19 June 2025
EMADOC-1700519818-2036370
Human Medicines Division

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

Cimzia

Certolizumab pegol

Procedure no: EMA/PAM/0000263734

Note

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

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Status of this report and steps taken for the assessment			
Current step[1]	Description	Planned date	Actual Date
☐	CHMP Rapporteur AR	26 May 2025	05 May 2025
☐	CHMP comments	10 June 2025	10 June 2025
☐	Updated CHMP Rapporteur AR	12 June 2025	n/a
☒	CHMP outcome	19 June 2025	19 June 2025

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Report
EC	European Commission
EMA	European Medicines Agency
EU	European Union
IL	interleukin
JIA	Juvenile Idiopathic Arthritis
MAH	marketing authorization holder
PAM	post-authorization measure
PEG	polyethylene glycol
PIP	paediatric investigation plan(s)
pcJIA	polyarticular-course Juvenile Idiopathic Arthritis
PFP	prefilled pen
PFS	prefilled syringe
PK	pharmacokinetic(s)
PsA	psoriatic arthritis
RA	rheumatoid arthritis
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
TNFα	tumor-necrosis factor alpha

1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

On 07 Oct 2024, the applicant submitted to the EMA the final CSR for study RA0043, "A Multicenter, Open- label Study to Assess the Pharmacokinetics, Safety, and Efficacy of Certolizumab Pegol in Children and Adolescents with Moderately to Severely Active Polyarticular-course Juvenile Idiopathic Arthritis," as a standalone PAM (EMEA/H/C/001037/P46/041) in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

The EMA issued an Opinion on 30 Jan 2025, recommending that the PAM is considered fulfilled but "in view of the available data regarding the paediatric population in the phase 3 study (RA0043) with Cimzia, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so."

The applicant has presented a scientific justification for not submitting a variation to include a brief summary of the main results from study RA0043 in the SmPC Section 5.1 and Section 5.2. Nevertheless, the MAH accepts the update to Section 4.2 of the SmPC and proposes submitting the update at the next regulatory opportunity.

CHMP overall conclusion and recommendation

The CHMP made the following overall conclusion and recommendation in the Opinion issued on 30 Jan 2025:

"Treatment with Cimzia across a range of doses was well tolerated in children and adolescents with moderately to severe active pcJIA. It can be agreed with the MAH that the safety results for the study participants were consistent with the established safety profile of TNFα inhibitors. No new safety signals evoked."

Considering that the statement in the SmPC Section 4.2 ("The safety and efficacy of Cimzia in children and adolescents below age 18 years have not yet been established. No data are available.") is no longer correct, the MAH is requested to submit a variation to update Section 4.2 (or provide a justification for not doing so) and include a brief summary of the main results from study RA0043 in the SmPC Section 5.1 and Section 5.2. If paediatric data are to be included in the SmPC, the MAH is also asked to consider whether any particular warnings regarding possible risks associated with pegylated products in the paediatric population are to be included."

2. Summary of data submitted

No new data has been submitted.

3. Scientific discussion

Applicant Positions

There is no medical need for Cimzia for paediatric pcJIA patients in Europe

Three TNFα inhibitors, etanercept, adalimumab, and golimumab, are currently approved in the EU for the treatment of patients with JIA. Additionally, the janus kinase inhibitors tofacitinib and baricitinib are approved in the EU for the same indication. Secukinumab, an IL-17 inhibitor, is also approved in

the treatment of 2 subtypes of JIA. This wide range of therapeutic options offer adequate coverage for EU paediatric patients with this condition from 2 to 18 years old.

A product-specific waiver (EMEA-001071-PIP02-12-M02; Decision date: 03 Jul 2017) was granted for Cimzia in all subsets of the paediatric population from birth to less than 18 years of age "on the grounds that the specific medicinal product *[Cimzia]* does not represent a significant therapeutic benefit over existing treatments" for paediatric patients. This PIP Opinion (ie, full waiver) covers the conditions/indications treatment of chronic idiopathic arthritis, including rheumatoid arthritis, ankylosing spondylitis, PsA, and JIA as well as JIA-associated uveitis.

Introduction of paediatric information in Section 5.1 and Section 5.2 of the SmPC could lead to off-label use and potential incorrect dosing

The MAH recognizes that in line with the SmPC guideline, results of pharmacodynamic (clinically relevant), efficacy, and PK studies conducted in children should be presented in Section 5.1 and Section 5.2 accordingly, even if there is no authorized indication in any subset of the population. Nevertheless, according to the same SmPC guideline, a scientific judgement on a case-by-case basis is needed to ascertain whether the results may be of relevance to healthcare professionals and patients and therefore included in the SmPC.

The MAH considers that presenting the RA0043 study data in Section 5.1 and Section 5.2 of the SmPC without an indication in that region or a posology recommendation in paediatric patients could lead to off-label use with administration of adult doses that have not been demonstrated to be safe and/or efficacious in the paediatric population. Furthermore, the paediatric data from the RA0043 study do not provide any additional benefit to support the approved indications in Section 4.1 of the SmPC.

