2 March 2015
EMA/COMP/66372/2012 Rev.1
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Ketoconazole for the treatment of Cushing's syndrome

First publication	25 April 2012
Rev.1: information about Marketing Authorisation	2 March 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 23 April 2012, orphan designation (EU/3/12/965) was granted by the European Commission to Laboratoire HRA Pharma, France, for ketoconazole for the 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 adrenocorticotropic hormone (ACTH), which in turn stimulates the production of excess cortisol from the adrenal glands, which are situated above the kidney. 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 affected by the condition?

At the time of designation, Cushing's syndrome affected approximately 0.9 in 10,000 people in the European Union (EU). This was equivalent to a total of around 46,000 people*, and is below the ceiling

*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 509,000,000 (Eurostat 2012).

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

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

The sponsor has provided sufficient information to show that ketoconazole might be of significant benefit for patients with Cushing's syndrome because it works in a different way to existing treatments and may be used in patients who cannot undergo surgery or take other authorised medicines. 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?

Ketoconazole 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, ketoconazole is expected to block the action of these enzymes, thereby reducing cortisol levels and relieving the symptoms of the disease.

What is the stage of development of this medicine?

The sponsor has provided non-clinical and clinical data from the published literature to support its application for orphan designation.

Ketoconazole has been authorised in several EU countries since 1980 for the treatment of fungal skin infections.

At the time of submission, ketoconazole was not authorised anywhere in the EU for Cushing's syndrome or designated as an orphan medicinal product elsewhere for this condition.

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

Update: Ketoconazole (Ketoconazole HRA) has been authorised in the EU since 19 November 2014 for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

More information on Ketoconazole HRA 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:

Laboratoire HRA Pharma
15, rue Béranger
75003 Paris
France
Tel. +33 1 40 33 11 30
Fax +33 1 40 33 12 31
E-mail: regulatory@hra-pharma.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	Ketoconazole	Treatment of Cushing's syndrome
Bulgarian	Кетоконазол	Лечение на синдром на Кушинг
Czech	Ketoconazol	Léčba Cushingova syndromu
Danish	Ketoconazol	Behandling af Cushings syndrom
Dutch	Ketoconazole	Behandeling van Cushing syndroom
Estonian	Ketokonasool	Cushingi sündroomi ravi
Finnish	Ketokonatsoli	Cushingin oireyhtymän hoito
French	Kétoconazole	Traitement du syndrome de Cushing
German	Ketoconazol	Behandlung des Cushing-Syndroms
Greek	Κετοκοναζόλη	Θεραπεία του συνδρόμου Cushing
Hungarian	Ketokonazol	A Cushing-szindróma kezelése
Italian	Ketoconazolo	Trattamento della sindrome di Cushing
Latvian	Ketakonazols	Kušinga sindroma ārstēšana
Lithuanian	Ketokonazolas	Kušingo (Cushing) sindromo gydymas
Maltese	Ketoconazole	Kura tas-sindromu ta' Cushing
Polish	Ketokonazol	Leczenie zespołu Cushinga
Portuguese	Cetoconazol	Tratamento da síndrome de Cushing
Romanian	Ketoconazol	Tratamentul sindromului Cushing
Slovak	Ketokonazol	Liečba Cushingovho syndrómu
Slovenian	Ketokonazol	Zdravljenje Cushingovega sindroma
Spanish	Ketoconazol	Tratamiento del síndrome de Cushing
Swedish	Ketokonazol	Behandling av Cushings syndrom
Norwegian	Ketokonazol	Behandling av Cushings syndrom
Icelandic	Ketókónasól	Meðferð við Cushingsheilkenni

[1] At the time of designation