15 November 2022
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EMADOC-1700519818-911267
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Enjaymo (humanised IgG4 monoclonal antibody against total complement component 1, subcomponent s)

Treatment of autoimmune haemolytic anaemia

EU/3/16/1609

Sponsor: Genzyme Europe B.V.

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Humanised IgG4 monoclonal antibody against total complement component 1, subcomponent s
Other name(s)	Enjaymo, Humanised IgG4 monoclonal antibody against total complement component 1, subcomponent s,
International Non-Proprietary Name	Sutimlimab
Tradename	-
Orphan condition	Treatment of autoimmune haemolytic anaemia
Sponsor's details:	Genzyme Europe B.V. Paasheuvelweg 25 1105 BP Amsterdam Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Assign Group Development UK Ltd
COMP opinion	21 January 2016
EC decision	17 February 2016
EC registration number	EU/3/16/1609
Post-designation procedural history	
Change of name and/or address of sponsor	20 November 2018
Transfer of sponsorship	Transfer from Celerion United Kingdom Limited to Celerion Austria GmbH – EC decision of 11 January 2019
Transfer of sponsorship	Transfer from Celerion Austria GmbH to Genzyme Europe B.V. – EC decision of 28 November 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Kristina Dunder/ Paula Boudewina van Hennik
Applicant	Genzyme Europe B.V.
Application submission	8 October 2021
Procedure start	28 October 2021
Procedure number	EMA/H/C/005776
Invented name	Enjaymo
Proposed therapeutic indication	Treatment of haemolysis in adult patients with cold agglutinin disease Further information on Enjaymo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/enjaymo

CHMP opinion	15 September 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Karri Penttila
Sponsor's report submission	2 February 2022
COMP discussion	6-8 September 2022
COMP opinion (adoption via written procedure)	16 September 2022

2. Grounds for the COMP opinion

The sponsor Assign Group Development UK Ltd submitted on 25 September 2015 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing humanized IgG4 monoclonal antibody against total complement component 1, subcomponent s (C1s) for treatment of autoimmune hemolytic anemia (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing humanized IgG4 monoclonal antibody against total complement component 1, subcomponent s was considered justified based on clinical data demonstrating decreased hemolysis and increased hemoglobin levels;
- the condition is chronically debilitating due to venous or arterial thrombotic events, infectious complications, requirement of red blood cell transfusion and decreased quality of life;
- the condition was estimated to be affecting less than 2.3 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorized in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanized IgG4 monoclonal antibody against total complement component 1, subcomponent s will be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vitro and early clinical data from persons affected by cold autoimmune hemolytic anemia that demonstrate that the product inhibits hemolysis and improves hemoglobin levels. The immediate effect of the treatment compares favorably to the authorized treatments and methods such as corticosteroids or splenectomy. The use of the product may also have a more long-lived effect compared to red blood cell transfusion. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Autoimmune haemolytic anaemia (AIHA) is a rare acquired autoimmune disorder in which various types of autoantibodies directed against red blood cells (RBC) membrane antigens lead to their accelerated destruction. There are two main types of autoimmune haemolytic anaemia: warm autoimmune haemolytic anaemia and cold autoimmune haemolytic anaemia (also known as Cold Agglutinin Disease). This classification depends on the type of antibodies involved in the disease. The most common type of AIHA, warm autoimmune haemolytic anaemia, involves IgG antibodies, which bind red blood cells at normal body temperature. Cold autoimmune haemolytic anaemia on the other hand only accounts for about 15% to 30% of AIHA cases (Berentsen S. 2021) and involve IgM autoantibodies that bind red blood cells at cooler temperatures compared to a body's usual core temperature. There's a wide variation in the temperature threshold at which a cold autoantibody will bind to red blood cells.

The target population for Enjaymo is patients with Cold Agglutinin Disease (CAD). Cold Agglutinin Disease is subdivided into "primary," now referred to simply as CAD (cold agglutinin disease), versus "secondary," now termed cold agglutinin syndrome (CAS). Patients with CAS have an associated condition, for example infection, autoimmune disorder, overt evidence of a B-cell lymphoma, or other malignancy. In contrast, patients with CAD may have a B-cell clonal lymphoproliferative disorder detectable in blood or marrow but no clinical or radiological evidence of malignancy (Berentsen S. 2021).

The approved therapeutic indication "Enjaymo is indicated for the treatment of haemolytic anaemia in adult patients with cold agglutinin disease (CAD)" falls within the scope of the designated orphan condition "Treatment of autoimmune haemolytic anaemia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

There have been no changes in the chronically debilitating aspects of the condition since the designation.

Although many medical textbooks still continue to refer to AIHA, in particular cold autoimmune haemolytic anaemia, as a mild disease typically able to be managed with non-specific, supportive measures, experts in haematology have called attention to the wide spectrum of severity of the clinical phenotype and the substantial number of patients for whom it is serious and/or life-threatening (Swiecicki 2013, Barcellinin W 2014, Röth A 2022, Broome CM 2020).

