21 June 2021
EMA/OD/0000049819
EMADOC-1700519818-685605
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment report

Darzalex (Daratumumab)
Treatment of AL amyloidosis
EU/3/18/2020

Sponsor: Janssen-Cilag International N.V.

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

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Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Daratumumab
Other name(s)	Darzalex, Daratumumab, Anti-CD38-monoclonal-antibody-Genmab; Dara-SC; Darasarex; DARZALEX; Humanised anti-CD38 monoclonal antibody; HuMax-CD38; HuMax®-CD38 - Genmab; ; JNJ-54767414 Daratumumab - Janssen Biotech
International Non-Proprietary Name	Daratumumab
Tradename	Darzalex
Orphan condition	Treatment of AL amyloidosis
Sponsor's details:	Janssen-Cilag International N.V. Turnhoutseweg 30 2340 Beerse Antwerp Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Janssen-Cilag International N.V.
COMP opinion	19 April 2018
EC decision	25 May 2018
EC registration number	EU/3/18/2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Sinan B. Sarac / Blanca Garcia-Ochoa
Applicant	Janssen-Cilag International N.V.
Application submission	20 January 2021
Procedure start	09 February 2021
Procedure number	EMEA/H/C/004077/II/0043
Invented name	Darzalex
Proposed therapeutic indication	DARZALEX is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis Further information on Darzalex can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Darzalex
CHMP opinion	20 May 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Frauke Naumann-Winter
Sponsor's report submission	03 December 2020
COMP discussion	10-12 May 2021
COMP opinion (adoption via written procedure)	21 May 2021

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

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 daratumumab was considered justified based on preliminary clinical observations supporting reduction of free plasma light chains in treated patients affected by the condition;
- the condition is chronically debilitating and life-threatening due to the accumulation of fibril deposits which disrupts normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues;
- the condition was estimated to be affecting approximately 1 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.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

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

No classification changes have been noted since designation. AL amyloidosis is a type of systemic amyloidosis where the deposited fibrils are formed by fragments of monoclonal Ig light chains. Affected patients may have AL amyloidosis alone or in association with other plasma cell dyscrasias (multiple myeloma, Waldenström macroglobulinemia). Manifestations depend on the affected tissue and commonly involve the kidneys. Diagnostic criteria require the presence of an amyloid-related systemic syndrome, positive histology, evidence that the amyloid is light chain-related and evidence of a monoclonal plasma cell proliferation disorder.

The proposed therapeutic indication ""*DARZALEX is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis*" falls within the scope of the designated orphan condition "Treatment of AL amyloidosis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed with the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any changes in the seriousness of the condition. The COMP has previously acknowledged that the condition is chronically debilitating and life-threatening due to the accumulation of fibril deposits which disrupts normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues. This view is retained.

Number of people affected or at risk

The prevalence estimate was derived from incidence rates multiplied by the duration of the disease based on a literature review.

- With regards to the duration of the disease, it is noted in particular that the median OS for patients with AL amyloidosis ranges from 3.2 years in a German institution study of 1,224 patients observed from July 2002 to March 2017 to 3.5 years among patients diagnosed in the Swedish National Registries from 2010 to 2013 (Dittrich 2019; Weiss 2016). Patients with Mayo 2012 stage I or II disease have a median survival from 6 to 10 years (Dittrich 2019).
- As for incidence rates, two recent European sources have been found (including UK). The first source is a population-level study of AL amyloidosis in the Limousin Region of France from 2012 through 2016 found a crude annual incidence rate of 12.5 cases per million person-years (95% confidence interval [CI], 5.6-19.4) (Duhamel 2017). The second source is the UK amyloidosis referral searches, which manages 48% of the country's cases and reporting approximately 1,600 cases were documented over 4 years, from 2016 to 2019 (Ravichandran 2020). Reference is also made to two older publications, in order to point out an increase in incidence rates in European sources over time (Magy-Bertrand 2008 and Hemminki 2012).

Even when multiplying the highest incidence rate of 12.5 cases per million person-years from the French Limousin Region to the longest median OS observed for patients with high prognosis, stage I AL amyloidosis (approximately 10 years), the prevalence of AL amyloidosis is still **1.25 cases per 10,000** persons. The sponsor also notes that due to OS being less than 5 years, limited duration prevalence may also serve as a proxy for complete. In the French study the 5-year limited duration prevalence of AL amyloidosis was estimated as **0.58 cases per 10,000** persons (95% CI: 0.430.73) (Duhamel 2017).

At the designation stage the COMP has considered an approximately 1 per 10,000 estimate which is line with the above estimate and the proposal from the sponsor to use **1.25** was considered acceptable.

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

There are no authorised products identified by the sponsor for the treatment of AL amyloidosis. As both AL amyloidosis and multiple myeloma are clonal plasma cell disorders, the treatment approach is to use multiple myeloma regimens to achieve rapid, deep, and durable hematologic responses.

Significant benefit

The sponsor discusses the improved efficacy of their products in comparison to standard of care. However, in the absence of authorised treatments for AL amyloidosis, a significant benefit discussion is not applicable.

4. COMP position adopted on 21 May 2021

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 AL amyloidosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.25 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to the accumulation of fibril deposits which disrupt normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues;
- there is, at present, no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

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 Darzalex, daratumumab, for treatment of AL amyloidosis (EU/3/18/2020) is not removed from the Community Register of Orphan Medicinal Products.