, considering its highly contagious nature are extremely likely to contract infection (Young, 2014). Groups at increased risk for complications of measles include immunocompromised patients, pregnant women, individuals with vitamin A deficiency or poor nutritional status, and individuals at the extremes of age (Cherry 2009; Kaplan, 1992).

Management

While vaccination is the most effective means to prevent the spread of measles in the vulnerable populations identified, there is a therapeutic need for alternative therapies that can protect these patients upon measles exposure especially for those whom vaccinations are not advised or ineffective. As these patients may not respond adequately to vaccinations due to developing or weakened immune systems, making intravenous immunoglobulin G (IVIG) an important option for prophylaxis and treatment. Specifically, IVIG, with a minimum neutralizing antibody titer for measles virus, is a safe and effective alternative to address this unmet medical need.

The practice of passive immunisation against measles has been used since 1920s (Haas, 1926). Polyclonal immunoglobulins are administered parenterally to susceptible individuals, who have been in contact with an infectious case of measles, to prevent the onset of disease (Keller, 2000; Young, 2014). Both intramuscular (IM) and intravenous products are in use. Immunoglobulin brands used for measles prevention in susceptible individuals vary from country to country, and present with variable level of measle-specific antibodies reflecting circulating antibody levels in the donating population. In some countries, minimum neutralizing antibody concentrations are regulated (Guideline on clinical evaluation of vaccines, EMEA/CHMP/VWP/164653/05 Rev. 1). The effectiveness of post-exposure prophylaxis against measles with immunoglobulins is generally accepted (Montroy, 2025; Young, 2014).

2.1.2. About the product

Privigen is an IVIG product, as defined by the European Pharmacopoeia monograph 0918. It is a ready-to-use 10% liquid formulation of polyvalent human IgG for IV administration. Privigen represents the antibody spectrum present in the donor population. The protein moiety of Privigen is highly purified IgG (> 98% purity; more than 99% consists of monomers and dimers) with a

maximum Immunoglobulin A content of 0.025 mg/mL. The distribution of IgG subclasses in Privigen is like that found in normal serum.

Privigen is approved in Europe as replacement therapy in adults, children, and adolescents (0-18 years) in primary and secondary immunodeficiency syndromes; as immunomodulation in adults, children, and adolescents (0-18 years) for primary immune thrombocytopenia (ITP), Guillain-Barré syndrome, Kawasaki disease, Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Multifocal motor neuropathy (MMN).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH proposes adding the measles indication to the SmPC based on clinical experience, and alignment with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/2007 Rev. 6) and the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 Rev. 4). As outlined in the above-mentioned guideline on clinical investigation of IVIg, the indication may be granted if the quality requirements regarding the minimum anti-measles titre level are met.

2.2. Quality aspects

2.1. Description of the Change

Background regarding Measles pre-/post exposure prophylaxis

In December 2021, EMA released a revised Guideline on the core summary of product characteristics for IVIGs. The revised Guideline includes the indication "Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunization is contraindicated or not advised." The additional indication is a class indication attainable via the core SmPC guideline for IVIGs (Real World Evidence) without further clinical programs. Dosage and further measles information is retrievable from the mentioned guideline.

Anti-Measles antibody by neutralization test (NT) method

The anti-measles antibody content in the IgPro10 final product is measured with the neutralization test (NT). Infection with measles virus leads to microscopically detectable changes in susceptible Vero cell cultures (cytopathic effect (CPE)). Anti-measles specific antibodies can neutralize the virus and thereby inhibit CPE. In the measles NT, serial dilutions of antibodies are made and incubated with a defined quantity of measles virus. Following the incubation, CPE is determined in the light microscope. The 50% neutralization dose (ND50) is calculated. It is defined as the sample dilution, at which the CPE is inhibited in 50% of investigated test units.

As standard, an in-house immunoglobulin solution is used that has been calibrated against the US/CBER reference.

<u>Change in the EU SmPC and Rationale</u>

With the current filing, the applicant also updates the IgPro10 EU SmPC with the new indication " measles pre-/post exposure prophylaxis" as specified in the EMA Guideline on the core SmPC for IVIGs.

In the EU SmPC, the minimum level anti-measles IgG level needs to be labeled and is assessed to account for is 9 IU/mL, as per CBER-based estimation.

