EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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/P46/034.1

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
CIDP	Chronic inflammatory demyelinating polyneuropathy
CSL	CSL Behring
CSR	Clinical Study Report
CRF	Case report form
eCRF	Electronic case report form
EMA	European Medicines Agency
FPFV	First patient first visit
GDPR	General Data Protection Regulation
IAC	Immunoaffinity chromatography
ID	Immunodeficiency
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INCAT	Inflammatory neuropathy cause and treatment
ITP	Immune thrombocytopenia
i.v.	Intravenous
IVIG	Intravenous immunoglobulin
LPLV	Last patient last visit
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMN	Multifocal motor neuropathy
N	Number
N%	Percentage
NIS	Non-interventional study
PID	Primary immunodeficiency
PSAF	Proven specific antibody failure
PT	Preferred term
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 Characteristic

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1. Introduction

On 30 January 2023, the MAH submitted a completed paediatric study for IgPro10 (Privigen), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A report and expert overview summarising the data from all paediatric patients included in the IgPro10_5001 study were previously submitted with eCTD sequence 0347 and assessed under Procedure EMA/H/C/000831/P46/034. The submission herewith includes the final study report and expert overview on the full set of patients enrolled in the observational study IgPro10_5001 (paediatrics and adults), however, as documented in Part 2 of the final CSR, the final report of study results in paediatric patient was February 2022. Upon request the MAH clarified that no additional paediatric data or analyses thereof are included.

Please find below a comparison of the data presented on the current P46 comparing with the data presented in the previous P46 034.

	P46 034	P46 Current
Reporting Period	11-Sep-2008 to 12-Nov-2013	11-Sep-2008 to 12-Nov-2013
Data Included	13 paediatric patients	5,047 patients (13 paediatrics + 5,034 adults)
Assessment/Conclusion	The data are consistent with the known efficacy and safety profile of Privigen®. No change to the formulation or to the European SmPC are proposed based on these study results.	The data are consistent with the known efficacy and safety profile of Privigen®. No change to the formulation or to the European SmPC are proposed based on these study results.

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 study 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)

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). This study was conducted at 243 centers in Germany.

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.

In addition, and following an amendment to the protocol on November 10, 2015, the study also assessed Privigen batches without isoagglutinin reduction ("original" Privigen) and Privigen batches containing a reduced concentration of anti-A and anti-B isoagglutinins after implementation of an immunoaffinity chromatography (IAC) column into the production process in 2015 and 2016 (hereafter referred to as the Ig-IsoLo procedure).
The administration of polyvalent intravenous immunoglobulin products (IVIG) is associated with known class effects, including hemolysis and hemolytic anemia. As a risk mitigation measure, CSL introduced an IAC in the manufacturing process to reduce isoagglutinin titres in the final product. The IAC step was implemented in the routine manufacturing process in 2015 and 2016, and as of 31 May 2016, batches manufactured with this new process started to be released in the European Union.

Owing to the protocol amendment, 2 Clinical Study Reports (CSRs) were prepared: Part 1 and Part 2. IgPro10_5001, Part 1 summarizes the data collected with the first version of the CRF (ie, CRF numbers 1-910, “short CRF”) while IgPro10_5001 Part 2 summarizes the data collected with the “extended” version of the CRF (CRF numbers ≥911).

Methods

Study design

Study IgPro10_5001 was a retrospective, observational, non-interventional, post-marketing surveillance as defined by §4, section 23, sentence 3 of German Medicinal Products Act (AMG), for which no specifications with respect to indication or administration of the product were set forth. Patients enrolled in the study had to have received Privigen for any approved indication as part of their regular medical care.

Study participants

In total, CRFs from 5,047 patients including 13 paediatric patients could be evaluated in Part 1 and Part 2. Treatment cycles of 273 patients were documented using the short version of the CRFs (Part 1). Treatment cycles of 4,880 patients were documented using the extended CRF version (Part 2). 105 patients had Privigen treatments documented with both the short and the extended CRF versions. 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.
Owing to a study protocol amendment, 2 Clinical Study Reports (CSRs) were prepared: Part 1 and Part 2. IgPro10_5001, Part 1 summarizes the data collected with the first version of the CRF (ie, CRF numbers 1-910, "short CRF") while IgPro10_5001 Part 2 summarizes the data collected with the "extended" version of the CRF (CRF numbers ≥911).

