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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Pepaxti (melphalan flufenamide)
Treatment of plasma cell myeloma
EU/3/15/1463

Sponsor: Oncopeptides AB

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	Melphalan flufenamide
Other names	-
International Non-Proprietary Name	Melphalan flufenamide
Tradename	Pepaxti
Orphan condition	Treatment of plasma cell myeloma
Sponsor's details:	Oncopeptides AB Vastra Tradgardsgatan 15 Stockholms 111 53 Stockholm Stockholms Lan Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	Oncopeptides AB
COMP opinion	12 February 2015
EC decision	19 March 2015
EC registration number	EU/3/15/1463
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Paula Boudewina van Hennik, Elita Poplavska
Applicant	Oncopeptides AB
Application submission	15 April 2021
Procedure start	20 May 2021
Procedure number	EMA/H/C/0005681
Invented name	Pepaxti
Proposed therapeutic indication	Pepaxti is indicated, in combination with dexamethasone in the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti CD38 monoclonal antibody, who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation (see section 5.1) Further information on Pepaxti can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Pepaxti
CHMP opinion	23 June 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Elisabeth Johanne Rook
Sponsor's report submission	4 June 2021

COMP discussion and adoption of list of questions	14-16 June 2022
Sponsor's removal request	22 June 2022

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2015 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 melphalan flufenamide was considered justified based on preclinical data in relevant models of the condition showing prolongation of survival and preliminary clinical data showing responses in patients who had relapsed or were refractory to previous treatment;
- 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 6 years;
- the condition was estimated to be affecting approximately 3.6 in 10,000 people 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 melphalan flufenamide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that show clinical responses in patients who had relapsed or were refractory to previous treatments. 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 melphalan flufenamide 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

Multiple myeloma (MM) (or plasma cell myeloma, as for this designation) is a debilitating malignancy part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukaemia (PCL).

The aetiology of multiple myeloma is unknown. The disease is often asymptomatic for a long period of time and therefore is often advanced at the time of diagnosis. MM is most frequently diagnosed among people >65 years of age and the median age at onset in Europe is 72 years. The incidence rates increase with age, particularly after the age of 40 years, and men are more likely to develop the disease than women.

The clinical course of MM can be highly variable. Multiple myeloma is a heterogeneous disease with some patients progressing rapidly despite treatment and others remaining stable without therapy for a number of years. Myeloma cells produce and secrete large quantities of one specific immunoglobulin (Ig) called monoclonal (M) protein, which can be measured in plasma, and serve as a reflection of the disease burden over time. The accumulation of excess of plasma cells in the bone marrow leads to inhibition of the production of normal blood cells, and as a result, patients frequently present with cytopenias (especially anaemia, but also thrombocytopenia, and neutropenia). Decreased production of antibodies leads to infections. In addition, patients develop osteolytic lesions in the bone that may lead to pathologic fractures (~75%), and to hypercalcemia. Renal impairment is also frequently associated with MM due to the protein overload.

The sponsor described the characteristics of the condition, which has been previously accepted by the COMP for an orphan designation.

The intended therapeutic indication "Pepaxti is indicated, in combination with dexamethasone in the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti CD38 monoclonal antibody, who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time between transplantation and progression should be at least 3 years (see section 5.1)" falls within the scope of the designated orphan condition "treatment of plasma cell myeloma".

Intention to diagnose, prevent or treat

The medical plausibility to be confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The most common presenting symptoms of MM are fatigue, persistent bone pain, especially in the lower back or thorax, and opportunistic infections (often pneumococcal). Other common symptoms include pathologic fractures, spinal cord compression (from pathologic fracture), weakness, malaise, anaemia and/or bleeding, hypercalcemia, renal insufficiency, and neuropathies (Shah and Besa, 2018). Clinical complications of progressive MM include recurrent infections due to decreased production of antibodies, cytopenias (especially anaemia, but also thrombocytopenia, and neutropenia), renal failure due to the protein overload, hyperviscosity syndrome, hypercalcemia, bone pain, and pathologic fractures (Munshi et al., 2012).

