25 August 2020
EMADOC-1700519818-499024
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

BLENREP (belantamab mafodotin)

Treatment of multiple myeloma

EU/3/17/1925

Sponsor: GlaxoSmithKline (Ireland) Limited

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 3

2. Grounds for the COMP opinion 4

3. Review of criteria for orphan designation at the time of marketing authorisation 5

Article 3(1)(a) of Regulation (EC) No 141/2000 5

Article 3(1)(b) of Regulation (EC) No 141/2000 6

4. COMP position adopted on 29 July 2020 10

1. Product and administrative information

Product	
Designated active substance	Humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F
Other name(s)	Humanised anti-BCMA (B cell maturation antigen) monoclonal antibody conjugated with an average of four mcMMAF (maleimidocaproyl monomethyl auristatin F) Belantamab mafodotin - anti-BCMA-ADC; GSK-2857916; J6M0-mcMMAF
International Non-Proprietary Name	Belantamab mafodotin
Tradename	BLENREP
orphan condition	Treatment of multiple myeloma
Sponsor's details:	GlaxoSmithKline (Ireland) Limited 12 Riverwalk Citywest Business Campus Dublin 24 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	GlaxoSmithKline Trading Services Limited
COMP opinion date	7 September 2017
EC decision date	16 October 2017
EC registration number	EU/3/17/1925
Post-designation procedural history	
Sponsor's name change	Name change from GlaxoSmithKline Trading Services Limited to GlaxoSmithKline (Ireland) Limited – EC letter of 01 April 2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Tuomo Lapveteläinen / Blanca Garcia-Ochoa
Applicant	GlaxoSmithKline (Ireland) Limited
Application submission date	18 December 2019
Procedure start date	30 January 2020
Procedure number	EMA/H/C/004935
Invented name	BLENREP

Proposed therapeutic indication	BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. Further information on BLENREP can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep)
CHMP opinion date	23 July 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Brigitte Schwarzer-Daum
Sponsor's report submission	10 February 2020
COMP discussion	18-20 May 2020
COMP opinion (adoption via written procedure)	29 July 2020

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2017 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F was considered justified based on preliminary clinical data showing responses in treated patients with relapsing or refractory multiple myeloma;
- the condition is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with a median survival of approximately 6 years;
- the condition was estimated to be affecting less than 4 in 10,000 persons in the European Union, at the time the application for orphan designation was submitted;
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in heavily pretreated relapsed/refractory patients who have responded to treatment with the proposed product. 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

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.

The proposed therapeutic indication "BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy" falls entirely within the scope of the designated orphan condition "treatment of multiple myeloma".

Intention to diagnose, prevent or treat

The medical plausibility was considered confirmed based on the positive benefit/risk assessment of the CHMP, please see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any changes in the seriousness of the proposed condition. It has previously been considered by the COMP that plasma cell myeloma (also referred to as "multiple myeloma") is chronically debilitating and life-threatening in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions. The seriousness of the condition is acknowledged.

Number of people affected or at risk

The sponsor proposed that the condition affects 2.5 per 10,000 people, on the basis of a) a 5-year partial prevalence consideration from GLOBOCAN (Ferlay PMID:25220842 2018) also using a correction factor of 0.8 based on Li et al (Cancer Causes Control 2016;27:8:1019-26), and b) an indirect calculation using GLOBOCAN age-adjusted incidence, multiplied by an assumed duration of 6.1 years (from Kumar 2014). Another source used by the sponsor was a market tool (CancerMPact®) which was used to draw data for 10-year partial prevalence, and then adjusted for full prevalence. It was however considered by the COMP that this would not be a valid epidemiological reference.

The following table which is sourced from the maintenance report of the sponsor summarizes the conclusions of the sponsor:

Table 1

Method	Prevalence Proportion per 10,000		Number of Affected Patients	
	Uncorrected	Corrected	Uncorrected	Corrected
#1 Prevalence estimates for EU-28 (using GLOBOCAN)	1.98	2.48	102,561	128,202
#2 Prevalence estimates for 40 European countries (using GLOBOCAN)	1.62	2.03	120,391	150,860
#3 Point prevalence using incidence from GLOBOCAN multiplied times median survival duration from literature review estimates	2.00	2.50	103,518	129,397

In the evaluation of the justifications submitted by the applicant for the recalculation of the prevalence, the COMP reflected on the methodology applied by the applicant and the conclusions drawn on the basis of it. It was noted that the sponsor has submitted both partial and complete prevalence estimates.

The COMP considered that, given that the condition is an incurable disease, with increasing relapses over time, the complete prevalence (and not any partial prevalence referring to limited time from diagnosis) is the appropriate index to report the number of affected individuals for the orphan framework.