The sponsor concludes that CAD is a serious and chronically debilitating condition due to decreased quality of life and haemolytic anaemia that may require red blood cell (RBC) transfusion, with an increased risk of venous or arterial thrombotic events.

The condition is considered to be chronically debilitating due to venous or arterial thrombotic events, infectious complications, requirement of RBC transfusion and decreased quality of life.

Number of people affected or at risk

The sponsor bases the prevalence estimate on an article by Hansen et al from 2020 in which AIHA patients from the Danish National Patient Register were reviewed. Prevalence estimates within this publication mainly reflects data from patients with an acquired haemolytic disorder diagnosis in 1977–2015/2016. The most recent reported overall prevalence estimated for AIHA patients in Denmark in 2015 is 1.7 per 10,000 persons. The figure is higher in patients over 50 (2.6 per 10,000) and also seem to be slightly more prevalent in women than men according to this article. See part of table 3 from the article:

Table 3 Prevalence of Acquired Hemolytic Diseases in Denmark, 1980–2015

		Prevalence per 100 000 (95% CI)		
		1980	2000	2015
AIHA				
	All	2.52 (2.10; 2.99)	9.46 (8.65; 10.32)	17.01 (15.96; 18.12)
	Age <20	1.77 (1.15; 2.59)	7.92 (6.44; 9.63)	12.39 (10.56; 14.44)
	Age 20–50	0.88 (0.53; 1.38)	5.39 (4.50; 6.42)	11.27 (9.93; 12.73)
	Age >50	5.59 (4.46; 6.92)	16.17 (14.32; 18.19)	26.38 (24.21; 28.70)
	Female	2.78 (2.17; 3.50)	10.57 (9.38; 11.87)	19.06 (17.49; 20.73)
	Male	2.25 (1.71; 2.92)	8.31 (7.25; 9.49)	14.94 (13.55; 16.44)

The proposed prevalence is lower than at the designation time in 2016. At the time the proposed prevalence was also 1.7 in 10,00 but a hypothetical "worst-case" estimate of the prevalence of AIHA was also presented by the sponsor. This was based on a mean incidence of 0.1 in 10,000, derived from the publications at the time and assumed that each acute, incident case of AIHA becomes a chronic, prevalent case (i.e., no remissions, no cures, and no fatalities occur) and a duration of the disease of 23 years: 0.1/10,000 X 23 = 2.3/10,000. If the same calculation would be done today with the incidence of 1.77 in 100,000 (Hansen 2020) the figure would be 4.1 in 10,000. However, it seems reasonable to base the estimate on the figures available and not a worst-case scenario.

It might be prudent to use the figure of 2.6 in 10,000 which is reported for patients above 50. The reasons are that the incidence rate and prevalence proportion increased over the study periods (Hansen et al) in all age groups and for both sexes (which can be due to better reporting). Therefore, the COMP could accept a prevalence of 2.6 in 10,000.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