The data collected in the short CRF version (CRF numbers 1-910) were:
☐ Baseline characteristics: sex, age, weight, height
☐ Indication for treatment with Privigen
☐ Previous treatment with IVIG
☐ Infusions: premedication, Privigen dose, duration of infusion
☐ Laboratory data: serum IgG, gamma globulin, thrombocyte count (if measured for clinical reasons)
☐ Assessment of effectiveness and tolerability of Privigen by the treating physician using a 4-item scale ("very good", "good", "moderate" and "insufficient")
☐ Reason for discontinuation of treatment with Privigen, if applicable
☐ Adverse drug reactions (ADRs) that occurred during or after the Privigen infusion
☐ Occurrence of special situations with potential safety relevance, such as use during pregnancy or breastfeeding, overdose, off-label use or lack of therapeutic effect.

Specific parameters for the assessment of the effectiveness of Privigen in specific indications (eg, data on infections in immunodeficiency patients, data on bleedings in patients with immune thrombocytopenia or data on mobility in neurological patients) were added to the "extended CRF" (CRF numbers ≥911). The extended CRF additionally included a standard panel of routine laboratory values (eg, hematology, liver and kidney function) as well as clinical signs and symptoms for the assessment of the effectiveness of Privigen in specific indications (eg, data on infections in immunodeficiency patients, data on bleedings in immune thrombocytopenia [ITP] and scores for activity and mobility in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy [CIDP]).

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 at least one documented Privigen application in the extended CRF version were included in the analysis presented in part 2 of the study report (CRF numbers ≥911; 4,880 patients).

A *treatment cycle* was defined as the time period between two Privigen infusions (dosing interval) if this interval spanned at least 18 days. If a Privigen infusion followed less than 18 days after the previous infusion, it was considered part of the same treatment cycle. The threshold of 18 days was chosen based on the lower margin of the recommended dosing interval 3-4 weeks for most indications, minus a tolerance of 3 days. A differing threshold of 10 days was chosen for ITP, based on the typical dynamics of the thrombocyte's response (peak after about 8 days).

The *observation period* was calculated as the time interval between the first and the last study visit (including follow-up after the last Privigen infusion).

The *treatment period* was calculated as the time interval between the first and the last documented Privigen infusion, disregarding dosing intervals >200 days. An interval between two infusions >200 days is regarded as a treatment interruption, and not as part of the regimen. Therefore, such interruptions were subtracted when calculating the treatment period of a patient, with the exception of the first 35 days of the interruption, in which a remaining pharmacological activity can be assumed ("wash-out"). Treatment intervals <200 days were not subtracted from the calculated treatment period since those are often part of the regimen, especially as "summer drug holiday" in immunodeficiencies, under the assumption that the infection risk is smaller in the warmer months.
The quantitative criteria were the number of cases as well as the maximum, minimum, 1st quantile, mean, 3rd quantile, median, standard error and standard deviation. No statistical hypotheses were formulated. The analyses were stratified by indication and administered type of Privigen ("original Privigen" vs. "Privigen including Ig-IsoLo procedure"). All observations pertaining to safety and tolerability were analyzed according to the clinical description, frequency, seriousness, likelihood of being related and outcome. Adverse drug reactions were coded according to Medical Dictionary for Regulatory Activities (MedDRA) (version 25.0) and grouped according to Preferred Term (PT) and System Organ Class (SOC).

Results

It should be noted that the transition from the short CRF version (Part 1 of the study) to the extended CRF version (Part 2 of the study) in 2009 occurred with an overlap, and 105 patients had Privigen treatments documented with both the short and the extended CRF versions. These patients are included in both parts of the analysis: Those of their treatments which are documented in CRF books with numbers 1-910 (short CRF version) are included in part 1 of the report, and those of their treatments which are documented in CRF books with numbers ≥911 (extended CRF version) are included in part 2 of the report (this document).

Results from Part 1 of Study IgPro10_5001
Part 1 of the study summarizes data collected in 273 patients from 73 centers with documentation of Privigen treatment as recorded in the short CRF version (CRF numbers 1-910). The analysis is