At the stage of triple class refractoriness there is a limited number of approved agents available. Median overall survival (OS) in 1 study in patients who were refractory to 1 anti CD38 monoclonal antibody (mAb), 1 PI and 1 IMiD was 5.3 months (Benyamini 2018). In another study, median OS in

patients refractory to anti CD38 mAbs was found to be only 4.5 months (Varnado et al 2018). Of note, patients with RRMM and EMD, a sign of advanced MM when the disease has manifested itself outside the bone marrow, who were also refractory to anti CD38 mAbs had particularly poor outcomes (Pick et al 2018). Further, in a study with heavily pretreated patients, the reported median OS was 6.6 months and 3.5 months in a subgroup of patients who progressed on daratumumab-based therapy (Pick et al 2018).

Patients whose disease has become triple refractory are in their late stage of the disease, are typically frail and have multiple comorbidities. Given the limited survival, as well as the inevitable aggressive relapses in patients with refractory disease, new drugs are needed.

The COMP concluded that the condition is chronically debilitating and life-threatening due to development of hypercalcemia, renal insufficiency, anaemia, bone lesions, and reduced life expectancy.

Number of people affected or at risk

At time of initial orphan designation in November 2014, the COMP concluded that the condition was estimated to be affecting approximately 3.6 in 10,000 persons in the European Union.

The Sponsor's position remains that multiple myeloma is an orphan disease, affecting not more than 5 in 10,000 in the EU, which is below the threshold for orphan designation. This was based on two different sources Globocan 2020 and NORDCAN, 2019 presented in Table 1 below:

Table 1. Prevalence of multiple myeloma in the EU

Source	**Prevalence proportion per 10,000**
Globocan 2020 Prevalence calculated based on age-standardised incidence rates	1.2 – 2.3
Globocan 2020 Prevalence calculated based on 5-year prevalence	3.9
NORDCAN, 2019	4.6

However, the sponsor did not conclude on a specific estimate of the prevalence.

The sponsor should provide a revised estimate for the prevalence. This estimate should be justified based on recent published epidemiological data including registries and supported by an indirect estimation of the prevalence.

It should be highlighted that recently the COMP accepted OS data of 5.8 years based on the the following publications (Greipp 2005; Cho 2017; Kastritis 2017; Usmani 2018). Based on these data, the median OS for International Staging System (ISS) stage I/II patients, who represent 60-70% of all MM patients, is approximately 7 years. For ISS stage III patients, who represent 30-40% of all MM patients, the median OS is approximately 1-4 years, i.e. using a 7-year mOS for ISS stage I/II, representing 60% of the population and 4-year mOS for ISS stage III, representing 40%.

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

Current treatment of multiple myeloma (MM) includes glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy, primarily alkylating agents (such as bendamustine, cyclophosphamide and melphalan), including high dose chemotherapy followed by autologous stem cell transplantation (ASCT), proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib), immunomodulatory agents (IMiDs, such as thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs, such as daratumumab, isatuximab, elotuzumab), the histone deacetylase inhibitor panobinostat, the antibody drug conjugate, belantamab mafodotin, the selective inhibitor of nuclear export (SINE) selinexor and autologous CAR-T-cell immunotherapy agent idecabtagene vicleucel, a genetically modified B-cell maturation antigen (BCMA)-directed therapy.

As per the European society for medical oncology (ESMO) guidelines on the diagnosis and treatment of multiple myeloma in later 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 (Dimopoulos et al 2021).

For the R/R MM setting in the EU the below medicinal products are authorised:

- Second- and later lines: bortezomib, carfilzomib, ixazomib, lenalidomide, pomalidomide, daratumumab, isatuximab, elotuzumab.
- Third- and later lines: pomalidomide, daratumumab, isatuximab, elotuzumab, Panobinostat.
- Fourth- and later lines: idecabtagene vicleucel (ide-cel), ciltacabtagene autoleucel.
- Fifth- and later lines: belantamab and Selinexor.

The proposed indication for melphalan flufenamide is the following:

Pepaxti is indicated, in combination with dexamethasone in the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti CD38 monoclonal antibody, who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time between transplantation and progression should be at least 3 years (see section 5.1).

The sponsor considered belantamab, selinexor and idecabtagene vicleucel as satisfactory methods.

