EMA/912642/2011

European Medicines Agency decision

P/294/2011

of 20 December 2011

on the acceptance of a modification of an agreed paediatric investigation plan for bosentan monohydrate (Tracleer), (EMEA-000425-PIP02-10-M01) 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 European Medicines Agency's decision P/128/2010 issued on 28 July 2010,

Having regard to the application submitted by Actelion Registration Ltd on 26 August 2011 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 11 November 2011, 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.

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

[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 bosentan monohydrate (tracleer), film-coated tablet, dispersible tablet, oral use, 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 Actelion Registration Ltd, 389 Chiswick High Road, W44 4AL UK, London, United Kingdom

Done at London, 20 December 2011

For the European Medicines Agency
Guido Rasi
Executive Director
(Signature on file)

EMA/PDCO/755574/2011

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

EMEA-000425-PIP02-10-M01

Scope of the application

Active substance(s):

Bosentan monohydrate

Invented name:

Tracleer

Condition(s):

Treatment of Pulmonary Arterial Hypertension (PAH)

Treatment of Systemic sclerosis

Treatment of Interstitial pulmonary fibrosis

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Film-coated tablet

Dispersible tablet

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Actelion Registration Ltd

Information about the authorised medicinal product:

See Annex II

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Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Actelion Registration Ltd submitted to the European Medicines Agency on 26 August 2011 an application for modification of the agreed paediatric investigation plan with a waiver as set out in the European Medicines Agency's decision P/128/2010 issued on 28 July 2010.

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

The procedure started on 14 September 2011.

Scope of the modification

The applicant is changing measures and timelines of the agreed plan.

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 in the scope set out in the Annex I of this opinion.

   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 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(es) and appendix.

London, 11 November 2011

On behalf of the Paediatric Committee
Dr Daniel Brasseur, Chairman
(Signature on file)

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

1. Waiver

1.1. Condition: treatment of Pulmonary Arterial Hypertension (PAH)

The waiver applies to:

- Infants from 28 days to less than 3 months;
- for Film-coated tablet and Dispersible tablet for oral use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible;
- Adolescents from 12 to less than 18 years;
- for Film-coated tablet and Dispersible tablet for oral use;
- 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.

1.2. Condition: treatment of Systemic sclerosis

The waiver applies to:

- All subsets of the paediatric population from birth to less than 18 years of age;
- for Film-coated tablet and Dispersible tablet for oral use;
- on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

1.3. Condition: treatment of Interstitial pulmonary fibrosis

The waiver applies to:

- All subsets of the paediatric population from birth to less than 18 years of age;
- for Film-coated tablet and Dispersible tablet for oral use;
- on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

2. Paediatric Investigation Plan

2.1. Condition: Treatment of Pulmonary arterial Hypertension (PAH)

2.1.1. Indication(s) targeted by the PIP

Treatment of Pulmonary Arterial Hypertension (PAH).

Treatment of Persistent Pulmonary Hypertension of the Newborn (PPHN).

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

From birth to less than 28 days of age.

From 3 months to less than 12 years of age.

2.1.3. Pharmaceutical form(s)

Film-coated tablet.

Dispersible tablet.

2.1.4. Studies

Area	Number of studies	Description
Quality	1	Study 1: Study on nasogastric tube administration of the bosentan dispersible tablet
Non-clinical	3	Study 2: 24 days dose-range-finding toxicity study in juvenile rats Study 3: 94 days toxicity study in juvenile rats Study 4: PK/safety and efficacy study in a model of chronic pulmonary hypertension in newborn sheep
Clinical	2	Study 5: Open-label, randomised multicentre, multiple dose trial to evaluate pharmacokinetics, safety of bosentan in children from 3 months to less than 12 years of age with Pulmonary Arterial Hypertension (PAH) Study 6: Double blind, randomised multicentre, add-on placebo controlled, trial to evaluate pharmacokinetics, safety, efficacy, of bosentan in neonates with persistent pulmonary hypertension of the newborn (PPHN).

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By June 2014
Deferral for one or more studies contained in the paediatric investigation plan:	No

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment of pulmonary arterial hypertension (PAH)

Authorised indications:

Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in:

• Primary (idiopathic and heritable) PAH;

• PAH secondary to scleroderma without significant interstitial pulmonary disease;

• PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.

Some improvements have also been shown in patients with PAH WHO functional class II (see section 5.1).

2. Treatment of systemic sclerosis

Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease (see section 5.1).

EU Number	(Invented) name	Strength	Pharmaceutical Form	Route of Administration	Packaging	Content (concentration)	Package size
EU/1/02/220/001	Tracleer	62.5 mg	Film-coated tablet	Oral use	blister (PVC/PE/PVDC/alu)		14 tablets
EU/1/02/220/002	Tracleer	62.5 mg	Film-coated tablet	Oral use	blister (PVC/PE/PVDC/alu)		56 tablets
EU/1/02/220/003	Tracleer	62.5 mg	Film-coated tablet	Oral use	blister (PVC/PE/PVDC/alu)		112 tablets
EU/1/02/220/004	Tracleer	125 mg	Film-coated tablet	Oral use	blister (PVC/PE/PVDC/alu)		56 tablets
EU/1/02/220/005	Tracleer	125 mg	Film-coated tablet	Oral use	blister (PVC/PE/PVDC/alu)		112 tablets
EU/1/02/220/006	Tracleer	32 mg	Dispersible tablet	Oral use	blister (alu/alu)		56 tablets