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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Synthetic double-stranded short interfering RNA oligonucleotide directed against proopiomelanocortin for the treatment of adrenocorticotropin-dependent Cushing's syndrome

On 1 October 2010, orphan designation (EU/3/10/798) was granted by the European Commission to UKR Regulatory Affairs Ltd, United Kingdom, for synthetic double-stranded short interfering RNA oligonucleotide directed against proopiomelanocortin for the treatment of adrenocorticotropin-dependent Cushing's syndrome.

The sponsorship was transferred to The University of Sheffield, United Kingdom, in September 2012.

What is adrenocorticotropin-dependent Cushing's syndrome?

Cushing's syndrome is a disorder characterised by an excess of the hormone cortisol in the blood. Adrenocorticotropin-dependent Cushing's syndrome 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.

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 and high blood pressure.

ACTH-dependent Cushing's syndrome is a severe disorder 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, ACTH-dependent Cushing's syndrome affected not more than 0.6 in 10,000 people in the European Union (EU). This was equivalent to a total of not more than 30,000 people*, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on 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).

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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 used in the EU to reduce the production of cortisol or prevent it from working.

The sponsor has provided sufficient information to show that the medicine 'synthetic double-stranded short interfering RNA oligonucleotide directed against proopiomelanocortin' might be of significant benefit for patients with ACTH-dependent Cushing's syndrome because it works in a different way to existing treatments, and early studies in experimental models show that it might be used in combination with existing treatments to improve the outcome of patients with this condition. 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?

This medicine contains a small strand of genetic material called RNA that has been designed to interfere with or block the gene for proopiomelanocortin, which is responsible for the production of ACTH. By blocking this gene, the production of ACTH is reduced, relieving the symptoms of ACTH-dependent Cushing's syndrome.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, the evaluation of the effects of this medicine was ongoing.

At the time of submission of the application for orphan designation, no clinical trials with this medicine in patients with ACTH-dependent Cushing's syndrome had been started.

At the time of submission, this medicine was not authorised anywhere in the EU for ACTH-dependent 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 8 July 2010 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

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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[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Synthetic double-stranded short interfering RNA oligonucleotide directed against proopiomelanocortin	Treatment of adrenocorticotropin-dependent Cushing's syndrome
Bulgarian	Синтетичен, двойно-верижен късо интерфериращ РНК олигонуклеотид, насочен срещу проопиомеланокортин	Лечение на аденокортикотропин-зависим СИндром на Кушинг
Czech	Syntetický dvojitý krátký řetězec oligonukleotidu interferující s RNA proti proopiomelanocortinu	Léčba adrenokortikotropně-dependentního Cushingova syndromu
Danish	Syntetisk dobbeltstrenget kort interfererende RNA oligonukleotid rettet mod proopiomelanocortin	Behandling af adrenokortikotropinafhængigt Cushings syndrom
Dutch	Synthetisch dubbelstrandig kort interfererend RNA oligonucleotide gericht tegenover proopiomelanocortine	Behandeling van adrenocorticotropine-dependent Cushing's Syndroom
Estonian	Proopiomelanokortiini vastu suunatud sünteetiline kaheahelaline *short interfering RNA*	AKTH-sõltuva Cushingi sündroomi ravi
Finnish	Pro-opiomelanokortiinin kohdistettu synteettinen, kaksijuosteinen, lyhyt, interferoiva RNA-oligonukleotidi	Adrenokortikotropiinista riippuvan Cushingin oireyhtymän hoito
French	Oligonucléotide court double brin de synthèse interférant avec l'ARN dirigé contre la proopiomélanocortine	Traitement du syndrome de Cushing dépendant de l'ACTH
German	Synthetische doppelsträngige siRNA Oligonukleotide gegen Proopiomelanocortin	Behandlung des ACTH abhängigen Cushing Syndroms (Morbus Cushing)
Greek	Συνθετικό δίκλωνο ολιγονουκλεοτίδιο βραχέως RNA παρεμβολής, κατευθυνόμενου εναντι της προοπιο-μελανοκορτίνης	Θεραπεία του εξαρτώμενου από αδρενοκορτικοτροπίνη συνδρόμου Cushing
Hungarian	Proopiomelanokortin-ellenes szintetikus duplaszálú rövid interferáló RNS oligonukleotid	Adrenokortikotropin-dependens Cushing-szindróma kezelése
Italian	Oligonucleotide siRNA sintetico a doppia elica, diretto contro la pro-opiomelanocortina	Trattamento della sindrome di Cushing ACTH-dipendente
Latvian	Sintētiskais dubultķēžu īsa savienojuma RNS oligonukleotīds pret proopiomelanokortīnu	Adrenokortikoatkarīgā Kušinga sindroma ārstēšana
Lithuanian	Trumpos interferencijos RNR dvigrandis sintetinis oligonukleotidas, nukreiptas prieš propiomelanokortiną	Kušingo sindromo, sukelto adrenokortikotropino, gydymas

[1] At the time of designation

Maltese	Oligonukleotide sintetiku qasir tar-RNA li jfixkel b'katina doppja dirett kontra l-proopjomelanokortina	Kura tas-sindrome ta' Cushing dipendenti fuq l-adrenokortikotropina
Polish	Syntetyczny dwuniciowy mały oligonukleotyd interferujący RNA przeciw proopiomelanokortynie	Leczenie zespołu Cushinga zależnego od ACTH
Portuguese	Oligonucleotideo sintético de RNA de interferência curto de cadeia dupla dirigido contra a proopiomelanocortina	Tratamento do Síndrome de Cushing adrenocorticotrofina dependente
Romanian	Oligonucleotid sintetic anti-proopiomelanocortină de tip ARNsi dublu spiralat cu lanţ scurt	Tratamentul sindromului Cushing ACTH-dependent
Slovak	Syntetický dvojvláknový siRNA oligonukleotid zameraný proti proopiomelanokortínu	Liečba adrenokortikotropín-dependentného Cushingovho syndrómu
Slovenian	Sintetični dvojnoverižni kratkodelujoči RNA oligonukleotid proti proopiomelanokortinu	Zdravljenje adrenokortin-odvisnega Cushingovega sindroma,
Spanish	ARN corto de interferencia sintético de cadena doble contra proopiomelanocortina	Tratamiento del síndrome de Cushing adrenocorticotropina-dependiente
Swedish	Syntetiskt dubbelsträngat kort interfererande RNA oligonukleotid som ar riktad mot proopiomelanokortin	Behandling av adrenokortikotropinberoende Cushings syndrom
Norwegian	Syntetisk dobbelttrådet kort interfererende RNA oligonukleotid rettet mot proopiomelanocortin	Behandling av adrenokortikotropin-avhengig Cushings syndrom
Icelandic	Nýnyndað tví-þráða stutt hamlandi RNA ólígónúkleótið beint gegn próópíómelanócortíni	Meðferð á adrenócorticótrópín-háðu Cushing heilkenni