Amsterdam, 19 May 2022
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Privigen

human normal immunoglobulin

Procedure no: EMEA/H/C/000831/P46/034

Note

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

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Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
BW	Body weight
CI	Confidence interval
CSL	CSL Behring
CRF	Case report form
eCRF	Electronic case report form
FPFV	First patient first visit
GDPR	General Data Protection Regulation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
ITP	Immune thrombocytopenia
i.v.	Intravenous
IVIG	Intravenous immunoglobulin
LPLV	Last patient last visit
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number
N%	Percentage
NIS	Non-interventional study
PID	Primary immunodeficiency
Q1	First quantile
Q3	Third quantile
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SID	Secondary immunodeficiency
SmPC	Summary of Product Characteristics

Table of contents

1. Introduction

On 24 February 2022, the MAH submitted a completed paediatric study for Privigen, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study IgPro10_5001, a Phase 4 observational, non-interventional post-marketing surveillance study in adult and paediatric patients treated with Privigen is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Privigen is a 10% liquid preparation of polyvalent human IgG for intravenous administration stabilized with L-proline that preserves IgG functional activity without refrigeration. Privigen is licensed as a maintenance therapy in primary and secondary immunodeficiency (PID and SID), and as an immunomodulatory therapy in autoimmune and inflammatory diseases in patients of all ages.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study number: IgPro10_5001, Title: Application of Privigen: An observational, non-interventional study

The EU registered therapeutics indications are as follows:

Replacement therapy in adults, and children and adolescents (0-18 years) in:
– Primary immunodeficiency syndromes (PID) with impaired antibody production.
– Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l.
* PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

Immunomodulation in adults, and children and adolescents (0-18 years) in:
– Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
– Guillain-Barré syndrome.
– Kawasaki disease (in conjunction with acetylsalicylic acid).
– Chronic inflammatory demyelinating polyneuropathy (CIDP). Only limited experience is available of use of intravenous immunoglobulins in children with CIDP.
– Multifocal motor neuropathy (MMN)

2.4. Clinical study

IgPro10_5001, Application of Privigen: An observational, non-interventional study

Description

The non-interventional observational study (NIS) with Privigen focusing on application of the IVIG in adult and paediatric patients started in September 2008 (launch of Privigen, FPFV) and ended in September 2021 (LPLV).

Study IgPro10_5001 was a Phase 4 multicenter, observational, non-interventional post-marketing surveillance study in adult and paediatric patients treated with Privigen performed in Germany; it was designed to evaluate effectiveness and tolerability of Privigen in patients with primary or secondary immunodeficiency as well as different autoimmune diseases in clinical practice.
The submitted study report summarises the data collected in 13 paediatric patients aged < 18 years.

Methods

Study participants

The intended number of patients was 5,000. These patients should be enrolled by approximately 200 centers. A patient could be included in the post-marketing surveillance study if the physician had selected Privigen as the intravenous immunoglobulin to be administered. Treatment decision was independent of participation in this observational study. The treatment should be handled according to the SmPC. Exclusion criteria were not defined.

Treatments

Administration of Privigen (IgPro10) should be handled according to the SmPC. Treatment decision was independent of participation in this observational study.

Objective(s)

The objective of this non-interventional study conducted in Germany was the evaluation of the effectiveness and tolerability of Privigen in patients with primary or secondary immunodeficiency as well as different autoimmune diseases of all ages in clinical practice.

Outcomes/endpoints

• Occurrence of infections in patients with immunodeficiency (including kind of infection, severity, duration and treatment)
• Occurrence of bleeding events in patients with ITP (including severity)
• Effectiveness and tolerability of Privigen as assessed by the treating physician
• (Serious) adverse drug reactions ((S)ADR)
• Selected clinical laboratory tests (IgG and thrombocytes for immunodeficiency and ITP respectively, where measured for the clinical indication).