2.2. Specification(s)

The following tables provide the proposed specifications for the final product.

An adequate specification has been set for anti-measles antibody content.

Analytical Procedures

Brief descriptions of the analytical methods used for testing the final drug product are listed in Table 1. Each test description indicates the SOP number and whether it follows a pharmacopoeial test.

Table 1: Description of Analytical Methods

Parameter	SOP	Description of Method
anti-Measles[3]	Bern: DOC-000230454	Method: Neutralization test A copy of the SOP summary is enclosed in section 3.2.P.5.2, DOC-000230455.

The new method is adequately included in the analytical method panel. A copy of the SOP summary is provided instead a summary itself. This is acceptable.

Validation of Analytical Procedures

Validation was carried out at the applicant's site in Bern (which is also the testing site). The results for the sufficient applied validation parameters show that the method has been in principal adequately validated for it's intended use.

Batch data

Batch data met the specification requirements.

Justification of Specification(s)

Table 2: Justification of Non-Compendial Parameters

Designation	Justification of Specification
anti-Measles	EMA released a revised IVIg Guideline 2021 including the addition of the indication "measles pre/post-exposure prophylaxis for susceptible persons in whom active immunisation is contraindicated or not advised."[1] As per this guideline, IgPro10 with this indication in the EU must meet the minimum measles antibody potency specification threshold of 0.36 x CBER standard. These details must be added to the product specification.

(excerpt by the assessor)

Rationale for anti-Measles Specification and EU SmPC:

With the current filing, CSL Behring (CSLB) updates the IgPro10 EU summary of product characteristics (SmPC) with the new indication "measles pre-/post exposure prophylaxis" as

specified in the EMA Guideline on the core SmPC for IVIGs2.In the EU SmPC, the minimum level anti-measles IgG level needs to be labeled and is assessed to account for is 9 IU/mL, as per CBER-based estimation. The anti-measles antibody activity in the final product is measured and indicated versus the FDA standard. These values can be translated into IU as follows based on FDA Letter to Immune Globulin (Human) Licensed Manufacturers3:

Information in the EU SmPC:

The accordingly revised EU SmPC includes verbatim, the wording of the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIGs).

2 Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) –EMA/CHMP/BPWP/94038/2007 Rev. 6, 16 December 2021

3 FDA Letter to Immune Globulin (Human) Licensed Manufacturers: Option to Lower Lot Release Specification for Required Measles Antibody Potency Testing, November 5, 2018

The justification of the anti-Measles specification is in line with regulatory requirements as specified in the EMA Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) –EMA/ CHMP/ BPWP/ 94038/ 2007 Rev. 6, 16 December 2021).

2.3. Reference Standards or Materials

Table 3: International Standards used in Analytical Procedures

Designation	Description of the International Standard In Use
Anti-Measles[1/2]	CBER/FDA Reference Immune Globuline Standard (currently valid lot)

(excerpt by the assessor)

It is stated that as standard, an in-house immunoglobulin solution is used that has been calibrated against the US/CBER reference (CBER/FDA Reference Immune Globuline Standard, i.e. the currently valid lot).

2.4. Stability

Stability Sections 2.3.P.8, 3.2.P.8.1, 3.2.P.8.2 and 3.2.P.8.3 were updated.

In the following: relevant content extracted from the CTD by the assessor:

3.2.P.8.1 Stability Summary and Conclusion

3.2.P.8.1.3.52 Stability of IgPro10 anti-Measles titer

To provide concluded long-term stability data, a representative set of 14 IgPro10 lots from the 2021 annual stability program was included in studies conducted at the long-term storage temperature of 25°C. These lots have completed full 36-month shelf-life period, and resulting data are summarized below.

The 36-month long-term data is documented in the reports presented in section 3.2.P.8.3. The results of the anti-Measles parameter at 25°C storage complied with the specification for all the 14 lots.

3.2.P.8.3 Stability Data

The applicant has confirmed that the test parameter anti-measles content is implemented in all ongoing stability studies and will be included in all future stability studies conducted for Privigen. In addition, the applicant provided long-term stability data of 14 lots from stability reports from the annual stability program: The 36-month long-term results of anti-Measles parameter at 25°C storage show that specification were met, and no critical trends are present. The CTD has been adequately updated. The other concern has been resolved.

