European Medicines Agency

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**EUROPEAN MEDICINES AGENCY DECISION**

**of 1 December 2008**

**on the application for agreement of a Paediatric Investigation Plan for treprostinil, (Remodulin and associated names) (EMEA-000207-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)

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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 United Therapeutics Europe Ltd on 5 June 2008 under Article 16(1) 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 14 November 2008, 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 a positive opinion.

(2) It is therefore appropriate to adopt a Decision following the Paediatric Committee's opinion on the Paediatric Investigation Plan.

(3) It is therefore appropriate to adopt a Decision granting a waiver.

(4) It is therefore appropriate to adopt a Decision granting a 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*

A Paediatric Investigation Plan for treprostinil, (Remodulin and associated names), nebuliser solution, solution for infusion, inhalation use, subcutaneous 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 waiver for treprostinil, (Remodulin and associated names), nebuliser solution, solution for infusion, inhalation use, subcutaneous 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 deferral for treprostinil, (Remodulin and associated names), nebuliser solution, solution for infusion, inhalation use, subcutaneous 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 United Therapeutics Europe Ltd, The Surrey Technology Centre, The Surrey Research Park, Guildford, Surrey, GU2 7YG.

Done at London, 1 December 2008

For the European Medicines Agency
Thomas Lönngren
Executive Director

(Signature on file)

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

EMEA/PDCO/517016/2008
EMEA-000207-PIP01-08

**POSITIVE OPINION OF THE PAEDIATRIC COMMITTEE ON A REQUEST FOR AGREEMENT OF A PAEDIATRIC INVESTIGATION PLAN FOR**

**Scope of the application**

Active substance:
Treprostinil

Invented name:
Remodulin and associated names

Condition(s):
Primary pulmonary hypertension
Other secondary pulmonary hypertension

Pharmaceutical form(s):
Nebuliser solution
Solution for infusion

Route(s) of administration:
Inhalation use
Subcutaneous use

Name/corporate name of the PIP applicant:
United Therapeutics Europe Ltd

Information about the authorised medicinal product: see Annex II

**Basis for opinion**

Pursuant to Article 16.1 of Regulation (EC) No 1901/2006 as amended, United Therapeutics Europe Ltd submitted for agreement to the EMEA on 6 March 2008 a paediatric investigation plan for the above mentioned medicinal product.

The procedure started on 5 June 2008.

Supplementary information was provided by the applicant on 8 September 2008.

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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 by consensus:

- To agree the paediatric investigation plan in accordance with Article 18 of Regulation (EC) No 1901/2006 as amended,
- To grant a deferral in accordance with Article 21 of Regulation (EC) No 1901/2006 as amended
- To grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 - of Regulation (EC) No 1901/2006 as amended and concluded in accordance with:
  Article 11(1)(a) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population; and
  Article 11(1)(c) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients

The Icelandic and the Norwegian Paediatric Committee members agree 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(ces).

London, 14 November 2008

On behalf of the Paediatric Committee
Dr Daniel Brasseur, Chairman

(Signature of file)

**ANNEX I**

**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**

**A. CONDITION(S)**

Primary pulmonary hypertension
Other secondary pulmonary hypertension

**B. WAIVER**

Primary pulmonary hypertension
Other secondary pulmonary hypertension

- **Condition**

The waiver applies to:

- Children from birth to less than 2 years, for nebuliser solution for inhalation administration

On the grounds that the specific medicinal product is likely to be ineffective

- Children from birth to less than 12 years, for solution for infusion for subcutaneous administration

On the grounds that clinical studies cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the paediatric population

## C. PAEDIATRIC INVESTIGATION PLAN

- **Condition to be investigated**

Primary pulmonary hypertension
Other secondary pulmonary hypertension

- **Proposed PIP indication**

**Treatment of Pulmonary Arterial Hypertension**

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

From birth to less than 18 years

- **Formulation(s)**

- Nebuliser solution for inhalation
- Solution for infusion for subcutaneous administration
- Solution for infusion for intravenous administration

- **Studies**

| Area | Number of studies | Description |
|---|---|---|
| Quality | 1 | Development of an age-appropriate inhalation device for children from 2 years old to less than 6 years old. |
| Quality | 1 | Development of an Intravenous formulation. |
| Clinical (inhaled form) | 1 | Multi-centre, open-label, single-dose, dose-escalating study of inhaled treprostinil sodium using an Inhalation Device in paediatric patients from 6 years old to less than 18 years old with pulmonary arterial hypertension. |
| Clinical (inhaled form) | 1 | Randomized, double blind, Placebo controlled add-on to baseline therapy, multiple-dose, parallel group study of the safety and efficacy of inhaled treprostinil sodium using an Inhalation Device in paediatric patients from 6 years to less than 18 years old with pulmonary arterial hypertension. |
| Clinical (inhaled form) | 1 | Open-label safety and tolerability study using an age-appropriate inhalation device, in paediatric patients from 2 years to less than 6 years old with pulmonary arterial hypertension. |
| Clinical (inhaled form) | 1 | Randomized, double-blind, Placebo controlled add-on to baseline therapy study using an age-appropriate inhalation device, in paediatric patients from 2 years to less than 6 years old with pulmonary arterial hypertension. |
| Clinical (Subcutaneous form) | 1 | Analyses of existing data to clarify the safety and efficacy of the parenteral formulation of treprostinil in children aged from 12 to less than 18 years, as systematic review. |
| Clinical | 1 | Randomized, double-blind, Placebo controlled add-on to baseline |

| | | |
|---|---|---|
| (Subcutaneous form) | | therapy parallel group study in paediatric patients from 12 years to less than 18 years old with pulmonary arterial hypertension. |
| Clinical (Intravenous form) | 1 | A comparative study of intravenously administered treprostinil in neonates or older children with acute Pulmonary Arterial Hypertension treated in Paediatric Intensive Care Unit. |

| | |
|---|---|
| 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 December 2017** |
| Deferral for initiation of some or all studies contained in the paediatric investigation plan: | **Yes** |
| Deferral for completion of some or all studies contained in the paediatric investigation plan: | **Yes** |

**ANNEX II**

**INFORMATION ABOUT THE AUTHORISED MEDICINAL PRODUCT**

| EU Number | Invented name Name | Strength | Pharmaceutical Form | Route of administration | Packaging | Content (concentration) | Package size |
|---|---|---|---|---|---|---|---|
| N/A | Remodulin and associated names | 1mg/ml, 2.5mg/ml, 5mg/ml, 10mg/ml | Solution for Infusion | Subcutaneous | N/A | N/A | N/A |