Sample size

As this was not a confirmatory study, an estimation of the sample size with statistical methods was not done. The number of patients was set to 5,000 on a practical basis, considering estimates for the number of centers willing to participate and the number of eligible patients, the expected percentage of patients willing to participate, and a feasible study duration.

Statistical Methods

The statistical analysis was based on the statistical analysis plan (SAP). All patients with an age of <18 years and at least one dose of Privigen were included in this analysis. Parts of the qualitative criteria were the number of patients, the absolute and the relative frequency of each characteristic. The quantitative criteria were the number of cases as well as the maximum, minimum, 1st quantile, median, 3rd quantile, mean, standard error and standard deviation. No statistical hypotheses were formulated.
All observations pertaining to safety and tolerability were analysed according to the clinical description, action taken, frequency, severity, likelihood of being related and outcome, as well as according to their correlation with the dose and infusion rate. Adverse drug reactions were coded according to MedDRA (version 24.1) and grouped according to PT (Preferred Term) and SOC (System Organ Class).

Results

Participant flow

In total, 5,049 patients were included in the NIS by 279 centers (243 active centers). Thirteen patients were less than 18 years old at inclusion (0.3% = 13/5,049). These patients were treated in 8 centers (2.9% = 8/279); 6 of them enrolled one paediatric patient each, one center enrolled 3 paediatric patients and one center 4 paediatric patients. Two of the 13 patients exceeded the age of 18 years during study treatment. The present analysis included only the therapy cycles that were performed during the time when these patients were less than 18 years old (47 therapy cycles in 2 patients excluded for age on reaching 18 years). The statistical analysis included a total of 42 CRFs with 223 therapy cycles with Privigen. The analysed therapy cycles were performed from 22-Sep-2008 to 18-Sep-2018. The mean (SD) observation period was 15.5 ± 30.1 months per patient (median: 3.6 months/patient).

Recruitment

Overall, 5049 patients were recruited, including 13 paediatric patients. First date of an infusion: 2008-09-11, last date of an study visit or follow up visit 2021-09-03.

