EMA/630196/2019

# European Medicines Agency decision

P/0403/2019

of 4 December 2019

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the refusal of a waiver for marizomib (EMEA-002452-PIP01-18) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

**Disclaimer**

This decision does not constitute entitlement to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006.

**Only the English text is authentic.**

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The European Medicines Agency,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[2],

Having regard to the application submitted by Celgene Europe B.V. on 29 October 2018 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said regulation and a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 18 October 2019, in accordance with Article 17 of Regulation (EC) No 1901/2006 and Article 21 of said Regulation and Article 13 of said Regulation,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

Whereas:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the agreement of a paediatric investigation plan and on the granting of a deferral and on the refusal of a waiver.

(2) It is therefore appropriate to adopt a decision agreeing a paediatric investigation plan.

(3) It is therefore appropriate to adopt a decision granting a deferral.

(4) It is therefore appropriate to adopt a decision refusing a waiver.

[1] OJ L 378, 27.12.2006, p.1.
[2] OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

***Article 1***

A paediatric investigation plan for marizomib, powder for solution for injection, intravenous use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

***Article 2***

A deferral for marizomib, powder for solution for injection, intravenous use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

***Article 3***

A waiver for marizomib, powder for solution for injection, intravenous use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby refused.

***Article 4***

This decision is addressed to Celgene Europe B.V., Winthontlaan 6 N, 3526 KV - Utrecht, Netherlands.

EMA/PDCO/413458/2019
Amsterdam, 18 October 2019

# Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and on the refusal of a waiver

EMEA-002452-PIP01-18

## Scope of the application

**Active substance(s):**

Marizomib

**Condition(s):**

Treatment of malignant glial tumours

**Pharmaceutical form(s):**

Powder for solution for injection

**Route(s) of administration:**

Intravenous use

**Name/corporate name of the PIP applicant:**

Celgene Europe B.V.

## Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Celgene Europe B.V. submitted for agreement to the European Medicines Agency on 29 October 2018 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 4 December 2018.

Supplementary information was provided by the applicant on 5 July 2019. The applicant proposed modifications to the paediatric investigation plan.

## Opinion

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - to agree the paediatric investigation plan in accordance with Article 17(1) of said Regulation;
   - to grant a deferral in accordance with Article 21 of said Regulation;
   - to refuse the granting of a waiver in accordance with Article 13 of said Regulation, for some of the subsets of the paediatric population and the above mentioned condition as it does not meet the grounds detailed in Article 11(1) of said Regulation.

   The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the agreed paediatric investigation plan are set out in the Annex I.

This opinion is forwarded to the applicant and the Executive Director of the European Medicines Agency, together with its annex and appendix.

# Annex I

# The subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed paediatric investigation plan (PIP)

# 1. Waiver

## *1.1. Condition:*

Treatment of malignant glial tumors

The request for the waiver applied to:

- the paediatric population from birth to less than 3 years of age;
- powder for solution for injection, intravenous use;
- on the grounds that the specific medicinal product is likely to be unsafe.

The waiver request does not provide evidence to support the following grounds set out in Article 11(1) of Regulation (EC) No 1901/2006 that:

- the specific medicinal product is likely to be ineffective or unsafe in the paediatric population.

Because:

- the PDCO disagreed with the applicant's argumentation that the specific medicinal product is likely to be ineffective or unsafe.

The waiver request is therefore refused by the PDCO.

# 2. Paediatric investigation plan

## *2.1. Condition:*

Treatment of malignant glial tumors

### 2.1.1. Indication(s) targeted by the PIP

Treatment of patients with diffuse intrinsic pontine glioma (DIPG) who have received prior radiation therapy

Treatment of patients with relapsed or refractory high-grade glioma (HGG)

### 2.1.2. Subset(s) of the paediatric population concerned by the paediatric development

From birth  to less than 18 years of age

### 2.1.3. Pharmaceutical form(s)

Powder for solution for injection

## 2.1.4. Measures

| Area | Number of measures | Description |
|---|---|---|
| Quality-related studies | 1 | **Study 1**<br><br>Development of a lyophilisate and solvent for solution for injection in a vial with a lower strength, age appropriate dose content (depending on the determined recommended phase 2 dose) |
| Non-clinical studies | 4 | **Study 2**<br><br>Investigation of antiproliferative activity of marizomib alone and in combination with other agents against selected paediatric diffuse intrinsic pontine glioma (DIPG) cell lines.<br><br>**Study 3**<br><br>Investigation of antitumor activity of marizomib alone and in combination against selected paediatric patient-derived DIPG xenograft models.<br><br>**Study 4**<br><br>Evaluation of pharmacokinetics (PK) and safety of marizomib alone and in combination with oral panobinostat in healthy nonhuman primates.<br><br>**Study 5**<br><br>Investigation of antiproliferative activity of marizomib alone and in combination with other agents against selected paediatric high-grade gliomas (HGG) cells lines. |
| Clinical studies | 3 | **Study 6**<br><br>Open-label, single arm trial to evaluate dose limiting toxicities, pharmacokinetics, safety and activity of marizomib alone and in combination with a histone deacetylase (HDAC) inhibitor, panobinostat, in children from birth to less than 18 years of age (and adults) with DIPG who received prior radiotherapy.<br><br>**Study 7**<br><br>Open-label, single arm trial to evaluate safety and efficacy of marizomib in combination with panobinostat compared against historical controls in children from birth to less than 18 years of age (and adults) with DIPG who received prior radiotherapy.<br><br>**Study 8**<br><br>Open-label, single arm, two phase trial to evaluate dose limiting toxicities, pharmacokinetics, safety and activity of marizomib in combination with another active substance to be identified as part of study 5 in children from birth to less than 18 years of age (and adults) with relapsed/ refractory high-grade glioma (HGG). |

| | | |
|---|---|---|
| Extrapolation, modelling and simulation studies | 0 | Not applicable. |
| Other studies | 0 | Not applicable. |
| Other measures | 0 | Not applicable. |

# 3. Follow-up, completion and deferral of PIP

| | |
|---|---|
| Concerns on potential long term safety/efficacy issues in relation to paediatric use: | Yes |
| Date of completion of the paediatric investigation plan: | By March 2028 |
| Deferral for one or more measures contained in the paediatric investigation plan: | Yes |