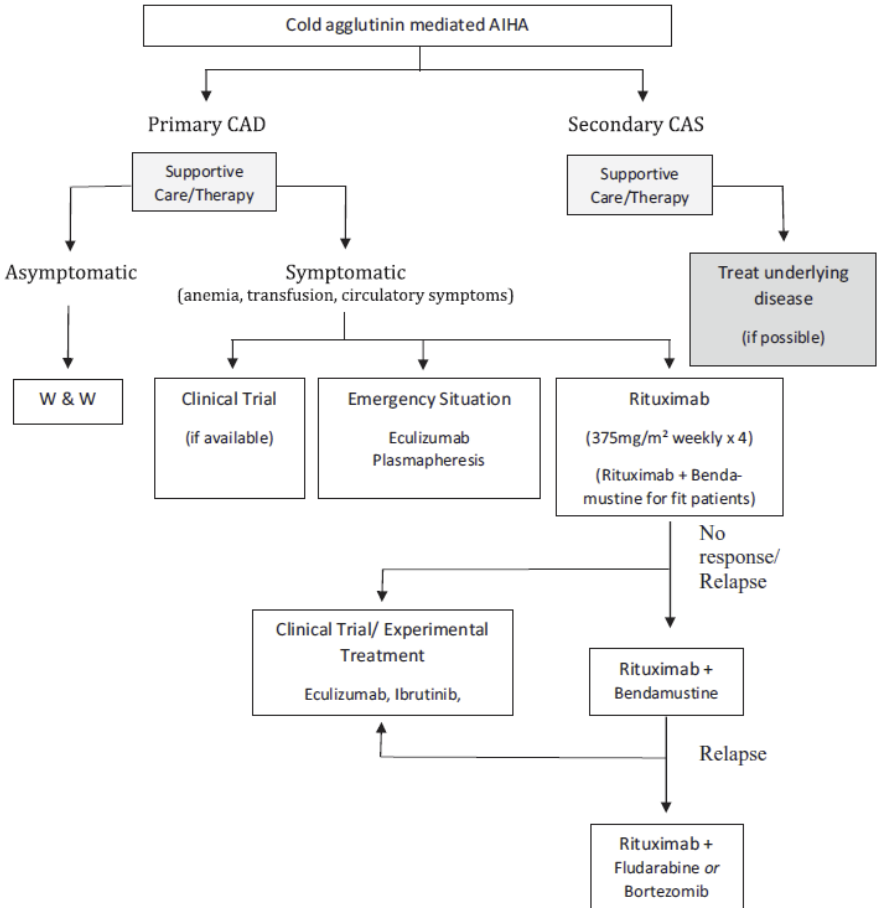
Existing methods

The sponsor has summarised the current options for treating AIHA including supportive measures like transfusions and plasma exchange. Splenectomy is among third line therapeutic options for warm AIHA. However, in CAD splenectomy is not effective as the sensitized red blood cells are mainly removed in the liver (S Berentsen, 2006).

Corticosteroids are registered in EU for the treatment of "acquired (autoimmune) haemolytic anaemia" and they remain first-line therapy for warm-AIHA (Jäger 2020). For patients with CAD, corticosteroids are typically ineffective (S Berentsen 2011 and 2006, Swiecicki PL 2013) or very high doses are needed in order to maintain the remission, therefore corticosteroids are not considered a satisfactory method for the target patient population for Enjaymo.

Treatment options are generally determined by guidelines for treatment (Jäger 2020). The therapeutic algorithm for cold agglutinin disease is shown below in Figure 3.

Figure 3. Therapeutic algorithm for cold agglutinin disease (from Jäger et al., Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting, Blood Reviews 41 (2020) 100648)



** W & W, watch and wait*

In symptomatic patients (non-emergency treatment situation), the recommended first-line therapy is rituximab, a monoclonal antibody directed against the CD20 antigen expressed on B-lymphocytes. Support for its use in warm and cold antibody AIHA comes from several studies and was also summarized in a meta-analysis in 2015 by Reynaud et al 2015.

The Complete Response Rate to rituximab was estimated as 21% (95% CI 6–51%) for cold autoimmune hemolytic anemia in 118 patients taken from 7 studies (Birgens H 2013). However, Rituximab is not specifically authorized for AIHA and neither are the five market complement inhibitors (Soliris®, Berinert®, Cetor®, Cinzyre®, Ruconest®) even though Soliris®/Eculizumab is recommended in emergency situations in the treatment guideline by Jäger et al 2020.

It is also recognized that clinical trial participation is a valid first-line option for symptomatic CAD patients.

Azathioprine is authorized in many EU countries for AIHA or AIHA caused by warm IgG antibodies. The sponsor gives the examples of:

- Azathioprin Heumann 25 mg &75 mg film coated tablets (AT/H/0270/001-002) registered since 28.07.2010 in Austria, Estonia, Belgium, Germany, and Sweden targeting AIHA
- Azatioprin "Mylan"(DK/H/0146/001) registered since 1999 in Denmark, Ireland and The Netherands targeting refractory warm AIHA
- Jayempi® (azathioprine) 10 mg/ml oral suspension (EMEA/H/C/005055) obtained its marketing authorisation on 21/06/2021 with an indication limited to refractory auto-immune hemolytic anemia, caused by warm IgG antibodies

The mechanisms whereby azathioprine affects autoimmune diseases are not known. The use of azathioprine for treatment of AIHA (specifically: warm AIHA) as it appears in expert recommendations for third-line therapy and, for the therapeutic indication listed in the SPC for azathioprine in some countries, rests upon a very limited foundation of clinical data (Jäger 2020). According to the sponsor's review, there are no controlled clinical trials of azathioprine in AIHA recorded in the clinical trial registers of FDA, EMA, and WHO or reported in PubMed. According to the recommendations from the First International Consensus Meeting 2020, treatment options such as those used in warm AIHA (corticosteroids, azathioprine or cyclophosphamide) are not effective in CAD and should not be used (Jäger 2020). Moreover, azathioprine is an immunosuppressive antimetabolite (Jayempi SmPC). Patients receiving immunosuppressants, such as azathioprine, are at increased risk of developing lymphoma and other malignancies, particularly of the skin. Physicians using azathioprine should be very familiar with this risk as well as with the mutagenic potential to both men and women and with possible hematologic toxicities (Berentsen S 2011). Due to the documented lack of effect in CAD, it can be considered that azathioprine is not a satisfactory method for treating patients with CAD.

The COMP concluded that there are no satisfactory methods of treatment for patients with CAD.

Significant benefit

Not applicable as there are no specific products for patients with CAD.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 16 September 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of autoimmune haemolytic anaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 2.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to venous or arterial thrombotic events, infections, requirement of red blood cell transfusion and decreased quality of life;
- there is, at present, no satisfactory method for the treatment of the entirety of patients covered by the therapeutic indication of Enjaymo.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Enjaymo, humanised IgG4 monoclonal antibody against total complement component 1, subcomponent s for treatment of autoimmune haemolytic anaemia (EU/3/16/1609) is not removed from the Community Register of Orphan Medicinal Products.