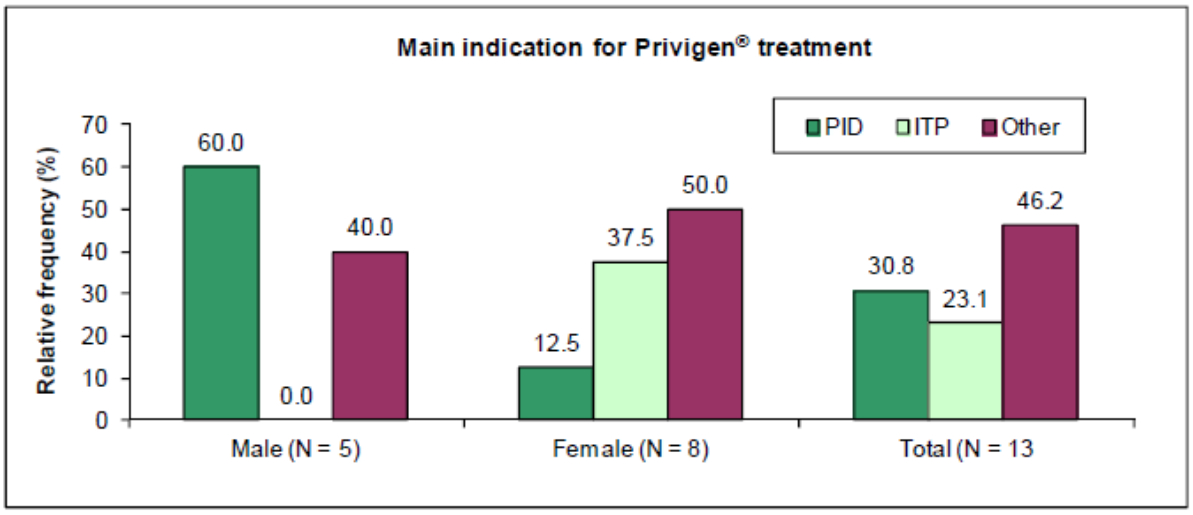
Baseline data

Out of the 13 paediatric patients, 8 patients were female (61.5%) and 5 were male (38.5%). The mean age was 12.3 ± 4.6 years at inclusion (median: 13 years). 3 patients had an age of 2 to 11 years (defined as children). The age of the other 10 patients was between 12 and <18 years (defined as adolescents). The mean weight was 44.7 ± 20.3 kg (median: 48 kg) and the mean height was 150.0 ± 24.7 cm (median: 162 cm). The baseline characteristics stratified by gender are shown in table 1.
The indication for Privigen treatment at inclusion was in 30.8% a primary immunodeficiency (PID, 4/13), in 23.1% immune thrombocytopenia (ITP, 3/13) and in 46.2% other indications (6/13) (figure 1). Previous treatments with intravenous immunoglobulins (IVIG) before start of study treatment were documented in seven paediatric patients (53.8% = 7/13). One of these patients was treated with IVIG more than 12 months before the first Privigen infusion, and five patients were treated with IVIG within 12 months before the first Privigen infusion. The time period of IVIG pre-treatment was unknown in one patient. There were no previous treatments with IVIG in six patients (46.2% = 6/13).

Table 1: Baseline characteristics, stratified by gender; paediatric patients (N = 13)

	Male (N = 5)	Female (N = 8)
Age (Mean (SD) [years])	11.0 (5.8)	13.1 (3.8)
Children (2-11 years) [N (%)]	2 (40.0)	1 (12.5)
Adolescents (12-<18 years) [N (%)]	3 (60.0)	7 (87.5)
Weight (Mean (SD) [kg])	38 (18)	49 (22)
Height (Mean (SD) [cm])	145 (33)	153 (20)

Figure 1: Indication for Privigen® treatment at inclusion, stratified by gender, paediatric patients (N = 13)



Number analysed

Efficacy results

The analysed paediatric patients received 230 Privigen infusions. The mean number of infusions was 18 ± 32 infusions per patient. Patients with PID received 122 infusions (31 ± 49 infusions/patient), patients with ITP were treated with a total of 18 infusions (6.0 ± 5.3 infusions/patient) and patients with other indications received 90 Privigen infusions (15 ± 28 infusions/patient). The average dose per infusion was 13.5 ± 4.9 g Privigen (median: 12.5 g/infusion). This corresponded to a body weight-related dose of 0.31 ± 0.13 g/kg body weight (BW) per infusion (median: 0.291 g/kg BW). The highest dose was administered in patients with ITP, and the lowest dose was given in patients with other indications. The duration of infusions was in the mean 68 ± 51 minutes per infusion (median: 60 min). Patients with ITP had the longest duration per infusion (table 2).
Data of Privigen treatment were also analysed in therapy cycles. In patients with ITP, one therapy cycle comprised all infusions given within a time period of 10 days. In patients with other indications than ITP, the time period was 18 days. In accordance with these definitions, a total of 223 therapy cycles were analysed. The patients had in the mean 17 therapy cycles (median: 6 therapy cycles). Most therapy cycles were documented in patients with PID (121 therapy cycles; 30 ± 49 therapy cycles/patient) and the least number in patients with ITP (12 therapy cycles; 4.0 ± 5.2 therapy

cycles/patient). Patients with other indication had 90 therapy cycles (15 ± 28 therapy cycles/patient). The total infused Privigen dose per therapy cycle was in the mean 13.9 ± 8.9 g (median: 12.5 g). This corresponded to a body weight-related dose of 0.32 ± 0.18 g/kg BW (median: 0.29 g/kg BW). The dose was the highest in patients with ITP and the lowest in patients with other indications (table 2).

