EMA/392701/2019

European Medicines Agency decision

P/0292/2019

of 14 August 2019

on the acceptance of a modification of an agreed paediatric investigation plan for daunorubicin / cytarabine (Vyxeos), (EMEA-001858-PIP02-16-M03) 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.

European Medicines Agency decision

P/0292/2019

of 14 August 2019

on the acceptance of a modification of an agreed paediatric investigation plan for daunorubicin / cytarabine (Vyxeos), (EMEA-001858-PIP02-16-M03) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

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 European Medicines Agency's decision P/0200/2017 issued on 21 July 2017, the decision P/0299/2017 issued on 4 October 2017 and the decision P/0388/2018 issued on 7 December 2018,

Having regard to the application submitted by Jazz Pharmaceuticals Ireland Limited on 22 March 2019 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 28 June 2019, in accordance with Article 22 of Regulation (EC) No 1901/2006,

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 acceptance of changes to the agreed paediatric investigation plan and to the deferral.

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan, including changes to the deferral.

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

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for daunorubicin / cytarabine (Vyxeos), powder for concentrate for infusion, intravenous use, including changes to the deferral, are hereby accepted in the scope set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices.

Article 2

This decision is addressed to Jazz Pharmaceuticals Ireland Limited Fifth Floor, Waterloo Exchange, Waterloo Road, 4 – Dublin, Ireland.

EMA/PDCO/239318/2019
Amsterdam, 28 June 2019

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan

EMEA-001858-PIP02-16-M03

Scope of the application

Active substance(s):

Daunorubicin / cytarabine

Invented name:

Vyxeos

Condition(s):

Treatment of acute myeloid leukaemia

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Powder for concentrate for infusion

Route(s) of administration:

Intravenous use

Name/corporate name of the PIP applicant:

Jazz Pharmaceuticals Ireland Limited

Information about the authorised medicinal product:

See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Jazz Pharmaceuticals Ireland Limited submitted to the European Medicines Agency on 22 March 2019 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/0200/2017 issued on 21 July 2017, the decision P/0299/2017 issued on 4 October 2017 and the decision P/0388/2018 issued on 7 December 2018.

The application for modification proposed changes to the agreed paediatric investigation plan and to the deferral.

The procedure started on 30 April 2019.

Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified.

Opinion

1. The Paediatric Committee, having assessed the application in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - to agree to changes to the paediatric investigation plan and to the deferral in the scope set out in the Annex I of this opinion.

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

2. The measures and timelines of the paediatric investigation plan and the subset(s) of the paediatric population and condition(s) covered by the waiver 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 annexes 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 acute myeloid leukaemia

The waiver applies to:

- the paediatric population from birth to less than 28 days of age;
- powder for concentrate for infusion, intravenous use;
- on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

2. Paediatric investigation plan

2.1. Condition:

Treatment of acute myeloid leukaemia

2.1.1. Indication(s) targeted by the PIP

Treatment of paediatric patients from 28 days to less than 18 years of age with relapsed/refractory acute myeloid leukaemia or in first relapse and with newly diagnosed acute myeloid leukaemia.

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

From 28 days to less than 18 years of age.

2.1.3. Pharmaceutical form(s)

Powder for concentrate for infusion.

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	0	Not applicable.
Non-clinical studies	0	Not applicable.
Clinical studies	3	**Study 1** Open-label, multiple dose trial to evaluate pharmacokinetics, safety and tolerability of liposomal combination of cytarabine and daunorubicin (CPX-351) in paediatric patients from 28 days to less than 18 years of age (and young adults) with a relapsed/refractory haematologic malignancy (CPX-MA-1201).

		Study 2 Open-label, multiple dose study to evaluate pharmacokinetics, safety, tolerability and anti-tumour activity of liposomal combination of cytarabine and daunorubicin (CPX-351) followed by fludarabine, cytarabine, and G-CSF (FLAG) in paediatric patients from 28 days to less than 18 years of age (and young adults) with relapsed/refractory acute myeloid leukaemia including a dose-finding phase and an expansion phase. (AAML1421). *Study 3 deleted in EMEA-001858-PIP02-16-M02* **Study 4** Open-label, randomised, active-controlled study to evaluate efficacy, safety and tolerability of liposomal combination of cytarabine and daunorubicin (CPX-351) and gemtuzumab ozogomicin (GO, to be used only in patients CD33 positive) compared to standard induction therapy with daunorubicin, cytarabine and GO in paediatric patients from 28 days to less than 18 years of age (and adults) with newly-diagnosed acute myeloid leukaemia (AAML1831, Arm A and arm B).
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 2026
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

5. Potential long-term safety/efficacy issues in relation to paediatric use for consideration in the Risk Management Plan/Pharmacovigilance activities

It is considered that the following issues are particular causes of concern in paediatric population:

- cardiotoxicity.

6. Reminder

Interventional clinical trials have to be registered with the EudraCT database.

All investigational medicinal products used in the studies or trials must be registered in the EudraVigilance Medicinal Product Dictionary by the sponsor.

Studies or trials which are inconclusive or not interpretable will be considered non-compliant.

The Clinical trials should be performed in accordance with Good Clinical Practice. Those conducted outside the community should be carried out in accordance with the ethical standards of Directive 2001/20/EC and those conducted within the community should be carried out in accordance with Directive 2001/20/EC.

Applicants are reminded that it is their responsibility to submit a request for modification of an agreed paediatric investigation plan, if they encounter difficulties with its implementation which render the plan unworkable or no longer appropriate.

Applicants are also reminded that in order to verify compliance with the agreed PIP, the study report must be submitted for any study that had to be completed (see Commission Guideline 2014/C338/01 of 27 September 2014 and EMA procedural advice). This is part of the validation of the application for marketing authorisation, variation or line extension. Applicants are therefore advised to consider the time necessary to produce the appropriate report for their planned date of submission. For authorised medicinal products, reports need to be submitted to the competent authority within 6 months of completion of the studies, according to article 46 of Regulation (EC) No 1901/2006.

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment of acute myeloid leukaemia

Authorised indication(s):

- Vyxeos is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

Authorised pharmaceutical form(s):

Powder for concentrate for solution for infusion

Authorised route(s) of administration:

Intravenous use