20 January 2020
EMADOC-1700519818-468939
EMA/OD/0000010020 Correction[1]
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Darzalex (daratumumab)

Treatment of plasma cell myeloma

EU/3/13/1153

Sponsor: Janssen-Cilag International N.V.

Note

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

[1] Correction of EMADOC-2005359794-218151: revision of second paragraph of Article 3(1)(b) of Regulation (EC) No 141/2000 - Existing methods.

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1. Product and administrative information

Product	
Active substances at the time of orphan designation	Daratumumab
Other name(s)	Anti-CD38-monoclonal-antibody-Genmab; Dara-SC; Darasarex; DARZALEX; Humanised anti-CD38 monoclonal antibody; HuMax-CD38; HuMax®-CD38 - Genmab; JNJ-54767414
International Non-Proprietary Name	Daratumumab
Tradename	Darzalex
Orphan condition	Treatment of plasma cell myeloma
Sponsor's details:	Janssen-Cilag International N.V. Turnhoutseweg 30 2340 Beerse Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Janssen-Cilag International NV
COMP opinion date	13 June 2013
EC decision date	19 July 2013
EC registration number	EU/3/13/1153
Post-designation procedural history	
COMP opinion on review of orphan designation at the time of marketing authorisation	21 April 2016
Type II variation procedural history	
Rapporteur / Co-rapporteur	S.B. Sarac / J. Camarero Jiménez
Applicant	Janssen-Cilag International N.V.
Application submission date	27 March 2019
Procedure start date	27 April 2019
Procedure number	EMA/H/C/004077/II/0030
Invented name	Darzalex
Proposed therapeutic indication	In combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (ASCT) Further information on <product> can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/darzalex
CHMP opinion date	12 December 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	F. Naumann-Winter / K. Penttila
Sponsor's report submission date	22 May 2019
COMP discussion	3-5 December 2019

COMP opinion date (adoption via written procedure)	16 December 2019

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 2013 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing daratumumab was considered justified based on preliminary clinical studies showing responses in previously relapsed or refractory patients, treated with the product;
- the condition is life-threatening due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of up to approximately 45 months for newly diagnosed patients;
- the condition was estimated to be affecting approximately 1.75 in 10,000 persons in the European Union, at the time the application was made;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing daratumumab may be of significant benefit to those affected by the condition. The sponsor has submitted preliminary clinical data in relapsed or refractory plasma cell myeloma patients; of the 12 patients treated in the higher dose cohorts, 5 partial responses according to the International Myeloma Working Group criteria have been reported. In addition, a prolongation of progression free survival is reported compared to the lower doses cohorts. The Committee considered that this constitutes a clinically relevant advantage.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2016 was based on the following grounds:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of plasma cell myeloma (hereinafter referred to as "the condition") is estimated to remain below 5 in 10,000 and was concluded to be less than 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of approximately 6 years;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Darzalex will be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data with the product in relapsed and refractory patients, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

The studied population was refractory to most authorised products, and the overall response rate to treatment was approximately 31% and the estimated overall survival 20 months. Furthermore, an indirect comparison of clinical data supports that daratumumab monotherapy is more efficacious and less toxic than the authorised product panobinostat. The COMP concluded that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of type II variation

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

Plasma cell myeloma (also commonly referred to as multiple myeloma) is a bone-marrow based multifocal neoplasm associated with an M-protein in serum or urine. Chronic antigen stimulation from infection or other disease and exposure to specific toxic substances or irradiation have been implicated in the aetiology of the condition. Symptomatic plasma cell myeloma is defined by the presence of end-organ damage (CRAB criteria: hypercalcemia, renal insufficiency, anaemia, bone lesions) in a patient with an M component and clonal BM cells. Asymptomatic, smouldering, non-secretory myeloma and Plasma cell leukaemia are variants of plasma cell myeloma.

Darzalex (daratumumab) has already received marketing authorisation in the EU and is indicated:

- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
- in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant

The sponsor applies simultaneously for extensions of indication as follows:

a) in combination with lenalidomide and dexamethasone (Rd) for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) and

b) ***in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (ASCT)*** (emphasis added).