Table 2: Dose and body weight-related dose of Privigen® per infusion and per therapy cycle, duration of infusion, stratified by indication for Privigen® treatment; paediatric patients

	PID	ITP	Other indication
Number of infusions	**122**	**18**	**90**
Dose per infusion (Mean (SD) [g])	14.0 (2.6)	26.1 (6.5)	10.3 (1.3)
Dose per infusion related to body weight (Mean (SD) [g/kg BW])	0.37 (0.08)	0.47 (0.15)	0.20 (0.07)
Duration of infusion (Mean (SD) [min])	60 (53)	173 (67)	61 (15)
Number of therapy cycles	**121**	**12**	**90**
Total dose per therapy cycle (Mean (SD) [g])	14.1 (2.5)	39.2 (26.4)	10.3 (1.3)
Total dose per therapy cycle related to body weight (Mean (SD) [g/kg BW])	0.37 (0.08)	0.71 (0.47)	0.20 (0.07)

The application of a premedication shortly before Privigen infusion was documented in nine therapy cycles (4.0% = 9/223); seven cycles in patients with PID, and one cycle each in patients with ITP and in patients with other indications. The used premedication was documented in eight of the nine cycles (88.9% = 8/9), most frequently corticosteroids (87.5% = 7/8; other: 12.5% = 1/8).

Laboratory data

With regard to laboratory data, the present statistics contains the analysis of IgG values in patients with PID and thrombocyte counts in patients with ITP.

An IgG value within seven days before start of a therapy cycle was documented in 70.2% of therapy cycles in paediatric patients with PID (70.2% = 85/121). The mean IgG value was 6.3 ± 1.2 g/l (median: 5.9 g/l). IgG values within seven days after the start of the therapy cycle were not documented.

Thrombocyte counts within seven days before start of the therapy cycle were available in all 12 therapy cycles in patients with ITP. Thrombocyte counts within seven days after the start of the therapy cycle were documented in five therapy cycles (41.7% = 5/12). The time period between the value before start of therapy cycle and the value after the start of the cycle was 3.4 ± 1.7 days in the mean (median: 3 days). The mean thrombocyte count within seven days before the therapy cycle was 16,000 ± 22,998 cells/µl (median: 8,500 cells/µl). The thrombocyte count within seven days after start of the therapy cycle was 183,600 ± 184,858 cell/µl (median: 144,000 cells/µl). The difference between both thrombocyte counts was calculated for the five therapy cycles with both values. Here, the thrombocyte count increased by 172,000 ± 177,665 cells/µl (median: 131,000 cell/µl) from determination before the therapy cycle to determination after start of the cycle.

Infections in paediatric patients with PID

Infections were documented in 34 therapy cycles in 4 paediatric patients with PID (28.1% = 34/121). With a total observation period of 9.2 patient years, this yields a rate of 3.7 infections per year. More than half of the infections were infections of the upper airways (58.8% = 20/34). Acute bronchitis or acute exacerbation of a chronic bronchitis was present in 5 therapy cycles (14.7% = 5/34) and other infections in 9 therapy cycles (26.5% = 9/34). A causal pathogen was identified in 4 infections (11.8% = 4/34). The majority of infections were mild (73.5% = 25/34); the other 9 infections were of moderate intensity (26.5% = 9/34). None of the documented infections was serious according to the definition in EMA/CHMP/BPWP/94033/2007 rev. 3 (8). The duration of the documented infections was 9.8 ± 13.8 days in the mean (median: 5 days). A therapy with antibiotics, antimycotics or antiviral agents was reported in 9 infections (26.5% = 9/34).

Bleeding events in paediatric patients with ITP

Surgical procedures in paediatric patients with ITP were not documented during study treatment. An event with prolonged or increased bleeding was reported in one therapy cycle (8.3% = 1/12). This event was of mild intensity. An additional medication for the treatment of ITP beside Privigen was documented in one therapy cycle (8.3% = 1/12). The medication was a corticosteroid. A splenectomy was not performed.