2.5. Discussion and conclusions on quality aspects

With this variation a minimum titre of antibodies against measles of 9 IU/ml, claimed in the SPC, is introduced for Privigen. The applicant updates the IgPro10 SmPC with the new indication "measles pre-/post exposure prophylaxis" as specified in the EMA Guideline on the core SmPC for IVIGs (*Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) – EMA/ CHMP/ BPWP/ 94038/ 2007 Rev. 6, 16 December 2021*). In the EU SmPC, the minimum level anti-measles IgG level needs to be labeled and is assessed to account for is 9 IU/mL, as per CBER-based estimation. The anti-measles antibody activity in the final product is measured and indicated versus the FDA standard. These values can be translated into IU as follows based on FDA Letter to Immune Globulin (Human) Licensed Manufacturers (FDA Letter to Immune Globulin (Human) Licensed Manufacturers: Option to Lower Lot Release Specification for Required Measles Antibody Potency Testing, November 5, 2018):

A suitable method is used: The anti-measles antibody content in the IgPro10 final product is measured with the neutralization test (NT). Anti-measles specific antibodies can neutralize the virus and thereby inhibit CPE. In the measles NT, serial dilutions of antibodies are made and incubated with a defined quantity of measles virus. Following the incubation, CPE is determined in the light microscope. The 50% neutralization dose (ND50) is calculated. It is defined as the sample dilution, at which the CPE is inhibited in 50% of investigated test units.

The assay validation study as well as the test instruction summary (System Suitability Test) has been provided. The results for the sufficient applied validation parameters show that the method has been in principal adequately validated for it's intended use.

In section "3.2.P.6 Reference Standards or Materials" it is stated that as standard, an in-house immunoglobulin solution is used that has been calibrated against the US/CBER reference (CBER/FDA Reference Immune Globuline Standard, i.e. the currently valid lot).

In conclusion, from the perspective of quality the application is considered as approvable.

2.6. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.6.1. Ecotoxicity/environmental risk assessment

Privigen is a protein isolated from human plasma and does not contain genetically modified organisms. According to the "Guideline for the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00), naturally occurring substances such as proteins are exempted from the requirement of an environmental risk assessment (ERA) report. The active substance of Privigen, a human plasma protein, undergoes a metabolism that is

identical to that of naturally occurring proteins and is therefore unlikely to pose a significant risk to the environment. Accordingly, the MAH did not predict any negative impact of Privigen on the environmental exposure.

2.6.2. Discussion and conclusion on non-clinical aspects

According to the current CHMP guideline on environmental risk assessment (CHMP/SWP/4447/00 rev1 corr*), for medicinal products comprised of naturally occurring substances, an ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment. As a human plasma protein, Privigen falls within the scope of this provision. The MAH's ERA, providing a justification for not performing a detailed environmental risk assessment for Privigen, was thereby considered acceptable. Privigen is not expected to pose a risk to the environment.

2.7. Clinical aspects

2.7.1. Clinical efficacy

Methods

Literature Search

To support the utility of IVIG as a prophylactic therapy after measles exposure, Embase was searched on 10 March 2025 for records that meet the following criteria:

- Mention measles in the title, abstract, or keyword, or are indexed as relating to measles
- Mention exposure prophylaxis and immunoglobulin anywhere within the record OR mention immunoglobulin within 10 words of prophylaxis.

This search retrieved a total of 187 results. Full search details, including synonyms and Embase syntax used, are available in Table 4. These results were then evaluated and identified relevant publications from studies that evaluated the use of immunoglobulins as prophylaxis for individuals exposed to measles. Case reports were excluded.

Table 4: Embase Search Strategy

#	Concept	Search String	Results
1	Measles	('measles'/exp OR measles*:ti,ab,kw)	43,959
2	Exposure prophylaxis	((expos* OR preexpos* OR postexpos*) NEAR/5 prophyla*))	22,825
3	Immuno-globulin	(immunoglob* OR immuneglob* OR 'immune glob*' OR 'immuno glob*')	986,196
4	Combine	#2 AND #3	1,793
5	Ig prophylaxis	((immunoglob* OR immuneglob* OR 'immune glob*' OR 'immuno glob*' OR 'ig') NEAR/10 (prevent* OR prophy*))	6,314
6	Combine	#4 OR #5	7,725
7	Combine	#1 AND #6	187
Copy and paste: ('measles'/exp OR measles*:ti,ab,kw) AND (((expos* OR preexpos* OR postexpos*) NEAR/5 prophyla*)) AND (immunoglob* OR immuneglob* OR 'immune glob*' OR 'immuno glob*') OR ((immunoglob* OR immuneglob* OR 'immune glob*' OR 'immuno glob*' OR 'ig') NEAR/10 (prevent* OR prophy*)))			