However, both belantamab and selinexor are authorised for R/R MM after 4 prior lines of treatment, therefore as fifth and later lines of therapy in the triple-class (PIs, IMiDs, anti-CD38 mAbs) patient population. Therefore, melphalan flufenamide covers a broader patient population, which is not covered by belantamab and selinexor.

Abecma (idecabtagene vicleucel) is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

In addition, Carvykti (ciltacabtagene autoleucel) is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Therefore, for the significant benefit idecabtagene vicleucel and ciltacabtagene autoleucel should be considered as satisfactory methods.

Significant benefit

The sponsor claimed the significant benefit based on safety and a major contribution to patient care as compared to the authorized CAR-T therapy ide-cel. The sponsor claims that treatment with ide-cel has limitations due to applicability and accessibility that may prevent it from being practical and clinically appropriate for all patients with heavily pretreated MM.

According to the sponsor, in order to qualify for CAR-T and related treatments, patients should be relatively fit (ECOG 0-1), without CNS-disorder, inadequate renal, cardiac and pulmonal function, further active infections, inflammatory disease are contraindications for use and viral re-activation of CMV and HBV with fatal outcome has occured and theoretically, patients should also be eligible for a second treatment. Further, due to the complex and highly advanced production process of ide-cel, drug availability is at least 4-5 weeks. Consequently, patients with progressing disease will not be subjects for such therapy, unless bridging treatment with other, readily available treatments to which the disease is not resistant nor the patient is intolerant or have developed intolerance to, can be utilized. In addition, ide-cel, like other CAR-T cell therapies, will only be available in academic hospitals with transplant/CAR-T cell capabilities, including participating in a mandatory educational programme for both HCPs and patients and the individualized and complex production and treatment associated with high costs, will limit the number of patients who can receive this type of treatment. In addition, only health care professionals specifically trained in cytokine release syndrome (CRS) and neurological toxicities (common adverse events with ide-cel) can administer ide-cel to patients, and the facilities treating patients with ide-cel should be certified for the Ide-cel administration and monitoring. The patients are also required to stay at the certified facility for at least 4 weeks after treatment with ide-cel due to serious and life-threatening adverse events such as CRS, neurologic toxicities and haemophagocytic lympohistiocytosis (HLH). As the majority of R/R MM patients are treated outside of this setting, ide-cel will probably only be available to a limited subset of patients, while Pepaxti will be widely available with its 30-minute monthly infusion and with a manageable safety profile.

The COMP acknowledged the above sponsor' s arguments that melphalan flufenamide will provide a major contribution to patient care as compared to the authorized CART therapy ide-cel, as it has limitations with regards to eligibility, safety and accessibility considerations that may prevent them from being practical and clinically appropriate for all patients with heavily pretreated multiple myeloma. However, from a regulatory perspective within the remits of this procedure, the sponsor is reminded that the (minimal) prerequisite for a significant benefit based on a major contribution to patient care is the demonstration of the product's equivalence in terms of efficacy, safety and benefit/risk balance as compared with the relevant authorized medicinal products. Reference is made to the "Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products" https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN

In conclusion the COMP considers that the significant benefit of melphalan flufenamide over the authorized CAR T therapy idecabtagene vicleucel has not been established based on the data presented. The sponsor is requested to provide indirect comparisons based on the available updated

clinical data between melphalan flufenamide and the authorised CAR-T cell therapies idecabtagene vicleucel and ciltacabtagene autoleucel.

4. COMP list of issues

- Prevalence

The sponsor should provide a revised estimate for the prevalence. This estimate should be justified based on recent published epidemiological data including registries and supported by an indirect estimation of the prevalence.

For the estimation and presentation of the prevalence estimate the sponsor is advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

The sponsor should discuss the significant benefit of melphalan flufenamide over the authorised medicinal product Carvikty (ciltacabtagene autoleucel) based on the updated data.

The significant benefit of melphalan flufenamide over Abecma (idecabtagene vicleucel) is not considered established, based on the data presented. Therefore, the sponsor is requested to further justify the assumption of significant benefit of melphalan flufenamide over idecabtagene vicleucel based on indirect comparisons of the available updated clinical data.