Discontinuation of treatment of Privigen

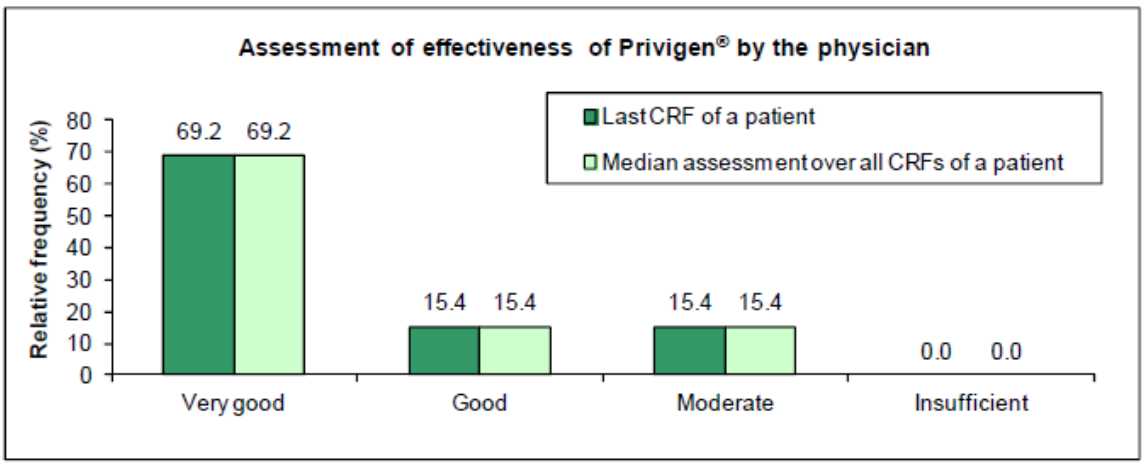
Privigen treatment was discontinued in eight patients (61.5% = 8/13). In total 11 entries regarding the reason for discontinuation could by analysed. The most frequent reasons were change of therapy to other IVIG, good response to Privigen therapy and insufficient tolerability (each: 18.2% = 2/11).

Assessment of effectiveness and tolerability of Privigen in paediatric patients

Assessments of the effectiveness and the tolerability of Privigen by the physicians were documented at the end of every CRF. Since long-term treatments were documented in more than one CRF, there was usually more than one assessment of effectiveness and tolerability per patient. The present report includes the assessment in the last CRF of each patient as well as the median assessment over all CRFs of a patient.

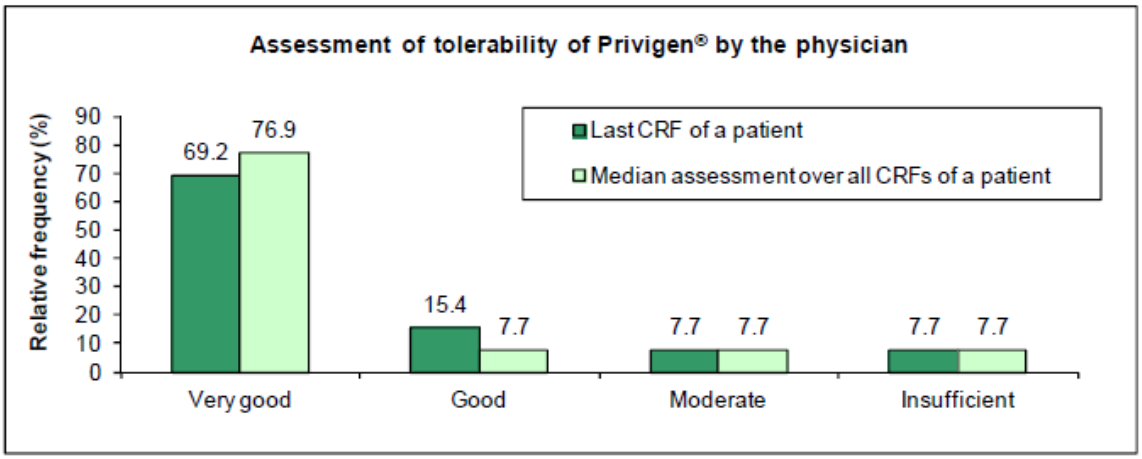
Effectiveness of Privigen documented in the last CRF of a patient was very good in 69.2% of paediatric patients (9/13), good in 15.4% (2/13) and moderate in 15.4% (2/13). Insufficient effectiveness was not documented. The median assessments over all CRFs of a patient did not differ from the assessments in the last CRFs (figure 2).