Results

Following review of the search results, 9 important and relevant publications were identified; confirmed cases of measles were used as an effectiveness measure. These publications reported on the effectiveness of immunoglobulin G (IG) when administered as post-exposure prophylaxis for measles. In publications where an effective dose was evaluated, the general recommendation for measles post-exposure prophylaxis was 400 mg/kg IV administered as a single dose. Most publications did not include reports of adverse events following IG administration. The results from the above-mentioned published studies are summarized below.

Caymaz and colleagues evaluated the effectiveness of IVIG administered to infants following exposure to measles. IVIG (0.4 g/kg) was administered to 187 infants < 6 months of age within the first 6 to 10 days following exposure to measles. The infants were monitored for rash and fever for up to 28 days after dosing. The infants were divided into 2 groups: those who received IVIG at 6 days and those who received it later. These groups were compared according to the development of measles. Only 2 of 187 infants developed measles following IVIG prophylaxis (Caymaz, 2025).

A second study in infants assessed the effectiveness of 400 mg/kg IVIG as post-exposure prophylaxis (Kohlmaier, 2021). 63 of 65 (96.9%) infants had IVIG administered as post-exposure prophylaxis. None of the infants with IVIG post-exposure prophylaxis contracted measles or symptoms suggestive of measles, but both infants who did not receive postexposure prophylaxis became infected.

In a large study, data were obtained on all cases of measles notified in New South Wales, Australia over approximately a 3-month period. 57 cases of measles were reported and 1760 measles contacts were identified, of which 553 were classified as susceptible. Contacts identified as susceptible were offered post-exposure prophylactic immunization with either measles, mumps, rubella (MMR) vaccine within 3 days of exposure, or IG within 7 days of exposure. The effectiveness of receiving either MMR or IG as prophylaxis compared to no prophylaxis in susceptible contacts was 83.3% (95% CI: 27–96). The effectiveness of prophylaxis with IG alone was 75.8% (CI: 0–94) and for MMR was 100% (Sheppeard, 2009).

The effectiveness of the MMR vaccine and IG post-exposure prophylaxis was evaluated in children exposed to measles during an outbreak in New York City in 2013 (Arciuolo, 2017). Children were administered IG 0.5 mL/kg within 6 days of exposure. No child who received IG developed measles. A similar study evaluating post-exposure prophylaxis from a 2014 measles outbreak was reported by Bigham and colleagues. IM immune serum globulin post-exposure prophylaxis was offered to 57 subjects whose initial exposure was assessed to be within the previous 6 days. 17 of 55 IM immune serum globulin post-exposure prophylaxis recipients developed clinically consistent measles in the following 8 to 21 days, corresponding to an estimated crude protective effectiveness of 69%. In school aged children 5 to 18 years, among whom potential exposure intensity and immune status confounders were considered less likely, estimated IM immune serum globulin post-exposure prophylaxis protective effectiveness was 50% (Bigham, 2017). However, a smaller study conducted in a paediatric hospital reported that hospital staff had difficulties with IM IG prophylaxis administration, which in some cases required 2 to 8 injections. As a result of the noted difficulties, the researchers recommended that IVIG be considered when large volumes of IG are recommended intramuscularly (Philips, 2020).

The prevention of measles spread in a paediatric ward was studied in 44 children and 101 adults exposed to an index patient. 25 children and 88 adults were considered immune, providing evidence of immunity. 19 children and 13 adults were either given vaccination or IVIG for post-exposure prophylaxis vaccination. Of the exposed 44 children, 9 had received 400 mg/kg IVIG, 10 had been vaccinated with MMR, and 25 fully immunized children did not receive either. There were no additional cases of measles after 3 weeks follow—up (Tapisiz, 2015).

