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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Sarclisa (isatuximab, humanised monoclonal antibody against CD38)
Treatment of plasma cell myeloma
EU/3/14/1268
Sponsor: Sanofi-Aventis Groupe

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	
Active substances at the time of orphan designation	Humanised monoclonal antibody against CD38
Other name(s)	SAR650984
International Non-Proprietary Name	Isatuximab
Tradename	Sarclisa
Orphan condition	Treatment of plasma cell myeloma
Sponsor's details:	Sanofi-Aventis Groupe 54 Rue La Boetie 75008 Paris France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Sanofi-Aventis Groupe
COMP opinion date	12 March 2014
EC decision date	29 April 2014
EC registration number	EU/3/14/1268
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	P. B. van Hennik / A. Moreau
Applicant	Sanofi-Aventis Groupe
Application submission date	30 April 2019
Procedure start date	23 May 2019
Procedure number	EMA/H/C/004977/0000
Invented name	Sarclisa
Proposed therapeutic indication	SARCLISA is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy. Further information on Sarclisa can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Sarclisa
CHMP opinion date	26 March 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	K. Penttila / E. J. Rook
Sponsor's report submission date	2 October 2019
COMP discussion and adoption of list of questions	18-20 February 2020
Oral explanation	22 April 2020
Sponsor's removal request	23 April 2020

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2014 designation was based on the following grounds:

The sponsor Sanofi-Aventis Groupe submitted on 6 December 2013 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing humanised monoclonal antibody against CD38 for treatment of plasma cell myeloma (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 humanised monoclonal antibody against CD38 was considered justified based on preclinical in vivo and preliminary clinical data in patients with the condition;
- the condition is chronically debilitating in particular due to the development of hypercalcaemia, 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 1.8 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 authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised monoclonal antibody against CD38 may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo and preliminary clinical data that demonstrate a prolongation of tumour free survival in the pre-clinical models when used in combination with other anti-neoplastic agents and the efficacy in patients with the condition who have relapsed or refractory disease when they have received the current standard of care. The Committee considered that this constitutes a clinically relevant advantage.

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

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing humanised monoclonal antibody against CD38, as an orphan medicinal product for the orphan indication: treatment of plasma cell myeloma.

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

Plasma cell myeloma (hereafter 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 multiple 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.

Multiple myeloma is characterised by the accumulation of clonal plasma cells in the bone marrow (BM) and accounts for 10% of all haematological malignancies.

The proposed therapeutic indication "SARCLISA is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and who have demonstrated disease progression on the last therapy" falls within the scope of the designated orphan condition "treatment of plasma cell myeloma".

Intention to diagnose, prevent or treat

On 26 March 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Sarclisa, intended for the treatment of multiple myeloma The medical plausibility was confirmed by the positive assessment of the benefit-risk balance by the CHMP.

Chronically debilitating and/or life-threatening nature

At the time of this review MM is presented to remain seriously debilitating and life-threatening disease with a median OS for patients with MM ranging from 2 to more than 10 years. The most frequent causes of death being disease progression, infection, and renal failure. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures.

The COMP concluded that the condition remains chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with a relevantly reduced life expectancy.

Number of people affected or at risk

The sponsor proposes a prevalence estimate between 1.6 and 3.0 in 10,000 and that it hasn't changed much since 2014 when they obtained their initial orphan designation.

The range is derived from partial prevalence calculations for 5 and 10yr prevalence's. The data used is obtained from the Haematological Malignancy Research Network (HMRN, York, UK). No other sources have been consulted. The disease duration has not been discussed. Only a reference being made to Orphanet which is not a primary source of epidemiological data.

ECIS 2018 provides updated incidence numbers, which should be taken into consideration without age standardisation. Disease duration may have changed since 2014 and thus needs to be addressed in more detail. The sponsor was invited to provide a revised prevalence calculation by taking into consideration additional epidemiological sources using crude incidence for the estimation. This remains an outstanding issue.

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 the condition. Central marketing authorisations include elotuzumab, doxorubicin, interferon-α2b, bortezomib, lenalidomide, thalidomide, pomalidomide, panobinostat, carfilzomib, daratumumab, ixazomib, and dexamethasone. There are also products authorised at the national level including carmustine, cyclophosphamide, doxorubicin, epirubicin, melphalan, and vincristine.