Figure 2: Assessment of effectiveness of Privigen® by the physician; assessment in the last CRF of a patient and median assessment over all CRFs of a patient; paediatric patients (N = 13)



The assessment of tolerability of Privigen was as follows: very good tolerability in 69.2% of the assessments in the last CRF of each patient (9/13) and good tolerability in 15.4% (2/13). Moderate and insufficient tolerability was documented in one case each (7.7% = 1/13). In the assessments over all CRFs of a patient using medians, the tolerability was very good in 76.9% (10/13). It was good, moderate and insufficient in one patient each (7.7% = 1/13) (figure 3).

Figure 3: Assessment of tolerability of Privigen® by the physician; assessment in the last CRF of a patient and median assessment over all CRFs of a patient; paediatric patients (N = 13)



Safety results

Adverse Events and Adverse Reactions in paediatric patients

Adverse drug reaction were documented in three paediatric patients (23.1% = 3/13). The investigators submitted six ADRs reports for these three patients. One patient was affected by one ADR, one patient by two ADRs and one patient by four ADRs. Thus, a total of seven adverse drug reactions were documented. The adverse drug reactions were coded according to MedDRA. The events were headache (SOC: nervous system disorders) (85.7% = 6/7) and nausea (SOC: gastrointestinal disorders) (14.3% = 1/7). None of the events was serious. A causal relationship to Privigen treatment was rated by the investigators highly probable in one case (14.3% = 1/7) and possible in all other cases (85.7% = 6/7). In the first phase of the study (2008-2015), reporting of adverse events without causal relationship to Privigen treatment was not required per protocol; only in the second phase (2016-2021), reporting of all adverse event (irrespective of causality) was required. Only 3 of the 13 patients (23%) had treatment cycles in the second phase (43 cycles, 19%), therefore we did not analyze adverse events rated as *not related* to Privigen by the investigator. An off label-use was documented in 4 patients: 2 patients with multiple sclerosis, 1 patient with Lennox-Gastaut syndrome, and 1 patient with Lennox-Gastaut syndrome and West syndrome.
No overdose of Privigen, pregnancy during study treatment or the death of a patient during study treatment were reported in the paediatric population. A lack of effect was stated in one patient (7.7% = 1/13; Lennox-Gastaut syndrome / West syndrome).

2.4.1. Discussion on clinical aspects

The submitted report is the final report of study results in paediatric patients; the MAH is currently preparing the full clinical study report, which will contain data from these paediatric and all adult patients and will be submitted as a second step as agreed with the EMA.

The objective of this non-interventional study conducted in Germany was the evaluation of the effectiveness and tolerability of Privigen in patients with primary or secondary immunodeficiency as well as different autoimmune diseases of all ages in clinical practice. Outcomes were defined as occurrence of infections in patients with immunodeficiency (including kind of infection, severity, duration and treatment), occurrence of bleeding events in patients with ITP, effectiveness and tolerability as assessed by the treating physician, adverse drug reactions and selected clinical laboratory tests.

5049 were included in this open-label multi-centre observational study between 11 September 2008 and 03 September 2021, thereof 13 paediatric patients. The analysed therapy cycles of the paediatric patient, were performed from 22 September 2008 to 18 September 2018. The mean (SD) observation period was 15.5 ± 30.1 months per patient. Privigen was administered based on physician's choice according to the SmPC, no specific exclusion criteria had been defined. Patients were specifically monitored as to the infusion rate, the safety, tolerability and efficacy. All medical measures were arranged by the physician according to the respective clinical practice and guidelines. Overall, up to 6 therapy cycles with Privigen could be recorded per patient, the respective treatment cycles comprised all Privigen infusions within a period of 18 days after the initial infusion. Data on undesirable events and drug reactions since the previous visit, laboratory test results (e.g. IgG, γ-globulin, and thrombocytes), dose, infusion rate, and indication-specific efficacy parameters were collected throughout the observation period. The statistical analysis included all patients with an age of <18 years and at least one dose of Privigen.