Both extensions fall entirely within the designated indication which is more broadly worded as "treatment of plasma cell myeloma". Moreover, the first extension (first line in ASCT ineligible patients) targets the same population as the already authorised indication, thereby not-requiring further confirmation of the orphan criteria. Therefore, this report will discuss the maintenance of the criteria in the second extension highlighted above.

Intention to diagnose, prevent or treat

The medical plausibility is confirmed with reference to the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any changes since designation. It has previously been considered by the COMP that plasma cell myeloma (also referred to as multiple myeloma) is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anemia and bone lesions, and life-threatening with an overall survival of up to approximately 6 years (Kumar, Leukemia. 2014 May;28(5):1122-8). The condition remains chronically debilitating and life-threatening.

Number of people affected or at risk

The sponsor provided estimates of 10-year prevalence projected to 2018, obtained for the 5 most populous EU countries from the CancerMPact® program, noting that this appears to be a close approximation of complete prevalence. The estimate provided was approximately 3.44 per 10,000 persons, with the highest computed estimate in Italy also remaining under 4 per 10,000 persons. It was considered that this reference is a market analysis tool and not an epidemiological source, and as such not acceptable for the purpose of establishing prevalence.

This limitation is mitigated by further estimates provided by the sponsor which refer to other credible data sources (NORDCAN and HMRN). Based on HMRN data from 2007 to 2016, the 10-year prevalence of multiple myeloma in the UK was estimated as 3 per 10,000. The sponsor also has referred to the NORDCAN database, citing a total point prevalence of approximately 3.5 per 10,000.

The COMP recently considered that the condition affects less than 4 in 10,000 people which was still considered relevant for this procedure and in line with the above.

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 medicinal products authorised in the EU for the treatment of multiple myeloma. In addition to the centrally approved products (carfilzomib, bortezomib, doxorubicin HCl, interferon alfa-2b, lenalidomide, thalidomide, panobinostat), there are also products authorised at the national level (carmustin, cyclophosphamide, doxorubicin, epirubicin, melphalan and vincristine). The sponsor notes that bortezomib, in combination with VTd or Vd is indicated specifically for the target population.

As per the ESMO guidelines on the diagnosis and treatment of multiple myeloma (Moreau et al. 2017 Annals of Oncology Volume 28, Supplement 4, Pages iv52–iv61) first line treatment depends on the eligibility for autologous stem cell transplantation. For younger patients, induction with bortezomib-dexamethasone plus one more drug (VTD, VCD, PAD, RVD) and then melphalan followed by autologous stem cell transplantation (ASCT) is the standard treatment.

With regards to second line treatment, the choice of therapy depends on several parameters such as age, performance status, comorbidities and the type, effects and tolerability of previous treatments.

Significant benefit

The COMP considered the scope of the extension, in first line adult patients who are eligible for autologous stem cell transplant. In those patients, induction with bortezomib-dexamethasone plus one more drug (VTD, VCD, PAD, RVD) and then melphalan followed by autologous stem cell transplantation (ASCT) is the standard treatment.

The sponsor argued improved efficacy when the product is added on to VTd. This is based on the main study MMY3006. Study MMY3006 was a large randomized, open-label, active-control, parallel-group, multicenter, Phase 3 study comparing DVTd with VTd in the treatment of newly diagnosed multiple myeloma in subjects aged up to 65 years who were eligible for ASCT. The treatment phase of Study MMY3006 study consists of 2 stages:

- Part 1 (Induction/ASCT/Consolidation): subjects were randomized in a 1:1 ratio to receive either DVTd or VTd. Planned enrolment was 1080 subjects. The number of planned cycles was 6 (4 cycles of induction therapy before ASCT and 2 cycles of consolidation therapy after ASCT). Response was assessed approximately 100 days post-ASCT and eligibility for the second randomization was determined.
- Part 2 (Maintenance): subjects with at least a partial response (PR) by Day 100 post-transplant were re-randomized in a 1:1 ratio to daratumumab maintenance or observation only. Approximately 800 subjects (400/arm) of the initial 1080 subjects were expected to be randomized to maintenance.