There are ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up guidelines from 2017 (Ann Oncol (2017) 28 (suppl 4): iv52–iv61). The ESMO guideline distinguishes elderly patients regarding the non-transplant setting and more fit patients in the transplant setting ASCT. Treatments are discussed by the sponsor regarding front line treatment, consolidation, maintenance and relapsed/refractory disease.

Significant benefit

Isatuximab (IPd) is a monoclonal antibody against CD38., which is a cell surface antigen expressed in haematological malignancies from B-lymphocyte, T-lymphocyte and myeloid origin.

The proposed indication is: *"SARCLISA is indicated, in combination with pomalidomide and dexamethasone, for the treatment of patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)."*

The Scientific Advice Working Party was consulted five times by the Sponsor. However, no protocol assistance on how to show significant benefit was requested by the Sponsor.

The sponsor is claiming that their product offers a clinically relevant advantage in the treatment of heavily pre-treated (at least two prior therapies) multiple myeloma patients who have relapsed or are refractory to both lenalidomide and proteasome inhibitor. To support this claim, data from their pivotal phase III study ICARIA has been submitted which was *"a Phase III randomised, open-label, multicentre study comparing isatuximab (SAR650984) in combination with pomalidomide and low-dose*

dexamethasone versus pomalidomide and low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma".

All 307 randomized patients (154 in the isatuximab + pomalidomide + low-dose dexamethasone (IPd)_ arm vs. 153 in the pomalidomide + low-dose dexamethasone (Pd) arm) were included in the intent-to-treat (ITT) population, which was the primary population for all efficacy parameters.

Prior anti-cancer therapy

The study population was heavily pre-treated; all patients had received at least 2 prior lines of treatment including prior lenalidomide and PI. The median number of prior lines was 3 (range 2 to 11), with 34.9% of patients having received 4 or more prior lines of treatment. The number of prior lines and class of therapies were well-balanced between the treatment arms.

All patients received lenalidomide and a PI; 92.5% were refractory to lenalidomide, 75.9% to an PI, and 72.6% to both. Nearly all patients (98.0%) were refractory to their last regimen and all patients (100%) were considered relapsed and refractory. Over half of patients (56.4%) had received a prior stem cell transplant, and 16.0% had received a double stem cell transplant.

Subsequent anti-myeloma treatment

A substantial part of the study population received additional systemic therapy post-study: 39% of patients in the IPd arm and 54% of patients in the Pd arm. Daratumumab was administered in 6 patients (4%) of the IPd arm vs. 45 (29%) of patients in the Pd arm.

The pivotal study showed a statistically significant improvement in IRC (independent review committee) judged PFS (progression free survival) with addition of isatuximab to Pd. The HR (hazard ratio) was 0.596 (95% Confidence Interval 0.436, 0.814; $p<0.001$), and median PFS increased by 5.06 months (11.53 IPd vs. 6.47 months for Pd). A total of 162 PFS events was reported at the time of data cut-off, similar to the number of PFS events defined in the study protocol. The observed treatment effect (HR 0.596) is consistent with the protocol-specified hypothesis on PFS (HR 0.6), although both treatment arms performed better than anticipated (predicted median PFS was 6.67 vs. 4 months for IPd and Pd, respectively). This can possibly be ascribed to differences in patient population between trials (the ICARIA trial patients' population received numerically fewer prior treatments, had fewer patients with baseline ECOG PS ≥2, and received less thalidomide compared to patients in the pomalidomide registration study MM 003), as well as better management of pomalidomide toxicity. The CHMP concluded that the clinical benefit of adding isatuximab to pomalidomide and dexamethasone is demonstrated in relapsed and refractory multiple myeloma patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Alternative treatment options

The ESMO guideline outlines for relapsed/refractory MM that the choice of therapy in this setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (table 1).