The pharmaceutical forms of Cimzia available in the European market do not allow administration of doses lower than 200mg (the pharmaceutical forms available in the European market are for 200mg or 400mg doses only, in the format of PFS and PFP presentations of 200mg solution for injection). Therefore, the commercially available presentations of Cimzia are not compatible with lower doses needed for children. In the absence of adequate presentations for children, introducing information on paediatric studies (efficacy and PK information) could lead to potential off-label use and incorrect dosing of paediatric patients.

CHMP comment:

The applicant proposes that presenting study data from RA0043 in SmPC Section 5.1 and Section 5.2 without an indication or a posology recommendation in paediatric patients could lead to off-label use. Since doses below 200 mg are not available in the EU, the applicant considers that children might be administered adult doses that have not been demonstrated to be safe and/or efficacious in the paediatric population.

Based on these assumptions, the applicant proposes not to introduce any data from RA0043 in SmPC Section 5.1 and Section 5.2, which is endorsed.

Proposed wording for SmPC Section 4.2 update

The MAH agrees with the CHMP that the statement in the SmPC Section 4.2 ("The safety and efficacy of Cimzia in children and adolescents below age 18 years have not yet been established. No data are available.") is no longer correct, and therefore proposes the following SmPC update:

Current SmPC text:

"*Paediatric population*

The safety and efficacy of Cimzia in children and adolescents below age 18 years have not yet been established. No data are available."

Proposed SmPC text:

"*Paediatric population*

Cimzia is not indicated for use in children and adolescents below 18 years of age."

The proposed wording addresses the fact that no paediatric indication has been granted, and therefore including a posology recommendation in children would be inappropriate.

The MAH considers that including data in Section 5.1 and Section 5.2 could lead to off-label use and incorrect dosing of Cimzia in paediatric patients. Therefore, the MAH considers that the proposed updated wording in Section 4.2 reflects more correctly the current position of Cimzia in the paediatric population in the EU.

The MAH proposes to submit the above-mentioned update at the next regulatory opportunity, as part of the next variation application or as a stand-alone variation before the end of the current year.

CHMP comment:

The applicant proposes to update SmPC section 4.2 with the text:

"*Paediatric population*

Cimzia is not indicated for use in children and adolescents below 18 years of age."

To align with the SmPC guideline, a small modification of the text is however suggested:

"*Paediatric population*

The safety and efficacy of Cimzia in children and adolescents below age 18 years have not been established. Cimzia should not be used in children and adolescents below 18 years of age."

It is acceptable that the update is performed at the next regulatory opportunity.

Considerations for PEG

No new safety signals were observed in the long-term study RA0043, which had a mean exposure of 4.336 years and a maximum exposure of 11.39 years. Cimzia exhibited an acceptable safety profile consistent with the known safety profile of Cimzia in adults with RA. Cimzia was well tolerated in paediatric study participants with pcJIA, and the majority of TEAEs were mild or moderate in intensity.

Given that no toxicities were observed in the juvenile monkey study with Cimzia (NCD2281), no serious adverse consequences were observed in paediatric populations with long-term exposure to PEGylated therapies (Stidl et al, 2016; Stidl et al, 2018; Turecek et al, 2016), and no new safety signals or concerns were observed in RA0043, no special warnings or precautions for the paediatric population would be considered necessary for the Cimzia SmPC, even if paediatric information was to be included in the label. Lastly, extensive clinical and post-marketing data in adults have not raised any safety concerns about PEG.

4. Overall conclusion

There are multiple treatments, including several TNFα inhibitors, approved in the EU for use in the JIA population from 2 to 18 years of age. A product-specific waiver (EMEA-001071-PIP02-12-M02; Decision date: 03 Jul 2017) was granted for Cimzia in all subsets of the paediatric population from birth to less than 18 years of age "on the grounds that the specific medicinal product *[Cimzia]* does not represent a significant therapeutic benefit over existing treatments" for paediatric patients. This PIP Opinion (ie, full waiver) covers the conditions/indications treatment of chronic idiopathic arthritis, including rheumatoid arthritis, ankylosing spondylitis, PsA, and JIA as well as JIA-associated uveitis.

The applicant proposes that adding information in the Cimzia SmPC for the paediatric population could lead to off-label use. Since doses below 200 mg are not available in the EU, the applicant considers that children might be administered adult doses that have not been demonstrated to be safe and/or efficacious in the paediatric population. Based on these assumptions, the applicant proposes not to add any data from RA0043 in SmPC Section 5.1 and Section 5.2, which is endorsed.

The safety information in the current SmPC is assessed as adequate and does not require any updates.

The applicant commits to update Section 4.2 of the SmPC to correct the statement that no data in the paediatric population is available. To align with the SmPC guideline, a small modification of the text is however suggested:

"*Paediatric population*

The safety and efficacy of Cimzia in children and adolescents below age 18 years have not been established. Cimzia should not be used in children and adolescents below 18 years of age."

It is acceptable that the update is performed at the next regulatory opportunity.

☒ **PAM fulfilled**

No regulatory action required.