The primary objective in Part 1 of Study MMY3006 was to determine if the addition of daratumumab to VTd increased the proportion of subjects achieving sCR 100 days post-ASCT compared to VTd alone. Key secondary endpoints in Part 1 of Study MMY3006 used a hierarchical testing procedure to determine if the addition of daratumumab to VTd improved:

- Minimal residual disease (MRD) negativity rate 100 days post-ASCT
- Complete response (CR) or better rate 100 days post-ASCT
- PFS from first randomization
- OS from first randomization

Randomization was stratified by site affiliation (IFM or HOVON), International Staging System (ISS) category (I, II, or III), and cytogenetics (standard risk or high risk as defined by presence of del17p or t(4;14), as centrally assessed during screening). Within each stratum, subjects were randomized using an equal allocation ratio of 1:1.

Subjects in Study MMY3006 were diagnosed with multiple myeloma as defined by the IMWG guidelines. Specifically, all subjects had documented multiple myeloma satisfying CRAB criteria (calcium elevation, renal insufficiency, anaemia, and bone abnormalities) or biomarkers of malignancy, as well as evidence of measurable secretory disease (as determined by a central laboratory). Enrolment was limited to subjects with newly diagnosed disease who had not had any exposure to prior therapy for multiple myeloma and who were considered candidates for HDT with ASCT. Subjects with a poor performance status (i.e., Eastern Cooperative Oncology Group [ECOG] Performance Status Score of 3 or worse) were excluded mainly for safety reasons, as this population of patients generally

has a greater risk for toxicity. Also excluded were subjects with peripheral neuropathy or Grade 2 or higher neuropathic pain as neuropathy is a known toxicity associated with bortezomib and thalidomide.

With regards to the Primary Efficacy Endpoint, the addition of daratumumab to VTd resulted in a statistically significant improvement in the sCR rate 100 days post-ASCT by validated computerized algorithm (28.9% vs. 20.3%; odds ratio=1.60 with 95% CI: 1.21, 2.12; p=0.0010) compared with VTd alone. Improvement in sCR rate at 100 days post-ASCT was robust across sensitivity analyses and consistent across predefined clinically relevant subgroups, except in the cytogenetic high-risk subgroup (odds ratio=0.83 with 95% CI: 0.42, 1.66) and ISS Stage III subgroup (odds ratio=1.07 with 95% CI: 0.54, 2.12). However, both subgroups showed improved PFS (HR= 0.67 and 0.66, respectively), CR or better rates at Day 100 post-ASCT (odds ratio=1.11 and 1.54, respectively), and MRD negativity rates at Day 100 post-ASCT (odds ratio=1.88 and 2.14, respectively), favouring the DVTd treatment group compared with the VTd regimen.

Results of a supplementary PFS analysis (during the CHMP assessment procedure), censoring patients who were randomized to daratumumab maintenance in the second randomization, were consistent with the previous result. The PFS analysis showed a hazard ratio [HR]=0.50; 95% CI: 0.34, 0.75; p=0.0005.

In evaluation of the sponsor's position, it can be acknowledged that addition of Darzalex to VTD results in improved efficacy in the target population, based on the results from study 3006. The COMP reflected on whether there is a need for additional comparisons (further to the VTD one). The ESMO guidelines were also taken into consideration towards this end. It was considered that the recommended therapy in younger patients would consist of bortezomib-dexamethasone plus one more drug (VTD, VCD, PAD, RVD) and then melphalan followed by autologous stem cell transplantation.

It was also considered that Velcade (mentioned in the regimens above as V or P) is only authorised in combination with Td and that the other recommended regiments that contain V(P) can be considered off-label. Therefore, significant benefit can be considered acceptable on the basis of the results from study 3006.

4. COMP list of issues

Not applicable

5. COMP position adopted on 16 December 2019

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 plasma cell myeloma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be less than 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anemia and bone lesions, and life-threatening with an overall survival of up to approximately 6 years;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Darzalex may be of potential significant benefit to those affected by the orphan condition still holds. The applicant has submitted clinical data that show improved progression free survival and complete response rates in newly diagnosed patients with multiple myeloma who are eligible for autologous stem cell transplantation, when the product is added on to bortezomib, thalidomide, and dexamethasone. The COMP considered that this constitutes a clinically relevant advantage.

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 plasma cell myeloma (EU/3/13/1153) is not removed from the Community Register of Orphan Medicinal Products.