Table 1: Recommended Treatment Options for Patients with Multiple Myeloma: ESMO Treatment Guidelines

Table 6. Major treatment regimens in multiple myeloma

Regimen	Usual dosing schedule
Front-line:	
Bortezomib/melphalan/prednisone (VMP) [11]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 8, 15, 22; melphalan 9 mg/m^2 orally days 1–4; prednisone 60 mg/m^2 orally days 1–4; repeated every 35 days
Lenalidomide/low-dose dexamethasone (Rd) [12]	Lenalidomide 25 mg orally days 1–21; dexamethasone 40 mg orally days 1, 8, 15, 22; repeated every 28 days
Melphalan/prednisone/thalidomide (MPT) [13]	Melphalan 0.25 mg/kg orally days 1–4 (use 0.20 mg/kg/day orally days 1–4 in patients over the age of 75); prednisone 2 mg/kg orally days 1–4; thalidomide 100–200 mg orally days 1–28 (use 100 mg dose in patients >75); repeated every 6 weeks
Bortezomib/cyclophosphamide/dexamethasone (VCD) [14]	Cyclophosphamide 300 mg/m^2 orally days 1, 8, 15 and 22; bortezomib 1.3 mg/m^2 i.v. on days 1, 8, 15, 22; dexamethasone 40 mg orally on days 1, 8, 15, 22; repeated every 4 weeks
Bortezomib/thalidomide/dexamethasone (VTD) [14]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 8, 15, 22; thalidomide 100–200 mg orally days 1–21; dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22); repeated every 4 weeks × 4 cycles as pre-transplant induction therapy
Bortezomib/lenalidomide/dexamethasone (VRd) [14]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 8, 15; lenalidomide 25 mg orally days 1–14; dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22); repeated every 3 weeks
Relapse/refractory disease:	
Carfilzomib/lenalidomide/dexamethasone (KRd) [24, 32]	Carfilzomib 20 mg/m^2 (cycle 1) and 27 mg/m^2 (subsequent cycles) i.v. on days 1, 2, 8, 9, 15, 16; lenalidomide 25 mg orally days 1–21; dexamethasone 40 mg on days 1, 8, 15, 22; 28-day cycles
Bortezomib/dexamethasone/panobinostat (VD-Pano) [31]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 8, 15, 22; dexamethasone 20 mg on day of and day after bortezomib; panobinostat 20 mg orally days 1, 3, 5 week 1 and 2; repeated every 3 weeks (cycles 1–8)
Carfilzomib/dexamethasone (Kd) [33]	Carfilzomib 56 mg/m^2 i.v. days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only); dexamethasone 20 mg days 1, 2, 8, 9, 15, 16, 22, 23; 28-day cycles
Lenalidomide/dexamethasone/elotuzumab (Rd-Elo) [34]	Lenalidomide 25 mg orally days 1–21; dexamethasone 40 mg weekly; elotuzumab 10 mg/kg i.v. weekly cycle 1 and 2, every other week cycles 3+; repeated every 28 days
Lenalidomide/dexamethasone/ixazomib (IRd) [35]	Lenalidomide 25 mg orally days 1–21; dexamethasone orally 40 mg days 1, 8, 15, 22; ixazomib 4 mg orally days 1, 8, 15; repeated every 28 days
Bortezomib/dexamethasone/daratumumab (DVd) [38]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 4, 8, 11 (cycles 1–8); dexamethasone 20 mg orally days 1, 2, 4, 5, 8, 9, 11, 12 (cycles 1–8); daratumumab 16 mg/kg i.v. every week (cycles 1–3), every 3 weeks (cycles 4–8), every 4 weeks (cycles 9+); cycles 1–8: repeated every 21 days; cycles 9+: repeated every 28 days
Lenalidomide/dexamethasone/daratumumab (DRd) [39]	Lenalidomide 25 mg orally days 1–21; dexamethasone 40 mg orally weekly; daratumumab 16 mg/kg i.v. weekly (cycles 1-2), every other week (cycles 3-6), every 4 weeks (cycles 7+)

