25 February 2021
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

of an orphan medicinal product submitted for marketing authorisation

Nexpovio (selinexor)
Treatment of plasma cell myeloma
EU/3/14/1355

Sponsor: Karyopharm Europe GmbH

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

2.1. Orphan medicinal product designation 4

3. Review of criteria for orphan designation at the time of marketing authorisation 4

Article 3(1)(a) of Regulation (EC) No 141/2000 4

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

4. COMP list of issues 7

1. Product and administrative information

Product	
Designated active substance(s)	Selinexor
Other name(s)	-
International Non-Proprietary Name	Selinexor
Tradename	Nexpovio
Initial orphan condition	Treatment of plasma cell myeloma
Sponsor's details:	Karyopharm Europe GmbH Franziska-Bilek-Weg 9 Schwanthalerhoehe-Laim 80339 Munich Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Karyopharm Europe GmbH - Germany
COMP opinion	09/10/2014
EC decision	19/11/2014
EC registration number	EU/3/14/1355
Post-designation procedural history	
Transfer of sponsorship	Transfer from Clinipace GmbH to Karyopharm Europe GmbH – EC decision of 12 August 2015
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Blanca Garcia-Ochoa/ Sinan B. Sarac
Applicant	Karyopharm Europe GmbH
Application submission	9 January 2019
Procedure start	25 January 2019
Procedure number	EMA/H/C/005127
Invented name	Nexpovio
Proposed therapeutic indication	Treatment of patients with relapsed refractory multiple myeloma Further information on Nexpovio can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio
CHMP opinion	26 January 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Karri Penttila
Sponsor's report submission	25 September 2020
COMP discussion and adoption of list of questions	19-21 January 2021
Oral explanation	16 February 2021
Sponsor's removal request	18 February 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 2014 was based on the following grounds:

After examination of the application by COMP, the COMP considered that the sponsor had established the following:

- the intention to treat the condition with the medicinal product containing selinexor was justified based on preclinical data and preliminary clinical data showing anti-cancer activity in patients affected by 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 for orphan medicinal products were 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 selinexor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a favourable response in heavily pretreated patients with progressive disease who are refractory or intolerant to alternative treatment options. The Committee considered that this constitutes a clinically relevant advantage for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 for orphan medicinal products was fulfilled. The COMP concluded that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products were fulfilled. The COMP therefore recommended the designation of this medicinal product, containing selinexor 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) is an incurable malignancy, characterized by an uncontrolled proliferation of one or few clones of differentiated plasma cells and increased production of monoclonal

immunoglobulins. It is also known as plasma cell myeloma (PCM). The condition is still recognised and classified in the same way it was at the time of initial OD.

The *approved* therapeutic indication *"NEXPOVIO is indicated in combination with dexamethasone 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 two proteasome inhibitors, two immunomodulatory agents, and an anti-CD38 monoclonal antibody, 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

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP (see EPAR).

Chronically debilitating and/or life-threatening nature

Multiple myeloma is a fatal malignant haematologic neoplasia that is characterized by a proliferation of plasma cells and immunoglobulins. This proliferation leads to end-organ damage, including bone marrow suppression with a reduction of functioning immune cells, erythrocytes, and thrombocytes. Patients with MM also commonly have renal impairment, hypercalcemia, lytic bony lesions, and are susceptible to infections.

Although the number of applicable treatment lines has improved, increasing the total time of survival to 5-6 years, none of these treatments are curative; all patients ultimately relapse and become refractory to available therapies and eventually succumb to the disease.

Therefore, the condition is still considered chronically debilitating and life threatening.

Number of people affected or at risk

Based on literature sources, GLOBOCAN and IARC databases, as well as assuming 5 years disease duration, the sponsor proposed the 5-year partial prevalence of the condition to be 1.6 in 10,000.

The sponsor does not attempt to estimate the complete prevalence of the condition, which would require longer assumed disease duration. In addition, there are more incidence sources that the sponsor failed to consult. The sponsor should provide a more detailed analysis of available sources and provide an estimate of complete prevalence of the condition.

The estimate of 1.6 in 10,000 is far below the recently accepted estimate of prevalence of MM at 4 in 10,000.

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

Since the initial application for orphan drug status, several medicines for MM have been added to the armamentarium of the MM-treatment options. These include carfilzomib, ixazomib, panobinostat, daratumumab, elotuzomab and belantamab mafodotin.