It was also considered that any prevalence calculation, in particular for multiple myeloma, would have to be based on updated information. This is because a) crude incidence rates are rising in the EU, probably due to the ageing population and b) the survival rate is improving in the EU, probably due to the newly available treatments.

The COMP reflected on the availability of several sources, including ECIS, NORDCAN (giving a 3.7 per 10,000 prevalence for 2016), HMRN (UK) and even extra-European sources such as SEER. It was also considered that a notable absence in the sponsor's position was the reference to ECIS (European Cancer Information System). According to the ECIS 2018 database the estimated crude incidence for 28 European (EU-28) countries was 0.81 per 10,000 persons. This could have been used to derive prevalence, taking into consideration the duration of the condition. However, the COMP also noted that there is an absence of up-to date European survival data, which would be important for such an exercise.

In light of these uncertainties, the Committee decided to use its knowledge as per previous procedures concerning multiple myeloma and considered an approximately 4 per 10,000 figure to be 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 several medicinal products authorised in the EU for the treatment of multiple myeloma. In addition to the centrally approved products (daratumumab, carfilzomib, bortezomib, doxorubicin, interferon alfa-2b, lenalidomide, thalidomide, panobinostat, elotuzumab, ixazomib, pomalidomide,

isatuximab), there are also products authorised at the national level (carmustine, cyclophosphamide, doxorubicin, bendamustine, epirubicin, melphalan and vincristine).

As per the ESMO guidelines on the diagnosis and treatment of multiple myeloma (Moreau et al. Annals of Oncology 28 (Supplement 4): iv52–iv61, 2017) in 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.

The following products are specifically authorised in late line indications:

- Pomalidomide: in combination with dexamethasone in patients after at least two prior treatment regimens, including both lenalidomide and bortezomib;
- Panobinostat: in combination with bortezomib and dexamethasone, for patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent;
- Daratumumab: in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for at least one prior therapy. Also, as a monotherapy for relapsed and refractory multiple myeloma, for patient whose prior therapy included a proteasome inhibitor and an immunomodulatory agent;
- Carfilzomib is authorised in combination with either lenalidomide and dexamethasone or dexamethasone alone after at least one prior therapy;
- Elotuzumab, in combination with lenalidomide and dexamethasone after at least one prior therapy, and in combination with pomalidomide and dexamethasone after at least two therapies including lenalidomide and a proteasome inhibitor;
- Bortezomib as a monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least one prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation;
- Isatuximab in combination with pomalidomide and dexamethasone, for the treatment of adult patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Significant benefit

The sponsor received protocol assistance in 2018 and COMP advised that "…the phase II study could be sufficient to demonstrate significant benefit, provided clinically relevant durable responses are observed compared to historical controls, and indirect comparison considers all relevant authorised medicinal products in the treatment of multiple myeloma".

In order to justify significant benefit, the sponsor elaborated on the results of the pivotal study, and also performed some indirect comparisons that are discussed below. It was reported that updated data (13 months data cut-off of 31st January 2020) of DREAMM-2 point to overall response rate (ORR) of 32%, medial duration of response (mDoR) of 11 months (95% CI: 4.2, NR) and median overall survival (mOS) of 13.7 months. The sponsor stressed that the DREAMM-2 patient population is not comparable to the patient population of the main trials of panobinostat, elotuzumab and other comparators due to differences in e.g. little to no prior exposure to anti- CD38 directed therapies and lower median number of prior lines.

Nevertheless, some indirect comparisons were in fact conducted. Firstly, a matching-adjusted indirect comparison (MAIC) was performed versus the STORM Part 2 single arm phase II trial of selinexor-dexamethasone (SelDex) in patients who received at least three prior lines of therapy including an anti-CD38 directed therapy and who were double refractory to proteasome inhibitor and an immunomodulatory agent. With regards to OS, the MAIC pointed to a favourable HR of 0.53 (p-value =0.005). This exercise was considered not to be of direct relevance for the significant benefit exercise, since selinexor was not authorised in the EU. However, it could be used as a "bridge" to conduct Bucher's indirect comparisons, as discussed below.