comprised of 1,215 treatment cycles with 1,538 Privigen infusions. The mean observation period was 4.7 months per patient. Across all indications, the average dose of Privigen per infusion was 14.6 g (0.20 g/kg body weight [BW]) and the total dose per treatment cycle was 18.5 g (0.26 g/kg BW). The mean IgG level in patients with secondary immunodeficiency (SID) without previous IVIG treatment before the first infusion was 5.1 g/L and the average trough level during study therapy was 6.0 g/L. Thrombocyte count increased in patients with ITP by an average of 79,833 cells/µl compared to the value before the start of the treatment cycle.
Effectiveness of Privigen was assessed as very good or good in 85.3% of patients and the tolerability of Privigen was assessed as very good or good in 93.0% of patients according to the final assessments performed by the treating physicians (across all indications).
The analysis of the tolerability of Privigen was based on the occurrence of ADRs and the assessment of tolerability by the treating physician. The CRF contained an ADR report form, but not a report form for unrelated AEs. In some cases, however, the physicians reported AEs for which they rated the relatedness to Privigen as "unlikely" or "unassessable" on the ADR report form. Since this was not required by the protocol, the "unrelated" AEs documented this way are not complete and not representative for the totality of unrelated AEs that have occurred to the patients – usually with severe underlying diseases – during participation in the study. The ADRs were coded according to MedDRA (version 24.1). The most frequently documented events were chills (preferred term) (treatment cycles: 0.91% = 11/1,215; patients: 3.30% = 9/273) and nausea (preferred term) (treatment cycles: 0.41% = 5/1,215; patients: 1.47% = 4/273). The investigators reported 6 serious ADRs in 2 patients. The reported serious ADRs were bronchospasm (n = 2), chills (1), dyspnea (1), hypersensitivity (1) and a decreased oxygen saturation (1).

Results from Part 2 of the Study
Part 2 presents the analysis of application of Privigen in a total of 4,880 patients from 232 centers with documentation of Privigen treatment as recorded in the extended CRF version (CRF numbers ≥911). The statistical analysis included 101,495 Privigen infusions administered across 87,987 treatment cycles. The mean observation period was 22 months per patient and the mean treatment period was 18.1 months per patient. Patients who had evaluable treatment periods with original Privigen received 23,179 infusions in 19,108 evaluable treatment cycles, and patients who had evaluable treatment periods with Privigen including Ig-IsoLo procedure received 32,590 infusions in 30,199 evaluable treatment cycles. A total of 45,726 infusions in 38,680 cycles were not CSL Behring IgPro10 evaluable for the analysis of Privigen including Ig-IsoLo procedure. Original Privigen was mainly administered in the "intermediate" period between July 2013 and December 2016, during which both types of Privigen could be infused. The overall effectiveness of Privigen as assessed by the treating physician at the last visit was documented in 4,833 patients. The assessment was very good or good in 86.1% of patients (4,162/4,833; very good: 38.0% = 1,835/4,833; good: 48.1% = 2,327/4,833). Insufficient effectiveness was reported in 103 patients (2.1% = 103/4,851). The assessments were similar in evaluable treatment periods with original Privigen and with Privigen including Ig-IsoLo procedure (original Privigen: very good or good in 85.5% [1,660/1,942], Privigen including Ig-IsoL procedure: 92.0% [1,609/1,749]).
The overall tolerability of Privigen as assessed by the treating physician at the last visit was documented in 4,828 patients (52 missing). The assessment was very good or good in 93.7% of patients (4,526/4,828; very good: 47.6% = 2,298/4,828; good: 46.1% = 2,228/4,828). Insufficient tolerability was reported in 91 cases (1.9% = 91/4,851). The assessments of tolerability in evaluable treatment periods with original Privigen and with Privigen including Ig-IsoLo were similar (original Privigen: very good or good: 93,0% = 1,803/1,938; Privigen including Ig-IsoLo procedure: very good or good: 96.3% = 1,685/1,750). Overall, the investigators reported 1,549 events in 808 ADR reports for 555 patients as at least possibly related to Privigen (11.4% = 555/4,880). A suspected relationship between serious adverse events and Privigen was reported in 0.05% of therapy cycles (43/87,987) and in 0.8% of patients (40/4,880).
The most frequent reason for assessment of an ADR as serious was hospitalization or prolonged hospitalization (67.5% = 27/40). Serious ADRs (causal relationship to Privigen assessed as possible or probable by investigator) reported more than once were chills (15 events), increased body temperature (9), dyspnea (8), pyrexia (7), hypersensitivity (5), nausea (3), rash (3), allergic

dermatitis (2), aseptic meningitis (2), chest discomfort (2), increased blood pressure (2), ischaemic cerebral infarction (2), headache (2), hypertensive crisis (2) and pain (2).