Belantamab mafodotin (Blenrep), a monoclonal antibody, is the most recent product to receive conditional approval (2020). Belantamab mafodotin is indicated as monotherapy for patients with RRMM who have received at least 4 previous therapies and whose disease did not respond to treatment with at least 1 PI, 1 ImiD, and an anti-CD38 monoclonal antibody. The therapeutic indication of Belantamab mafodotin overlaps with the one of selinexor. Therefore, significant benefit over Belantamab mafodotin has to be demonstrated.

In describing treatment algorithm of MM, the sponsor referred to the current ESMO Clinical practice guideline (Moreau 2017). In view of the recently approved medicines, this guideline is already slightly outdated.

Significant benefit

There is currently only one authorized treatment (belantamab mafodotin, Blenrep) (under conditional marketing authorization) in the EU for patients with triple-class refractory MM. 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.

All patients in the pivotal STORM Part 2 study had penta-exposed, triple-class refractory MM. The baseline and disease characteristics of this study population is representative of real-world patients with heavily pre-treated MM (Usmani 2016, Khozin 2017, Pick 2018). All patients entered the study with progressing disease refractory to the most recent therapy.

In STORM study, selinexor in combination with dexamethasone (Sd) demonstrated an ORR of 26.2% with a median duration of response of 4.4 months. Considering that 79% of patients had stabilization of disease (SD or better), it is claimed that Sd conferred a relevant benefit to a significant majority of the patients treated in the study. These responses (and their durations) were independently assessed by an IRC and then further confirmed by review of two of the authors of the IMWG response criteria. This observed ORR is consistent with the ORR of bortezomib, carfilzomib, pomalidomide, and daratumumab of 22.9% to 29.2% observed in single-arm, phase 2 studies. However, the results of this study need to be treated with caution in view of the single arm study design resulting in a lack of comparative control arm.

The rate of serious AEs and AEs leading to death in STORM Part 2 were similar to those observed with other small molecule drugs that have been used to treat patients with RRMM and have been approved in patients with less heavily pre-treated MM.

The sponsor dismissed the CHMP assessment of the clinical effect of belantamab mafodotin based on the fact that the study used to support the conditional marketing authorisation was a single arm study. Based on the information available in the Blenrep EPAR (https://www.ema.europa.eu/en/documents/assessment-report/blenrep-epar-public-assessment-report_en.pdf) the following was established:

The ORR of Blenrep per IRC based on IMWG criteria was 32% (97.5%CI: 21.7, 43.6) in the 2.5 mg/kg dose cohort (13 months follow up). There was a further deepening of response, with 58% of responders achieving VGPR or better, including 2 sCRs and 5 CRs.

- The mDOR was 11 months.
- The point estimate of median PFS for 2.5 mg/kg and 3.4 mg/kg was 2.8 months versus 3.9 months with the Hazard ratio (HR) estimate of 3.4 mg/kg versus 2.5 mg/kg being 0.92.

- The mOS was 13.7 months in the 2.5 mg/kg cohort.

While it is difficult to quantify the effects observed in the context of a single arm study, the effects were considered to be clinically meaningful. In addition, in the Phase 2 study supporting the CMA of belantamab mafodotin, 50% of patients were beyond the 6th line of treatment and all were triple-class refractory (similar to STORM study). The populations were therefore comparable with respect to their refractoriness. The numerical comparison of ORR in the STORM study of selinexor (22%) and that of belantamab mafodotin (32%) puts the comparability of the responses observed into question. In addition, the same concern applies to the harder endpoints, for which selinexor seems to be numerically inferior. The median progression-free survival (PFS) in STORM study was 3.7 months (95% CI: 2.8, 4.7) and median overall survival (OS) was 8.4 months.

The major contribution to patient care of selinexor (administered orally) over belantamab mafodotin (administered IV) can only be established if the efficacy of both products in the same clinical setting is comparable. In addition, some quantitation of the improvement of the quality of life of patients would have to be provided to further discuss the argument of major contribution to patient care. The assumption of significant benefit is therefore currently not supported.

The company should further justify the claim of comparable/improved efficacy and major contribution to patient care in comparison to belantamab mafodotin.

4. COMP list of issues

- Prevalence

The sponsor presented an estimation of prevalence based on a small number of member states as sources of epidemiological data. The duration of the condition was assumed to be 5 years but it seems the median survival of patients has improved beyond this estimate in recent years. In addition, more sources of incidence should be consulted (ECIS), and in view of the associated uncertainties the sponsor should provide sensitivity analyses of the proposed estimate of the prevalence of the condition.

- Significant benefit

The sponsor provided a discussion of the currently used products in late lines of treatment of multiple myeloma. However, the limitations of the indirect comparison to belantamab mafodotin, were not sufficiently discussed. The sponsor is asked to provide a more complete discussion of the specific advantages of selinexor in the proposed therapeutic indication.