Secondly, the sponsor also presented an indirect comparison of the DREAMM-2 study versus the observational MAMMOTH study, published by Gandhi et al, 2019 (Leukemia 33, 2266–2275). With regards to MAMMOTH, it evaluated the outcome in patient's refractory to anti-CD38 directed therapy (N=275) across 14 academic centres in the US, and the sponsor considers this to be reflecting the standard of care. Patients in that study had received a median of 4 lines of therapy (range 1–16) with most patients being refractory to daratumumab (93%), lenalidomide (77%), pomalidomide (65%), and bortezomib (68%). The mOS among patients who were refractory to an anti-CD38 directed therapy was 8.6 months (7.5–9.9), ranging from 11.2 for patients not simultaneously refractory to an immunomodulatory agent and a proteasome inhibitor to 5.6 months for patients refractory to an anti-CD38 directed therapy, two PIs and two immunomodulatory agents (penta-refractory).

Importantly, the efficacy of belantamab mafodotin versus the standard of care of the MAMMOTH study was estimated for OS using Bucher indirect treatment comparisons. In order to perform the comparisons, an abstract by Costa et al was also used (Blood. 2019; 134 (Supplement_1): 3125) discussing the effects of SelDex in triple class refractory patients with reference to the MAMMOTH study. Estimates were derived using the covariate-adjusted HR reported by Costa et al. and the naïve of reweighted HR of belantamab mafodotin versus SelDex. This approach found a favourable OS for belantamab mafodotin.

The COMP considered that the therapeutic indication for belantamab mafodotin already provides information relevant for the significant benefit versus the majority of the authorized medicinal products for the indication. This is because BLENREP is indicated "as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, [emphasis added] and who have demonstrated disease progression on the last therapy."

It was considered that the only two products authorized in late R/R settings that do not fall in the above classes of products are elotuzumab, being an anti-SLAMF7 antibody, and panobinostat, being an HDAC inhibitor. These products were considered relevant for the discussion of significant benefit, because they are authorized after at least two prior lines therapies, thereby encompassing the fifth line therapeutic indication of belantamab mafodotin. During the discussions with the sponsor, the latter was specifically asked to provide further justifications to support the significant benefit versus elotuzumab and panobinostat.

- As regards elotuzumab, the sponsor pointed out that the study DREAMM-2 included a number of patients who were refractory to elotuzumab. In particular, 13 treated patients were reported to be refractory to prior elotuzumab use. In those 13 patients, 3 responded to treatment with belantamab mafodotin monotherapy (3/13, 23.1% ORR). The COMP accepted this as an argument of improved efficacy of belantamab mafodotin, versus elotuzumab, because of the documented responses in patients who had previously failed to treatment with elotuzumab.

- As for panobinostat, the sponsor postulated that if it was to be used as monotherapy in the population described in the therapeutic indication of belantamab mafodotin, a very low remission rate could be expected (which the sponsor expected to be in the area of 10%). The sponsor referred to a real-world evidence, unpublished, abstract by Bird and co-workers (Royal Marsden Hospital), reporting on the treatment of 46 patients with 5 prior lines of therapy (range 2-8) who were treated with panobinostat, bortezomib and dexamethasone. This abstract reported that while the ORR was 45% in the treated population, the median PFS of the whole group was 3.5 months and the OS was 7.8 months. The COMP considered that while real world data would have limitations compared to trial data, the reported OS for belantamab mafodotin would compare favourably to the outcomes of patients treated with panobinostat (as part of panobinostat, bortezomib and dexamethasone), despite the studied population in the DREAMM-2 study being more heavily pre-treated (median 6, range 3–21).

The COMP reflected on the submitted evidence and acknowledged that for patients who have received at least 4 prior therapies and who are refractory to at least one immunomodulatory drug, one proteasome inhibitor, and one anti-CD-38 antibody, and whose disease has progressed on the last therapy, as detailed in the therapeutic indication for belantamab mafodotin, the treatment options become very limited. It was also considered that the available data support improved efficacy compared to those very limited options. This was considered to constitute a clinically relevant advantage, on the basis of which significant benefit has been considered established for belantamab mafodotin versus the other currently authorised methods for treatment of the condition.

4. COMP position adopted on 29 July 2020

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 multiple myeloma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating, in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that BLENREP is of significant benefit for the subset population of the orphan condition as defined in the granted therapeutic indication still holds;
- the sponsor has provided clinical data that demonstrate the efficacy of BLENREP in heavily pre-treated multiple myeloma patients who were refractory to several classes of products;
- for patients who have progressed after at least four prior therapies and who are refractory to at least one immunomodulatory drug, one proteasome inhibitor, and one anti-CD38 antibody treatment options become very limited and the available clinical data support improved efficacy of BLENREP compared to those options;
- the Committee considers 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 BLENREP, humanised monoclonal antibody targeting B-cell maturation antigen conjugated with maleimidocaproyl monomethyl auristatin F, for treatment of multiple myeloma (EU/3/17/1925) is not removed from the Community Register of Orphan Medicinal Products.