4 February 2015
EMA/COMP/306721/2010 Rev.3
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Everolimus for the treatment of tuberous sclerosis

First publication	9 August 2010
Rev.1: administrative update	16 March 2011
Rev.2: information about Marketing Authorisation	24 July 2013
Rev.3: sponsor's change of address	4 February 2015
Disclaimer Please note that revisions to the Public Summary of Opinion are purely administrative updates. Therefore, the scientific content of the document reflects the outcome of the Committee for Orphan Medicinal Products (COMP) at the time of designation and is not updated after first publication.	

On 4 August 2010, orphan designation (EU/3/10/764) was granted by the European Commission to Novartis Europharm Limited, United Kingdom, for everolimus for the treatment of tuberous sclerosis.

What is tuberous sclerosis?

Tuberous sclerosis is a genetic disease that causes growth of benign tumours in different organs of the body, including the brain, lungs, heart, kidneys, skin and eyes. The symptoms and severity of the disease vary greatly from patient to patient. Depending on where the tumours are located, symptoms may include epilepsy, learning difficulties, skin abnormalities and kidney problems.

Tuberous sclerosis is a long-term debilitating disease that can be life threatening in patients with severe symptoms, who may develop severe mental retardation, uncontrollable seizures and kidney failure.

What is the estimated number of patients affected by the condition?

At the time of designation, tuberous sclerosis affected approximately 1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 51,000 people*, and is below the

*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 27), Norway, Iceland and Liechtenstein.
At the time of designation, this represented a population of 506,300,000 (Eurostat 2010).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

At the time of designation, no satisfactory methods were authorised in the EU for the treatment of tuberous sclerosis. Patients were mainly treated with surgery to remove the benign tumours in the affected organs. Different treatments to control the symptoms of the disease were also used, such as antiepileptic medicines, and some patients needed a lung or kidney transplant.

How is this medicine expected to work?

Patients with tuberous sclerosis have abnormalities in the *TSC1* or *TSC2* genes. These genes help to regulate cell growth and division by indirectly controlling the activity of a protein called 'mammalian target of rapamycin' (mTOR). Abnormalities in the *TSC1* or *TSC2* genes result in loss of the ability to regulate mTOR in affected cells, causing uncontrolled cell growth.

Everolimus acts directly on mTOR by blocking its activity. In tuberous sclerosis, this is expected to help regulate cell division and reduce the number or size of the benign tumours that cause the symptoms of the disease.

What is the stage of development of this medicine?

The effects of everolimus have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with everolimus in patients with tuberous sclerosis were ongoing.

Everolimus was first authorised for the prevention of organ transplant rejection in several countries inside and outside the EU. It has also received authorisation for the treatment of advanced renal cell carcinoma (kidney cancer that has started to spread) in the EU and in several countries worldwide.

At the time of submission, everolimus was not authorised anywhere in the EU for tuberous sclerosis. Orphan designation of everolimus had been granted in the United States of America and in Switzerland for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 6 May 2010 recommending the granting of this designation.

Update: everolimus (Votubia) has been authorised in the EU since 2 September 2011 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.

More information on Votubia can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom
Tel. +41 61 324 11 11 (Switzerland)
E-mail: orphan.enquiries@novartis.com

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- Orphanet, a database containing information on rare diseases which includes a directory of patients' organisations registered in Europe.
- European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Translations of the active ingredient and indication in all official EU languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Everolimus	Treatment of tuberous sclerosis
Bulgarian	Еверолимус	Лечение на туберозна склероза
Czech	Everolimus	Léčba tuberózní sklerózy
Danish	Everolimus	Behandling af tuberøs sklerose
Dutch	Everolimus	Behandeling van tubereuze sclerose
Estonian	Everoliimus	Tuberoosse skleroosi ravi
Finnish	Everolimuusi	Tuberoosiskleroosin hoito
French	Évérolimus	Traitement de la sclérose tubéreuse
German	Everolimus	Behandlung der tuberösen Sklerose
Greek	Everolimus	Θεραπεία της οζώδους σκλήρυνσης
Hungarian	Everolimus	Sclerosis tuberosa kezelése
Italian	Everolimus	Trattamento della sclerosi tuberosa
Latvian	Everolīms	Tuberozās sklerozes ārstēšana
Lithuanian	Everolimuzas	Tuberozinės sklerozės gydymas
Maltese	Everolimus	Kura tal-isklerosi tuberuża
Polish	Ewerolimus	Leczenie stwardnienia guzowatego
Portuguese	Everolimus	Tratamento da esclerose tuberosa
Romanian	Everolimus	Tratamentul sclerozei tuberoase
Slovak	Everolimus	Liečba tuberóznej sklerózy
Slovenian	Everolimus	zdravljenje tuberozne skleroze
Spanish	Everolimus	Tratamiento de la esclerosis tuberosa
Swedish	Everolimus	Behandling av tuberös skleros
Norwegian	Everolimus	Behandling av tuberøs sklerose
Icelandic	Everolímus	Meðferð við hnjóskahersli (tuberous sclerosis)

[1] At the time of designation