The effectiveness of post-exposure prophylaxis with IG was assessed in 33 children within 5 days after exposure to measles. The children were administered IG 0.33 mL/kg (50 mg/kg) from commercially available lots containing various titers of measles antibody. The research was focused on the effectiveness in light of the relatively low antibody titers in present-day pooled IG preparations. Measles antibody titers in IG varied from 16 to 45 IU/mL as determined by hemagglutination inhibition. Successful prevention of measles was observed in 24 children with a mean dose of 0.33 mL/kg and mean titer of measles antibody of 10.9 IU/kg. Unsuccessful prevention of measles was observed in 9 children with a mean dose of 0.32 mL/kg and mean titer of measles 5.7 IU/kg (Endo, 2001).

2.7.2. Discussion on clinical efficacy

In this variation, the MAH proposed to add the indication of *Measles pre-/post-exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunisation is contraindicated or not advised.*

The proposed extension of indication was made in accordance with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 Rev. 6) and the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 rev. 4). The latter states that *If the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard is met and added to the product specification, the indication "measles pre-/post exposure prophylaxis" as specified in the core SmPC could be added to the product information*. As mentioned in section 2.2. Quality aspects, the quality requirements regarding the minimum anti-measles titre level are met.

No new clinical efficacy data were submitted to support this application. The MAH submitted supportive literature data to substantiate the effectiveness of IVIg treatment, administered at the

recommended dosage, for the pre- and post-exposure prophylaxis against clinically manifest measles. The literature research was acknowledged and no concern was raised.

Overall, the proposed amendments of the SmPC to include the measle indication were made in accordance with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/2007 Rev. 6) and considered acceptable. Further, the format and wording of the Privigen product information have been aligned with this guideline.

2.7.3. Conclusions on the clinical efficacy

The addition of the following indication to Privigen is acceptable: *Measles pre-/post-exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunisation is contraindicated or not advised.*

Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre-/post-exposure prophylaxis and active immunisation.

2.8. Clinical safety

The safety profile of Privigen aligns with that of other IVIG preparations and is well established.

Adverse events are generally mild and transient, including headache, fever, and infusion-related reactions. Rare but serious adverse events such as thromboembolism and renal dysfunction are known and manageable with existing precautions (EMA, 2020). In the reviewed literature, IVIG for measles post-exposure prophylaxis was well-tolerated. Kohlmaier (2021) reported no serious adverse events in 65 infants; only 2 developed self-limited fever after discharge. Other studies, including Caymaz (2024), Kaman (2022), and Tapisiz (2015), did not report any safety signals.

2.8.1. Discussion on clinical safety

No new clinical safety data were submitted in this application, which was acceptable. Privigen has a well-established safety profile.

According to the reviewed literature, there are currently no safety concerns resulting from IVIG administration for measles post-exposure prophylaxis. Hence, no issue was raised.

2.8.2. Conclusions on clinical safety

It was concluded that IVIg for measles post-exposure prophylaxis does not introduce new safety concerns. Hence, from a clinical perspective, no issue was raised.

2.8.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines' web-portal.

2.9. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.1 is acceptable.

Safety concerns

Table 5: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Aseptic meningitis syndrome • Haemolysis • Hypersensitivity and anaphylactic reactions • Thromboembolic events • Acute renal failure
Important potential risks	• Transfusion-related acute lung injury • Potential for transmission of infectious agents
Missing information	• Neurotoxicity of L-proline in the paediatric population when used at high dose

Pharmacovigilance plan

There are no additional pharmacovigilance activities.

Table 6: Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Aseptic meningitis syndrome	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Hemolysis	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Hypersensitivity and anaphylactic reactions	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Thromboembolic events	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Acute renal failure	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Transfusion-related acute lung injury	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Potential for transmission of infectious agents	Routine risk minimisation measures: SmPC section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Missing information: Neurotoxicity of L-proline in the paediatric population when used at high dose	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

SmPC = Summary of Product Characteristics

2.10. Update of the Product information

As a consequence of this new indication, sections 2, 4.1, 4.2, 4.4, and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template, and the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 Rev. 6), which were reviewed and accepted by the CHMP.

2.10.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: The new indication does not introduce major changes in the package leaflet. In addition, Privigen remains a prescription-only medicinal product intended exclusively for hospital use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Measles is a preventable, highly contagious, acute febrile viral illness. Following exposure, approximately 90% of susceptible individuals will develop measles. The period of contagiousness is estimated to be from 5 days before the appearance of the rash to 4 days afterward. The illness is airborne and is readily transmitted in public spaces, even in the absence of physical person-to-person contact.

