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EMA/COMP/391433/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Modified mRNA encoding the UGT1A1 protein for the treatment of Crigler-Najjar syndrome

On 27 June 2016, orphan designation (EU/3/16/1684) was granted by the European Commission to Alexion Europe SAS, France, for modified mRNA encoding the UGT1A1 protein for the treatment of Crigler-Najjar syndrome.

What is Crigler-Najjar syndrome?

Crigler-Najjar syndrome is an inherited disorder in which harmful levels of bilirubin build up in the body. Bilirubin is a waste product of the breakdown of haemoglobin from old or damaged red blood cells.

Normally bilirubin is converted in the liver to a less toxic form called 'conjugated' bilirubin that is removed from the body via the gut. However, patients with Crigler-Najjar syndrome lack the enzyme that converts bilirubin into the less toxic form and as a result it builds up in the liver and then in the blood stream and body tissues where it can cause damage.

Because of the yellow colour of bilirubin, jaundice, which is the yellowing of the skin and eyes, is usually seen within a few days of birth. The most severe complication is kernicterus, where bilirubin damages brain tissue and leads to serious problems with muscle tone, movement, hearing and intellectual ability.

The condition is long-term debilitating and life threatening due to the development of kernicterus.

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

At the time of designation, Crigler-Najjar syndrome affected less than 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 5,000 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).

*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 28), Norway, Iceland and Liechtenstein. This represents a population of 513,700,000 (Eurostat 2016).

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What treatments are available?

At the time of designation, no satisfactory methods of treatment were authorised in the EU for patients with Crigler-Najjar syndrome. Some patients were given treatments such as phototherapy (using light to help break down the bilirubin) and liver transplantation.

How is this medicine expected to work?

Patients with Crigler-Najjar syndrome lack UGT1A1, the enzyme that converts bilirubin to conjugated bilirubin. The medicine consists of genetic material (mRNA) that cells need to produce the missing enzyme. In this medicine, the mRNA is enclosed in microscopic fat particles, which help it to be taken up by liver cells. The mRNA is then released inside the liver cells where it can act as a template for producing UGT1A1. This is expected to increase the conversion of bilirubin to conjugated bilirubin and improve the symptoms of Crigler-Najjar 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 the medicine in experimental models was ongoing.

At the time of submission of the application for orphan designation, no clinical trials with the medicine in patients with Crigler-Najjar syndrome had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for Crigler-Najjar 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 19 May 2016 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:

Contact details of the current sponsor for this orphan designation can be found on EMA website, on the medicine's rare disease designations page.

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	Modified mRNA encoding the UGT1A1 protein	Treatment of Crigler-Najjar syndrome
Bulgarian	Модифицирана мРНК, кодираща протеина UGT1A1	Лечение на синдром на Crigler-Najjar
Croatian	Modificirana mRNK koja kodira protein UGT1A1	Liječenje Crigler-Najjarovog sindroma
Czech	Modifikovaná mRNA kódující protein UGT1A1	Léčba Crigler-Najjarova syndromu
Danish	ModificeretmRNA, som koder for UGT1A1-protein	Behandling af Crigler-Najjar syndrom
Dutch	Gemodificeerd mRNA dat UGT1A1-eiwit codeert	Behandeling van Crigler-Najjar syndroom
Estonian	UGT1A1 valku kodeeriv modifitseeritud mRNA	Crigler-Najjar'i sündroomi ravi
Finnish	Modifioitu mRNA:ta koodaava UGT1A1-proteiini	Crigler-Najjar syndrooman hoito
French	ARNm modifié codant pour la protéine UGT1A1	Traitement du syndrome de Crigler-Najjar
German	Modifizierte mRNA-die für das UGT1A1 Protein kodiert	Behandlung des Crigler-Najjar Syndroms
Greek	Τροποποιημένο mRNA για την κωδικοποίηση της πρωτεΐνης UGT1A1	Θεραπεία του συνδρόμου Crigler-Najjar
Hungarian	Az UGT1A1-proteint kódoló módosított mRNS	Crigler-Najjar szindróma kezelése
Italian	mRNA modificato codificante per la proteina UGT1A1	Trattamento della sindrome di Crigler-Najjar
Latvian	UGT1A1 proteīnu kodējoša modificēta mRNS	Krīglera un Nadžāra sindroma ārstēšana
Lithuanian	Modifikuota mRNR, koduojanti UGT1A1 baltymą	Crigler Nadjjar'o sindromo gydymas
Maltese	mRNA mmodifikat li jikkodifika l-proteina UGT1A1	Kura tas-sindrome ta' Crigler Najjar
Polish	Zmodyfikowane mRNA kodujące białko UGT1A1	Leczenie zespolu Criglera-Najjara
Portuguese	ARNm modificado que codifica a proteína UGT1A1	Tratamento de síndrome de Crigler-Najjar
Romanian	ARNm modificat ce codifică proteina UGT1A1	Tratamentul sindromului Crigler Najjar
Slovak	Modifikovaná mRNA kódujúca proteín UGT1A1	Liečba Criglerovho-Najjarovho syndrómu

[1] At the time of designation

Language	Active ingredient	Indication
Slovenian	Modificirana mRNA, ki kodira beljakovino UGT1A1	Zdravljenje sindroma Crigler-Najjar
Spanish	ARNm modificado que codifica la proteína UGT1A1	Tratamiento del síndrome de Crigler-Najjar
Swedish	Modifierat mRNA som kodar för UGT1A1-protein	Behandling av Crigler-Najjar syndrom
Norwegian	Modifisert mRNA som koder for UGT1A1-protein	Behandling av Crigler Najjar syndrom
Icelandic	Aðlagað mRNA sem kóðar fyrir UGT1A1 próteini	Meðfrð við Crigler-Najjar heilkenni