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COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF

mifepristone

for the treatment of Cushing's syndrome secondary to ectopic ACTH secretion

On 27 July 2005, orphan designation (EU/3/05/298) was granted by the European Commission to Laboratoire HRA Pharma, France, for mifepristone for the treatment of Cushing's syndrome secondary to ectopic ACTH secretion.

What is Cushing's syndrome?

Cushing's syndrome is defined as a set of clinical symptoms caused by a prolonged exposure to a high concentration of a certain substance called adrenocorticotrophic hormone (ACTH). ACTH is a naturally produced hormone that stimulates the adrenal glands (two small glands located above the kidneys, in the abdomen) to secrete other hormones, the glucocorticoid hormones. ACTH is normally produced in the body by a small oval shaped gland situated at the base of the brain (pituitary gland), but can also be (over) produced by several types of tumours. This abnormal production is called "ectopic ACTH secretion". The glucocorticoids (e.g. cortisol) are substances involved in the metabolism of sugars, lipids and proteins as well as on the inflammatory and defence mechanism of the organism. The clinical symptoms of overproduction of ACTH are hypertension, body shape modifications; vascular fragility; muscular weakness and osteoporosis (a reduction in the amount of bone mass, leading to fractures after minimal trauma); diminished resistance to infection; psychiatric disorders; healing defects; gonadal dysfunction (malfunctioning of sex organs, such as ovaries or testicles); hirsutism (abnormal hairiness), female balding and acne. Cushing's disease is chronically debilitating and in some cases can be life threatening due to an overall decreased life expectancy.

What are the methods of treatment available?

Several products with anti-cortisol activity were authorised for the condition in some countries in the Community at the time of submission of the application for orphan drug designation. Mifepristone could be of potential significant benefit for the treatment of Cushing's syndrome secondary to ectopic ACTH secretion, because it might improve the long-term outcome of the patients. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

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

According to the information provided by the sponsor, Cushing's syndrome secondary to ectopic ACTH secretion was considered to affect less than 5,000 persons in the European Union.

How is this medicinal product expected to act?

Mifepristone is a drug that is supposed to bind to a certain structure of the cells (the cortisol receptor). By binding to these receptors, the cortisol itself cannot bind anymore and therefore it cannot exert its function anymore. Then, having blocked the receptor, it neutralises the effect of the abnormally

elevated cortisol levels in Cushing's syndrome. Its action is reversible, which means that the receptor can exert its normal action after the effect of the drug stops.

What is the stage of development of this medicinal product?

At the time of submission of the application for orphan designation, no clinical trials in patients with Cushing's syndrome were planned.

Mifepristone was not marketed anywhere worldwide for Cushing's syndrome secondary to ectopic ACTH secretion, at the time of submission.

The medicinal product was designated as orphan medicinal product in the United States for this condition, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 15 June 2005 a positive opinion recommending the grant of the above-mentioned designation.

Opinions on orphan medicinal products designations are based on the following cumulative criteria: (i) the seriousness of the condition, (ii) the existence or not of alternative methods of diagnosis, prevention or treatment and (iii) either the rarity of the condition (considered to affect not more than five in ten thousand persons in the Community) or the insufficient return of development investments.

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

For more information:

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*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union (EU 25), Norway, Iceland and Lichtenstein. This represents a population of 459,700,000 (Eurostat 2004). This estimate is based on available information and calculations presented by the sponsor at the time of the application.

Patients' associations contact points:

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**Translations of the active ingredient and indication in all EU languages
and Norwegian and Icelandic**

Language	Active Ingredient	Indication
English	Mifepristone	Treatment of Cushing's syndrome secondary to ectopic ACTH secretion
Czech	Mifepristone	Sekundární léčba Cushingova syndromu při ektopické sekreci adrenokortikotropního hormonu (ACTH)
Danish	Mifepriston	Behandling af Cushings syndrom, forårsaget af ektopisk produktion af ACTH
Dutch	Mifepristone	Behandeling van Cushing syndroom als gevolg van ectopische ACTH secretie
Estonian	Mifepristoon	Ektoopilisest AKTH produktsioonist tingitud sekundaarse Cushing'i sündroomi ravi
Finnish	Mifepristone	Ektooppisesta kortikotropiinin erityksestä aiheutuvan Cushingin oireyhtymän hoito
French	Mifepristone	Traitement du syndrome de Cushing secondaire à une secretion ectopique d'ACTH
German	Mifepristone	Behandlung des Cushing-Syndroms in Folge ektopischer ACTH-Sekretion
Greek	Mifepristone	Θεραπεία του δευτεροπαθούς προς έκτοπη έκκριση ACTH, συνδρόμου Cushing
Hungarian	Mifepriston	Ektópiás ACTH szekréció következtében kialakult Cushing szindróma kezelése
Italian	Mifepristone	Trattamento della sindrome di Cushing successiva a secrezione ectopica di ACTH
Latvian	Mifepristone	Ektopiskas AKTH sekrēcijas izraisīta Kušinga sindroma ārstēšana
Lithuanian	Mifepristonas	Antrinio Kušingo sindromo gydymas dėl ektopinės AKTH (adrenokortikotropinio hormono) sekrecijos
Polish	Mifepriston	Leczenie zespołu Cushinga, wtórnego do ektopowego wydzielania hormonu ACTH
Portuguese	Mifepristone	Tratamento da síndrome de Cushing secundário a secreção ectópica de ACTH
Slovak	Mifepriston	Liečba Cushingovho syndrómu pre ektopické vylučovanie adrenokortikotropného hormónu (ACTH)
Slovenian	Mifepriston	Zdravljenje Cushingovega sindroma, ki je posledica ektopičnega izločanja ACTH
Spanish	Mifepristona	Tratamiento del síndrome de Cushing secundario a secreción ectópica de ACTH
Swedish	Mifepristone	Behandling av Cushings syndrom sekundärt till ektopisk ACTH sekretion
Norwegian	Mifepriston	Behandling av Cushings syndrom sekundært til ektopisk ACTH-sekresjon
Icelandic	Mifepristone	Meðferð við Cushings heilkenni sem stafar af mikilli ACTH framleiðslu utan heiladinguls (ectopic ACTH secretion)