3.1.2. Available therapies and unmet medical need

While vaccination is the most effective means to prevent the spread of measles in the vulnerable populations identified, there is a therapeutic need for alternative therapies that can protect these patients upon measles exposure especially for those whom vaccinations are not advised or contraindicated.

3.2. Benefit-risk assessment and discussion

The applied indication for Privigen was "*measles pre-/post-exposure prophylaxis for susceptible adults, children and adolescents (0 to 18 years) in whom active immunisation is contraindicated or not advised. Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre-/post-exposure prophylaxis and active immunisation.*"

The proposed extension of indication was made in accordance with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 Rev. 6) and the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 rev. 4). The latter states that *If the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard is met and added to the product specification, the indication "measles pre-/post exposure prophylaxis" as specified in the core SmPC could be added to the product information*. The quality requirements regarding the minimum anti-measles titre level are met for Privigen.

Efficacy

The indication was supported by longstanding clinical practice and current public health recommendations, including those from the WHO (WHO, 2017), the UK Health Security Agency (UKHSA, 2024), and the European Medicines Agency (EMA, 2020). Measles specific neutralizing antibodies present in IVIG preparations have demonstrated consistent effectiveness in reducing the incidence and severity of measles among high-risk populations, particularly when administered within six days of exposure.

Key publications provide evidence of high effectiveness of IVIG in measles post-exposure prophylaxis. For example, Caymaz and colleagues retrospectively analyzed 187 infants < 6 months old who received IVIG after exposure; only 2 developed measles, supporting a protective effect of approximately 99% (Caymaz, 2024). Similarly, Kohlmaier (2021) reported a 99.3% effectiveness rate among 65 infants who received IVIG during a measles outbreak in Austria. Arciuolo et al. (2017) documented 100% effectiveness in children receiving IG for post-exposure prophylaxis

during a New York City outbreak. These findings consistently reinforce the protective role of IVIG in high-risk populations.

Publications also suggest a time-dependent effect, with administration within the first 3 to 6 days post-exposure yielding the greatest benefit (Caymaz, 2024; Endo, 2001; Sheppeard, 2009). The CDC and UKHSA currently recommend IVIG at a dose of 400 mg/kg body weight for post-exposure prophylaxis in patients with contraindications to vaccination, including immunocompromised patients, pregnant women, individuals with vitamin A deficiency or poor nutritional status, and individuals at the extremes of age (Cherry 2009; Kaplan, 1992).

Safety

The safety profile of Privigen aligns with that of other IVIG preparations and is well established. Adverse events are generally mild and transient, including headache, fever, and infusion-related reactions. Rare but serious adverse events such as thromboembolism and renal dysfunction are known and manageable with existing precautions (EMA, 2020). In the reviewed literature, IVIG for measles post-exposure prophylaxis was well-tolerated. Kohlmaier (2021) reported no serious adverse events in 65 infants; only 2 developed self-limited fever after discharge. Other studies, including Caymaz (2024), Kaman (2022), and Tapisiz (2015), did not report any safety signals. IVIG for measles post-exposure prophylaxis does not introduce new safety concerns.

Overall, the proposed amendments of the SmPC to include the measle indication were made in accordance with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/2007 Rev. 6) and considered acceptable. Further, the format and wording of the Privigen product information have been aligned with this guideline.

3.3. Conclusions

The overall B/R of Privigen is positive in the following indication:

Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunisation is contraindicated or not advised.

Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre-/post-exposure prophylaxis and active immunisation.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, and IIIB
B.II.d.1.c	B.II.d.1.c Addition of a new specification parameter to the specification with its corresponding test method	Variation type IB	N/A

A grouped application consisting of:

C.I.6: Extension of indication to include measles pre/post-exposure prophylaxis for patients in whom active immunisation is contraindicated or not advised, for PRIVIGEN, in alignment with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/2007 Rev. 6) and the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 Rev. 4); as a consequence, sections 2, 4.1, 4.2 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP version 9.1 has also been submitted. Furthermore, the SmPC, Annex II, and Package leaflet were brought in line with the latest QRD template.

B.II.d.1.c: To add anti-measles as immunological requirement to the specifications of the finished product with its corresponding test method.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

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