



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

19 July 2012  
EMA/COMP/357657/2012  
Committee for Orphan Medicinal Products

## Public summary of opinion on orphan designation

### 2S, 4R ketoconazole for treatment of Cushing's syndrome

On 4 July 2012, orphan designation (EU/3/12/1012) was granted by the European Commission to Cortendo AB, Sweden, for 2S, 4R ketoconazole for treatment of Cushing's syndrome.

#### What is Cushing's syndrome?

Cushing's syndrome is a disease characterised by an excess of the hormone cortisol in the blood. It is usually caused by a tumour of the pituitary gland (a gland located at the base of the brain) that produces large amounts of adrenocorticotrophic hormone (ACTH), which in turn stimulates the production of excess cortisol from the adrenal glands, which are situated above the kidneys. Patients with Cushing's syndrome have 'central' weight gain (affecting the face and torso but not the limbs), growth of fat above the collar bone and the back of the neck, a roundish face, easy bruising, excessive growth of coarse hair on the face, weakening of the muscles and bones, depression, diabetes and high blood pressure.

Cushing's syndrome is a severe disease that is long lasting and may be life threatening because of its complications, including diabetes, high blood pressure and mental problems.

#### What is the estimated number of patients?

At the time of designation, Cushing's syndrome affected approximately 0.4 in 10,000 people in the European Union (EU)\*. This is equivalent to a total of around 20,000 people, and is below the ceiling 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, the main treatment for ACTH-dependent Cushing's syndrome involved surgery to remove the tumour responsible for causing the high cortisol levels, sometimes followed by radiotherapy (treatment with radiation). Several medicines were authorised in the EU to reduce the

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\*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. This represents a population of 506,300,000 (Eurostat 2011).



production of cortisol or prevent it from working, including pasireotide, metyrapone, aminoglutethimide and mitotane.

The sponsor has provided sufficient information to show that 2S, 4R ketoconazole might be of significant benefit for patients with Cushing's syndrome because it works in a different way to existing treatments and early studies show that it might be used in patients before surgery or when surgery is not possible, in combination with existing treatments or when these are not indicated. These assumptions will need to be confirmed at the time of marketing authorisation, in order to maintain the orphan status.

## **How is this medicine expected to work?**

2S, 4R ketoconazole is closely related to ketoconazole which is an antifungal medicine used to treat fungal skin infections. Apart from its well-known antifungal activity, studies show that ketoconazole also blocks the activity of enzymes involved in production of steroids, including cortisol. In Cushing's syndrome, 2S, 4R ketoconazole is expected to block the action of these enzymes via different pathways, thereby decreasing the production of cortisol and relieving the symptoms of the disease. 2S, 4R ketoconazole works in the same way as ketoconazole but it is expected to be safer and more potent in its ability to decrease cortisol levels.

## **What is the stage of development of this medicine?**

The effects of 2S, 4R ketoconazole have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with 2S, 4R ketoconazole in patients with Cushing's syndrome were planned.

At the time of submission, 2S, 4R ketoconazole was not authorised anywhere in the EU for Cushing's syndrome. Orphan designation has been granted in the United States of America for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 11 May 2012 recommending the granting of this designation.

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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:

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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<sup>1</sup>, Norwegian and Icelandic

Language	Active ingredient	Indication
English	2S, 4R ketoconazole	Treatment of Cushing's syndrome
Bulgarian	2S, 4R кетоконазол	Лечение на синдром на Кушинг
Czech	2S, 4R ketokonazol	Léčba Cushingova syndromu
Danish	2S, 4R ketoconazol	Behandling af Cushings syndrom
Dutch	2S, 4R ketoconazole	Behandeling van Cushing syndroom
Estonian	2S, 4R ketokonasool	Cushingi sündroomi ravi
Finnish	Ketokonatsolin 2S, 4R	Cushingin oireyhtymän hoito
French	2S, 4R kétoconazole	Traitement du syndrome de Cushing
German	2S, 4R-Ketoconazol	Behandlung des Cushing-Syndroms
Greek	2S, 4R κετοκοναζόλη	Θεραπεία του συνδρόμου Cushing
Hungarian	2S, 4R ketokonazol	A Cushing-szindróma kezelése
Italian	2S, 4R ketoconazolo	Trattamento della sindrome di Cushing
Latvian	2S, 4R ketokonazols	Kušinga sindroma ārstēšana
Lithuanian	2S, 4R ketokonazolas	Kušingo (Cushing) sindromo gydymas
Maltese	2S, 4R ketoconazole	Kura tas-sindromu ta' Cushing
Polish	2S, 4R ketokonazol	Leczenie zespołu Cushinga
Portuguese	2S, 4R cetconazol	Tratamento da síndrome de Cushing
Romanian	2S, 4R ketoconazol	Tratamentul sindromului Cushing
Slovak	2S, 4R ketokonazol	Liečba Cushingovho syndrómu
Slovenian	2S, 4R ketokonazola	Zdravljenje Cushingovega sindroma
Spanish	2S, 4R ketoconazol	Tratamiento del síndrome de Cushing
Swedish	2S, 4R ketokonazol	Behandling av Cushings syndrom
Norwegian	2S, 4R ketokonazol	Behandling av Cushings syndrom
Icelandic	2S, 4R ketókónazóls	Meðferð við Cushingsheilkenni

<sup>1</sup> At the time of designation