European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

Doc. Ref. EMA/27223/2010
P/2/2010

EUROPEAN MEDICINES AGENCY DECISION

of 25 January 2010

on the agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the refusal of a waiver for (1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,-22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxaza-cyclohentriacontin-3-yl]propyl}-2-methoxycyclohexyldimethyl-phosphinate (MK-8669, or AP23573) (EMEA-000458-PIP01-08) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended

(ONLY THE ENGLISH TEXT IS AUTHENTIC)

DISCLAIMER: This Decision does not entitle to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006, as amended.

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THE EUROPEAN MEDICINES AGENCY,

Having regard to the Treaty establishing the European Community,

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 as amended 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 Merck Sharp and Dohme (Europe), Inc. on 26 March 2009 under Article 16(1) of Regulation (EC) No 1901/2006 as amended also requesting a waiver under Article 13 of said Regulation and a deferral under Article 20 of said Regulation,

Having regard to the Opinion of the Paediatric Committee of the European Medicines Agency, issued on 11 December 2009, in accordance with Article 18 of Regulation (EC) No 1901/2006 as amended, and Article 13 of said Regulation and Article 21 of said Regulation**,**

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

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 (1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E, 21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxycyclohexyldimethyl-phosphinate (MK-8669, or AP23573), gastro-resistant tablet and age-appropriate oral or parenteral formulation, oral use and 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 agreed.

Article 2

A deferral for (1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E, 21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxycyclohexyldimethyl-phosphinate (MK-8669, or AP23573), gastro-resistant tablet and age-appropriate oral or parenteral formulation, oral use and 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 (1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E, 21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxycyclohexyldimethyl-phosphinate (MK-8669, or AP23573), gastro-resistant tablet and age-appropriate oral or parenteral formulation, oral use and 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 Merck Sharp and Dohme (Europe), Inc., 5 Clos du Lynx, B-1200 Brussels, Belgium.

Done at London, 25 January 2010

For the European Medicines Agency
Thomas Lönngren
Executive Director
(Signature on file)

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

Doc. Ref. EMEA/PDCO/697746/2009
EMEA-000458-PIP01-08

OPINION OF THE PAEDIATRIC COMMITTEE ON THE AGREEMENT OF A PAEDIATRIC INVESTIGATION PLAN AND A DEFERRAL AND ON THE REFUSAL OF A WAIVER

Scope of the application

Active substance(s):
(1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,-14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]-oxazacyclohentriacontin-3-yl]propyl}-2-methoxycyclohexyldimethyl-phosphinate
(MK-8669, or AP23573)

Condition(s):
Solid malignant tumours

Pharmaceutical form(s):
Gastro-resistant tablet
Age-appropriate oral or parenteral formulation

Route(s) of administration:
Oral use
Intravenous use

Name/corporate name of the PIP applicant:
Merck Sharp and Dohme (Europe), Inc.

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Merck Sharp and Dohme (Europe), Inc. submitted for agreement to the EMEA on 26 March 2009 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 30 April 2009.

Supplementary information was provided by the applicant on 2 October 2009.

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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 refuse the granting of a waiver in accordance with Article 13 of said Regulation, for a subset of the paediatric population, 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 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 Agency, together with its annex(es) and appendix.

London, 11 December 2009

On behalf of the Paediatric Committee
Dr Daniel Brasseur, Chairman

(Signature on file)

ANNEX I

THE MEASURES AND TIMELINES OF THE AGREED PAEDIATRIC INVESTIGATION PLAN AND THE SUBSET(S) OF THE PAEDIATRIC POPULATION

A. CONDITION(S)

Solid malignant tumours

B. WAIVER

Not applicable

C. PAEDIATRIC INVESTIGATION PLAN

- **Condition to be investigated**

  Solid malignant tumours

- **Proposed PIP indication**

  Treatment of solid malignant tumours

- **Subset(s) of the paediatric population concerned by the paediatric development**

  From birth to less than 18 years.

- **Formulation(s)**

  Gastro-resistant tablet
  Age-appropriate oral or parenteral formulation

- **Studies**

Area	Number of studies	Description
Quality	1	1. Development of age-appropriate oral or parenteral formulation, for use in children younger than six years of age or in children from 6 to less than 18 years who are unable to swallow a tablet.
Non-clinical		Not applicable.
Clinical	4	2. Biocomparison study in adults 3. Pharmacokinetics, safety, and tolerability study of oral MK-8669 in children and adolescents from 6 years to less than 18 years of age with paediatric solid malignant tumours. 4. Pharmacokinetics, safety, and tolerability study of oral MK-8669 in children and adolescents younger than 6 years of age with paediatric solid malignant tumours. 5. Randomized, controlled, parallel-group safety and efficacy study of MK-8669 in paediatric patients with specific paediatric solid tumours.

Measures to address long term follow-up of potential safety issues in relation to paediatric use:	**Yes**
Date of completion of the paediatric investigation plan:	**By June 2019**
Deferral for some or all studies contained in the paediatric investigation plan:	**Yes**