6/13 (46.2%) patients had been treatment-naïve, 7/13 (53.8%) patients had had previous treatments with intravenous immunoglobulins (IVIG) before study entry (treatment duration > 1 year in 1/7, 1 year in 5/7, unknown in 1/7 patients). 4/13 (30.8%) had a diagnosis of PID, 3/13 (23.1%) suffered from ITP and 6/13 (46.2%) had other indications such as Acute lymphoblastic leukemia (1), Lennox-Gastaut syndrome (1), West syndrome (1), Multiple sclerosis (2), and Susceptibility to infections with complications (1). Privigen was used off-label in 4/13 patients with Multiple sclerosis, Lennox-Gastaut syndrome and West syndrome.

The patients had in the mean 17 therapy cycles (median: 6 therapy cycles). Most therapy cycles were documented in patients with PID (121 therapy cycles; 30 ± 49 therapy cycles/patient) and in patients with ITP (12 therapy cycles; 4.0 ± 5.2 therapy cycles/patient). Patients with other indication had 90 therapy cycles (15 ± 28 therapy cycles/patient). PID and ITP patients received a mean dose of Privigen consistent with the recommended posology. In paediatric patients with PID, the dose regimen achieved a trough IgG level of at least 6 g/l in all documented treatment cycles (85/121), which is an acceptable target for infection prevention in PID. No serious bacterial infection was reported. The observed annual infection rate is consistent with the rate in the pivotal trial and comparable to a paediatric population without primary diseases. ITP patients had an adequate increase of thrombocyte counts after Privigen administration, and only one mild bleeding event was recorded; however, the difference between the thrombocyte counts seven days before and after the start of the therapy cycle was only calculated for 5/12 therapy cycles of the ITP patients.
Treating physicians assessed the overall effectiveness of Privigen as good or very good for 11 out of 13 (85%) patients, and moderate for 2 out of 13 patients (15%). The tolerability was acceptable for the majority of the 13 patients, and moderate and insufficient in 2/13 (15%), which resulted in discontinuation of Privigen. Moreover, 4 patients changed the IVIG product for unknown reasons.

It is noted that a revision of safety reporting was introduced in 2016; since then reporting of all adverse events irrespective of causality was required per protocol, whereas within 2008-2015 reporting of adverse events without causal relationship to Privigen treatment was not. As 3 out of 13 patients were treated during the second treatment phase since 2016, the MAH decided to only provide data on ADRs; thus, no additional adverse event data are available throughout the second phase. Overall, 7 ADRs were documented in 3 patients, 6 thereof were treatment-related headache, and 1 nausea. These observed ADRs are (very) commonly observed under IVIG therapy. However, the included patient number is too limited to assess the quantity and quality of ADRs in this unselected patient population under real life conditions.

3. CHMP overall conclusion and recommendation

Based on the submitted report, post-marketing information is available for merely 13 paediatric patients. Available data indicate an adequate effectiveness; however, efficacy parameters were only documented for a limited number of treatment cycles in all included indications. The overall tolerability was acceptable based on the physician's assessment. The MAH provided data on documented ADRs, however, no adverse event data is available for the longest period of the study. These facts are a shortcoming regarding the usability and interpretability of the collected paediatric safety data. Based on these data it is impossible to draw any reliable conclusion on the paediatric safety profile of Privigen. Currently, no urgent action as to amendments of the product information is deemed necessary until the availability of the final study report, which is expected in September 2022.

No comments from member states were received.

☒ **Fulfilled:**

No regulatory action required.