16 October 2025

EMADOC-1700519818-2283313
Human Medicines Division

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

Hizentra

Human normal immunoglobulin

Procedure no: EMA/PAM/0000285945

Note

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

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1. Introduction

On 10 July 2025, the MAH submitted a completed paediatric study for Hizentra, 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 HZT-NIS-2011: Hizentra in patients with primary or secondary immunodeficiency or CIDP is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Commercial Hizentra (IgPro20) was used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- HZT-NIS-2011: Hizentra in patients with primary or secondary immunodeficiency or CIDP

CHMP comment:

As this is a p46 procedure of a Phase 4 observational, non-interventional post-marketing surveillance study, only the paediatric data are assessed.

2.3.2. Clinical study

HZT-NIS-2011: *Hizentra in patients with primary or secondary immunodeficiency or CIDP*

Description

Study HZT-NIS-2011 was a Phase 4 observational, non-interventional post-marketing surveillance study in adult and paediatric patients treated with the subcutaneous immunoglobulin product Hizentra. It was conducted in Germany from August 2011 to January 2025.

A total of 200 patients in approximately 40 outpatient clinics and practices treating patients with an immunodeficiency and 20 clinics and practices treating CIDP patients were anticipated. Five study visits could be documented in a paper case report form (CRF): one baseline visit and four follow-up visits, each approximately 3 months apart. Hence, the CRF covered a 12 months follow-up period. CIDP patients could be under observation for up to 36 months, using up to three sequential CRFs for an individual patient. At the end of the observation period of a patient as well as in case of premature discontinuation, an end of study (EOS) visit had to be documented.

Methods

Study participants

Inclusion criteria:

1. Substitution therapy for primary antibody deficiency syndrome
   or
   Substitution therapy for myeloma or chronic lymphocytic leukemia with severe secondary hypogammaglobulinemia and recurrent infections
   or
   Immunomodulation therapy for CIDP
2. Indication for the administration of Hizentra
3. Consent of the patient or his/her legal representative to the use of their data in the context of this study

Exclusion criteria:

1. Hypersensitivity to one of the components of Hizentra
2. Hyperprolinemia
3. Doubts about the patient's mental state

Treatments

Hizentra as per label

Objective(s)

The objective of this non-interventional study was to evaluate the effectiveness and tolerability of Hizentra in patients with PID, SID or CIDP of all ages in clinical practice

Outcomes/endpoints

The endpoints were:

- Occurrence of infections during the study (including type and number of infections, causal pathogen, severity, duration, and therapy)
- Serum IgG levels during the study
- In CIDP patients: INCAT (Inflammatory Neuropathy Cause and Treatment) Disability Score (Hughes 2001); grip strength (if measured for clinical reasons)
- Effectiveness assessed by patient and physician at the end of the observation period
- Tolerability assessed by patient and physician at the end of the observation period

Sample size

A total of 200 patients in approximately 40 centers treating patients with an immunodeficiency and 20 centers treating CIDP patients were anticipated.

Statistical Methods

Only descriptive analyses were performed. Analysis of patient disposition were performed for all paediatric patients enrolled in this study, any other evaluation in the full analysis set (FAS). The FAS included all paediatric patients (age < 18 years) whose legal representative gave written informed consent and to whom at least one dose of Hizentra was applied during the study.

Results

Participant flow

In total, 181 patients were enrolled by 22 active centers.

At the time of inclusion, nine patients were younger than 18 years. These patients were included by two centers (one hospital and one office-based physician).

All paediatric patients completed the planned observation period of 12 months; 2 patients had a delayed final study visit in month 15. At the individual last study visit, it was stated for 6 patients (67%) that they would continue the Hizentra therapy after the study; 2 patients (22%) would not because of ADRs (missing information for 1 patient).

CHMP comment:
As mentioned by the MAH, an underreporting of infections is likely (see also below) due to an error in the CRF. As it was identified in the late stage of the study (December 2020), the recruitment of patients with immunodeficiencies was halted on 6 January 2021.

Baseline data

At baseline, the mean age of the paediatric patients was 9.9 years (range: 3 – 16 years). All paediatric patients were male. The mean BMI was 17.5 kg/m². All paediatric patients had PID, most frequently CVID (55.6%) and XLA (33.3%). Patients were diagnosed on average 4.6 years (range: 1.0 – 13.2 years) before study inclusion.