Results Across the Entire Study
Under real-world conditions in an observational study, the ADR rates for Privigen were reported to be lower than previously observed in the pivotal trials. This may be partly due to the differences in the study settings, with a closer monitoring in the pivotal trials, sensitizing patients and study personnel to observe and report even minor changes in the patient's health status. Lack of effectiveness of Privigen treatment was documented for 158/4,880 patients (3.2%), most frequently in patients with autoimmune diseases (10.0% = 106/1,057). Privigen overdose (administration of higher Privigen dosage than approved in the SmPC for the respective indication) was observed in 1,220 infusions (1.2% = 1,220/101,495) of 822 treatment cycles (0.9% = 822/87,987) across 141 patients (2.9% = 141/4,880); most frequently in patients with autoimmune diseases (infusions: 4.7% = 1,203/25,421; therapy cycles: 4.7% = 815/17,419; patients: 12.9% = 136/1,057). The occurrence of an ADR (causal relationship to Privigen considered at least possible by investigator) was documented in 18 treatment cycles with an overdose of Privigen (2.2% = 18/822); none of the events was serious (for comparison: reported CSL Behring IgPro10 ADRs in therapy cycles without overdose: 0.9% = 771/86,487). Events reported more than once in treatment cycles with overdose were headache (7 events), chills (2), nausea (2), rash (2) and hypertensive crisis (2 in 1 patient).
Across the study duration from 2008 to 2021, death was reported in 355 patients (7.3% = 355/4,880). The documented causes of death were most frequently the underlying disease (38.6% = 137/355), infections (23.1% = 82/355), and cardiac disorders (6.5% = 23/355). A relationship between death and an ADR to Privigen treatment was considered possible by the investigator in 2 patients: 1 patient with an ischaemic cerebral infarction in the area of the arteria cerebri media 1 day after the first administration of Privigen (30 g) for ITP; 1 patient with dizziness, nausea and vomiting, hospitalized with suspected brain stem ischaemia / lacunar brain infarction (not confirmed by MRT).

Conclusion
In summary, effectiveness and tolerability of Privigen administered in a clinical practice setting in patients with primary or secondary immunodeficiency, as well as different autoimmune diseases, were assessed as very good or good in the majority of the pediatric and adult patients included in Study IgPro10_5001 according to the assessment of treating physicians. The data are consistent with the known efficacy and safety profile of Privigen. No change to the formulation or to the European SmPC are proposed based on these study results.

2.3.2. Discussion on clinical aspects

The submitted report is the full clinical study report, which contains the data from 5,047 patients including 13 paediatric patients enrolled in study IgPro10_5001; as agreed with the EMA in 2022, it was submitted as a second step following procedure EMA/H/C/000831/P46/034. It is to be noted that no new paediatric data or analyses thereof were provided with this full CSR.

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.

5047 subjects were included in this open-label multi-centre observational study between 11 September 2008 and 03 September 2021. As mentioned above, two Clinical Study Reports (CSRs) were prepared following a protocol amendment: Part 1 and Part 2. Part 2 includes more evaluable data as the number of treatment cycles and Privigen infusions was much higher compared with Part 1: In Part 1, the statistical analysis comprised 1,215 treatment cycles with 1,538 Privigen infusions, whereas in Part 2 it included included 87,987 treatment cycles with 101,495 Privigen infusions administered; 23,179

infusions in 19,108 evaluable treatment cycles thereof were evaluable for the administration of the original Privigen and regarding the administration of Privigen including Ig-IsoLo procedure, 32,590 infusions in 30,199 treatment cycles were suitable for evaluation.

The overall mean observation period was 4.7 months per patient in Part I, in Part 2 22 months per patient, and thus, slightly longer than in the 13 paediatric patients (17 months).

Part 1 included a single female paediatric subject, in Part 2 five male and seven female subjects were included, thus overall 13 subjects. Across all indications, trough levels were comparable between the paediatric and adult population and no serious bacterial infections were reported in either of them. In adults, events with prolonged or increased bleeding occurred less frequently, however, severe bleedings were occurred more often than in the paediatric ITP patients (8.3%). The overall effectiveness and tolerability of Privigen was comparable between the paediatric and adult study population. As P46 procedures focus on assessment of paediatric data, please refer to FAR of procedure EMEA/H/C/000831/P46/034.

3. CHMP overall conclusion and recommendation

The submitted final study report does not provide dedicated analyses of paediatric data. This was, however, submitted in February 2022, and no regulatory action resulted from their assessment. The MAH confirmed that no additional paediatric data or further analyses of the already submitted data are included in the submitted final CSR.

☒ **Fulfilled:**

No regulatory action required.