EMA/574574/2017

European Medicines Agency decision

P/0285/2017

of 4 October 2017

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for entospletinib (EMEA-002058-PIP01-16) 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 Gilead Sciences International Ltd on 28 November 2016 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 August 2017, in accordance with Article 18 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 granting 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 granting 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 entospletinib, film-coated tablet, age-appropriate oral solid dosage form, oral use, gastric 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 agreed.

Article 2

A deferral for entospletinib, film-coated tablet, age-appropriate oral solid dosage form, oral use, gastric 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 entospletinib, film-coated tablet, age-appropriate oral solid dosage form, oral use, gastric 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 4

This decision is addressed to Gilead Sciences International Ltd, Flowers Building, Granta Park, Abington, CB21 6GT - Cambridge, United Kingdom.

EMA/PDCO/354024/2017
London, 18 August 2017

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

EMEA-002058-PIP01-16

Scope of the application

Active substance(s):

Entospletinib

Condition(s):

Treatment of acute myeloid leukaemia

Pharmaceutical form(s):

Film-coated tablet

Age-appropriate oral solid dosage form

Route(s) of administration:

Oral use

Gastric use

Name/corporate name of the PIP applicant:

Gilead Sciences International Ltd

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Gilead Sciences International Ltd submitted for agreement to the European Medicines Agency on 28 November 2016 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 3 January 2017.

Supplementary information was provided by the applicant on 29 May 2017. 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 18 of said Regulation;
   - to grant a deferral in accordance with Article 21 of said Regulation;
   - to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

   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 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 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 acute myeloid leukaemia

The request for the waiver applied to:

- the paediatric population from birth to less than 28 days;
- film-coated tablet, age-appropriate oral solid dosage form, oral use, gastric 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 patients from 28 days to less than 18 years of age with relapsed or refractory acute myeloid leukaemia or 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)

Film-coated tablet, age-appropriate oral solid dosage form

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	2	**Study 1** Development of film-coated tablets smaller and of lower strength (compared to the existing pharmaceutical form) appropriate to children from 6 to less than 12 years of age who can swallow tablets and for adolescents from 12 to less than 18 years of age who are unable to swallow the adult-sized tablet. **Study 2** Development of an age-appropriate oral dosage form (mini-tablets or dispersible tablets or granules) for children younger than 6 years of age.

Non-clinical studies	2	**Study 3** In vitro study to measure cell viability, cytotoxicity, and spleen tyrosine kinase (SYK) pathway activation in paediatric and adult acute myeloid leukaemia cell lines and to test the ability of entospletinib to attenuate cellular signalling, reduce viability, and induce apoptosis in paediatric and adult cell lines (In Vitro Study 1). **Study 4** In vitro study, based on the results of In Vitro Study 1, to evaluate anti-leukemic activity of entospletinib on primary paediatric and adult acute myeloid leukaemia patient samples (In Vitro Study 2).
Clinical studies	3	**Study 5** Open-label, single-arm study to assess the safety, pharmacokinetics and anti-tumour activity of entospletinib used in monotherapy (first phase) and in combination with FLAG or VCR/DEX according to study population (second phase) in paediatric patients with relapsed or refractory acute myeloid leukaemia or acute lymphoblastic leukaemia (Paediatric Study 1). **Study 6** Open-label, single-arm study to assess the safety, pharmacokinetics and anti-tumour activity of entospletinib used in combination with FLAG (and a standard-of- care liposomal anthracycline, if applicable) in paediatric patients with relapsed or refractory acute myeloid leukaemia (Paediatric Study 2). **Study 7** Multi-centre, randomised, double-blind, placebo-controlled, add-on study, with a run-in phase, to evaluate the efficacy and safety of entospletinib as add-on to cytarabine and daunorubicin (7+ 3 regimen) in paediatric patients from 28 days to less than 18 years of age with newly-diagnosed acute myeloid leukaemia (Paediatric Study 3).
Extrapolation, modelling and simulation studies	1	**Study 8** Modelling and simulation study to simulate and predict entospletinib exposure in children from 28 days to less than 18 years of age with relapse/refractory acute myeloid leukaemia.
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:	No
Date of completion of the paediatric investigation plan:	By November 2031
Deferral for one or more measures contained in the paediatric investigation plan:	Yes