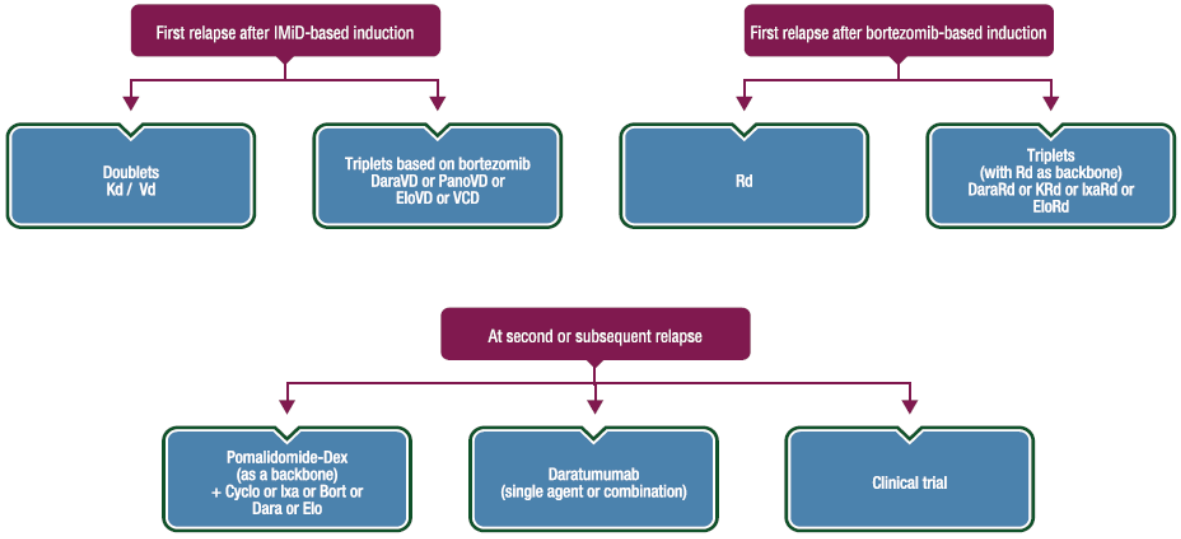

Figure 2. Treatment of relapse.
Bort, bortezomib; Cyclo, cyclophosphamide; Dara, daratumumab; DaraRd, daratumumab, lenalidomide, low dose dexamethasone; DaraVD, daratumumab, bortezomib, dexamethasone; Dex, dexamethasone; Elo, elotuzumab; EloRd, elotuzumab, lenalidomide, low dose dexamethasone; EloVD, elotuzumab, bortezomib, dexamethasone; IMiD, immunomodulatory drug; Ixa, izaxomib; IxaRd, izaxomib, lenalidomide, low dose dexamethasone; Kd, carfilzomib, low dose dexamethasone; KRd, carfilzomib, lenalidomide, low dose dexamethasone; PanoVD, panobinostat, bortezomib, dexamethasone; Rd, lenalidomide, low-dose dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; Vd, bortezomib, low dose dexamethasone.

Taking into consideration the ESMO guideline and the authorisation status of medicinal products in the target patient population the therapeutic indication is defining, it was considered that the significant benefit would need to be established versus:

1. Daratumumab (single agent or combinations).
2. Pomalidomide in combination with dexamethasone (as a backbone) with either cyclophosphamide or izaxomib or bortezomib, daratumumab or elotuzumab.

The data submitted by the sponsor would indicate that there could be a therapeutic equivalence as the only comparator group considered was pomalidomide+dexamethasone as a backbone + placebo. The clinically relevant advantage and/or major contribution to patient care needs to be further clarified versus the other triplets or daratumumab monotherapy or daratumumab in combinations as recommended in the current ESMO guidelines algorithm highlighted in Figure 2. The sponsor should further elaborate on what the clinically relevant advantage is using their product in the target patient population described in the proposed indication as opposed to other approved alternatives

The COMP should therefore request that the sponsor further elaborate the basis of their claim of significant benefit within the context of their proposed indication.

4. COMP list of issues

Prevalence:

The sponsor should provide a more current prevalence calculation as the assumptions provided do not appear to represent the impact of more recently authorised products have had on survival. In addition, there are recent sources of data which would offer a better understanding of the current situation such as the European Cancer Institute Registry (ECIS).

Significant benefit:

The current clinical data submitted by the sponsor does not establish the clinically relevant advantage versus all products and regimes authorized for use in the target patient population. The sponsor should further elaborate on the significant benefit with the clinical data they have with the product in the target population.