All paediatric patients were treated with IgG before study inclusion. Most frequently, patients were treated with Hizentra (88.9%) in the past 12 months and directly before study inclusion. These eight patients received Hizentra on average for 25.7 months (range: 4.5 – 71.7 months), with a mean dose of 4.0 g (range: 2.0 – 8.0 g) and a dosing interval of 7 days. One patient each was treated with Gamunex or Vivaglobin in the prior 12 months. In general, prior treatments were tolerated well or very well (80%). Two patients showed a moderate tolerability of Hizentra. All patients performed self-infusions at home before study inclusion.

Number analysed

All nine patients fulfilled all eligibility criteria and were included in the FAS.

Efficacy results

During the observation period, 5 infections requiring antimicrobial treatment were documented in 3 paediatric patients (4 upper airway infections, 1 conjunctivitis; none was severe). However, infections were possibly underreported because of an error in the CRF design: erroneously, patients were asked at each study visit if infections had occurred since the last Hizentra administration instead of since the last study visit. Given that study visits took place approximately every three months while Hizentra is typically administered once a week (at home), an underreporting of infections may have occurred.

For all paediatric patients, effectiveness of Hizentra was rated as good (11.1%) or very good (88.9%) by both the physicians and the patients at EOS.

<u>IgG</u>

The average serum IgG slightly increased from 10.2 g/L at baseline to 10.7 g/L after 12 months (range: 6.2–17.4 g/L).

Safety results

<u>Exposure</u>

The Hizentra infusions during the study were administered at the patients' homes, typically by their parents or by themselves (after appropriate training). Over 12 months of observation, the mean total dose per week was on average 127 mg/kg BW (range 83–162).

Adverse events

In three paediatric patients (33.3%), at least one ADR occurred.

Subject ID	Diagnosis	Age group	ADR term (original entry)	ADR term	Serious AE	Outcome	Causality	Start date	End date
[redacted]	PID	Child	Painful granulomas after each s.c. administration over 4 weeks		No	Recovering	Very likely	--/--/2013	
	PID	Child	S.c. granuomas, palpable over two weeks each		No	Unknown	Very likely	seit 2013	andauernd
	PID	Child	(1) Indurations lasting for several days after infusion, and meanwhile not disappearing at all any more. (2) Itching after application		Yes	Recovering	Very likely	12/2013	

Tolerability

The physicians rated the tolerability of Hizentra for seven paediatric patients as good (33.3%) or very good (44.4%). Similarly, 66.6% of the patients rated the tolerability as at least good. Both physicians and patients reported an insufficient tolerability in two cases (22.2%).

2.3.3. Discussion on clinical aspects

Study HZT-NIS-2011 was a non-interventional study conducted in Germany to assess the effectiveness and tolerability of Hizentra in patients with PID/SID or CIDP.

A total of nine paediatric patients with PID were enrolled and were included in the FAS set. All nine subjects had received immunoglobulins prior to the study.

While the submission contained only limited data on efficacy, both investigators and patients reported satisfactory effectiveness with Hizentra. 5 infections requiring antimicrobial treatment were documented in 3 paediatric patients. Of note, the MAH pointed out a likely underreporting of infections due to an error in the CRF design. As it was identified in the late stage of the study (December 2020), the recruitment of patients with immunodeficiencies was halted on 6 January 2021. Nevertheless, efficacy of IVIg/SCIg are well-established in PID and the efficacy results with Hizentra in this study appear to be in line with prior experiences.

Furthermore, the safety findings seem to be consistent with the established safety profile of Hizentra and related SCIg products, and no safety concerns were identified.

3. CHMP overall conclusion and recommendation

The effectiveness of Hizentra in the paediatric subpopulation of study HZT-NIS-2011 appears to be in line with the previous experience of Hizentra. The safety profile in the paediatric population of Study HZT-NIS-2011 seems to be consistent with the known safety profile of Hizentra.

It is agreed that no changes to the Product Information are required.

The benefit/risk ratio for Hizentra remains unchanged.

☒ **Fulfilled:**

No regulatory action required.