



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/111742/2013

European Medicines Agency decision

P/0058/2013

of 26 March 2013

on the refusal of a modification of an agreed paediatric investigation plan for everolimus (Votubia), (EMA-000019-PIP02-07-M04) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

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 726/2004¹,

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 Agency²,

Having regard to the European Medicines Agency's decision P/124/2008 issued on 5 December 2008, the decision P/105/2010 issued on 25 June 2010, and the decision P/127/2011 issued on 8 June 2011,

Having regard to the application submitted by Novartis Europharm Ltd on 16 November 2012 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 8 February 2013, 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 refusal of changes to the agreed paediatric investigation.
- (2) It is therefore appropriate to adopt a decision on the refusal 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 everolimus (Votubia), tablet, dispersible tablet, oral 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, are hereby refused.

Article 2

This decision is addressed to, Novartis Europharm Ltd, Wimblehurst Road, RH12 5AB - Horsham, United Kingdom.

Done at London, 26 March 2013

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



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EMA/PDCO/753146/2012 **Corr**

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

EMA-000019-PIP02-07-M04

Scope of the application

Active substance(s):

Everolimus

Invented name:

Votubia

Condition(s):

Treatment of subependymal giant cell astrocytoma

Treatment of angiomyolipoma

Authorised indication(s):

See Annex II

Pharmaceutical form(s):

Tablet

Dispersible tablet

Route(s) of administration:

Oral use

Name / corporate name of the PIP applicant:

Novartis Europharm Ltd

Information about the authorised medicinal product:

See Annex II



Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Novartis Europharm Ltd submitted to the European Medicines Agency on 16 November 2012 an application for modification of the agreed paediatric investigation plan with a deferral and with a waiver as set out in the European Medicines Agency's decision P/124/2008 issued on 5 December 2008, the decision P/105/2010 issued on 25 June 2010, and the decision P/127/2011 issued on 8 June 2011.

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

The procedure started on 12 December 2012.

Scope of the modification

The applicant requested that the requirement for development of a 1 mg dispersible tablet for oral use be removed from the current agreed paediatric investigation 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 refuse the changes proposed by the applicant regarding the paediatric investigation plan, as the applicant has failed to justify difficulties with its implementation that may render the plan unworkable or no longer appropriate. In particular, the PDCO considered that a 1 mg dispersible tablet was required to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.

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 remain unchanged and 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.

London, 8 February 2013

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 and condition(s) covered by the waiver

1. Waiver

1.1. Condition: treatment of angiomyolipoma

The waiver applies to:

- all subsets of the paediatric population from birth to less than 18 years of age;
- for tablet for oral use 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 subependymal giant cell astrocytoma

2.1.1. Indication targeted by the PIP

Treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC)

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

From birth to less than 18 years

2.1.3. Pharmaceutical form(s)

Tablet for oral use, including strength of 2.5 mg, 5 mg and 10 mg

Dispersible tablet for oral use, including strengths of 1 mg, 2 mg, 3 mg and 5 mg

2.1.4. Measures

Area	Number of studies	Description
Quality		Not applicable.
Non-clinical		Not applicable.
Clinical	3	Measure 1: Relative bioavailability study between intact 1 mg tablet and 1 mg tablet dispersed in water in adults Measure 2: Bioequivalence study between intact 1 mg tablet and 5 mg dispersible tablet in adults. Measure 3: Randomized, double-blind, placebo-controlled, parallel-group, dose-titration, comparative, multi-centre study to evaluate pharmacokinetics, safety, tolerability and activity of everolimus in children from birth to less than 18 years of age.

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 December 2012
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Condition(s) and authorised indication(s):

1. Treatment of subependymal giant cell astrocytoma associated with tuberous sclerosis complex

Authorised indication(s):

Votubia is indicated for the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.

The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

2. Renal angiomyolipoma associated with tuberous sclerosis complex

Authorised indication(s):

Votubia is indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.

The evidence is based on analysis of change in sum of angiomyolipoma volume.

Authorised pharmaceutical formulation(s):

Tablet

Authorised route(s) of administration:

Oral use