European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF heterologous human adult liver derived stem cells for the treatment of Crigler-Najjar syndrome

On 29 November 2007, orphan designation (EU/3/07/506) was granted by the European Commission to Prof Etienne Sokal, Belgium, for heterologous human adult liver derived stem cells for the treatment of Crigler-Najjar syndrome.

What is Crigler-Najjar syndrome?
Crigler-Najjar syndrome is an inherited disorder that results in failure of proper bilirubin elimination from the liver via the bile. Bilirubin is a product that results from the breakdown of hemoglobin from old or damaged red blood cells. When bilirubin cannot be excreted from the liver, it accumulates in the body and becomes toxic for the brain and apparent with jaundice (yellowish colour of the skin and the eyes). The condition is chronically debilitating and life-threatening.

What are the methods of treatment available?
Phototherapy is used in these patients. However, the only curative treatment is liver transplantation. Liver transplantation refers to a procedure in which a failed liver is removed from the patient's body and liver tissue from a healthy donor is transplanted into the same location. The procedure is the most common method used to transplant livers. However, liver transplantation is a complex operation, with important surgical risks, and is often associated with significant postoperative mortality. At the time of submission of the application for orphan drug designation, other methods of treatment for Crigler-Najjar syndrome were authorised in the Community.
Heterologous human adult liver derived stem cells might be of potential significant benefit for the treatment of Crigler-Najjar syndrome because they might improve the long-term outcome of the patients. The 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, Crigler-Najjar syndrome was considered to affect about 5,000 persons in the European Union.

How is this medicinal product expected to act?
Liver cells are specialised to perform certain specific functions. Heterologous human adult liver derived stem cells are stem cells isolated from the adult liver itself and they have the capacity to differentiate (to change their characteristics and capacities and acquire new specific functions) into more mature liver cells. The cells will come from a donor, and not the patient (heterologous). It is planned to isolate and treat the cells in such a way that they might be used for infusion to patients

*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 27), Norway, Iceland and Lichtenstein. This represents a population of 498,000,000 (Eurostat 2006). This estimate is based on available information and calculations presented by the sponsor at the time of the application.

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suffering from Crigler-Najjar syndrome. The mechanism of action is not fully understood but it is believed that the heterologous human adult liver derived stem cells will become mature and functional liver cells, giving support to the liver function.

What is the stage of development of this medicinal product?
At the time of submission of the application for orphan designation, the effects of heterologous human adult liver derived stem cells had been evaluated in experimental models.

Heterologous human adult liver derived stem cells were not authorised anywhere in the world for the treatment of Crigler-Najjar syndrome, or designated as an orphan medicinal product elsewhere 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 10 October 2007 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.

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Patients' association(s) contact point(s): Pending

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

Language	Active Ingredient	Indication
English	Heterologous Human Adult Liver Derived Stem Cells	Treatment of Crigler-Najjar syndrome
Bulgarian	Човешки хетероложни стволови клетки, получени от черен дроб на възрастен	Лечение на синдром на Crigler-Najjar
Czech	Heterologní buňky získané z jater dospělého člověka	Léčba Crigler-Najjarova syndromu
Danish	Heterologe humane leverderiverede stamceller fra voksne	Behandling af Crigler-Najjar syndrom
Dutch	Uit adulte lever afgeleide heterologe humane stamcellen	Behandeling van Crigler-Najjar syndroom
Estonian	Heteroloogilised täiskasvanu inimese maksast pärinevad tüvirakud	Crigler-Najjar'i sündroomi ravi
Finnish	heterologisia aikuisen ihmisen maksaperäisiä kantasoluja	Crigler-Najjar syndrooman hoito
French	Cellules souches heterologues extraites de foie adulte humain	Traitement du syndrome de Crigler-Najjar
German	Aus Lebergewebe isolierte heterologe adulte humane Stammzellen	Behandlung des Crigler-Najjar Syndroms
Greek	ΑνΘρώπινα ετερόλογα βλαστικά κύτταρα από ήπαρ ενήλικος	Θεραπεία σύνδρομο Crigler-Najjar
Hungarian	Heterológ human felnőtt máj eredetű őssejt	Crigler-Najjar szindróma kezelése
Italian	cellule staminali eterologhe di fegato umano adulto	Trattamento della sindrome di Crigler-Najjar
Latvian	Heteroloģisku pieaugušā cilvēka aknu cilmes šūnas	Krīglera un Nadžāra sindroma ārstēšana
Lithuanian	Heterologinės suaugusiojo žmogaus kepenų kamieninės ląstelės	Crigler Nadjjar'o sindromo gydymas
Maltese	Ċelloli staminali eteroloġi mnisslin minn fwied adult uman	Kura tas-sindrome ta' Crigler Najjar
Polish	Ludzkie heterologiczne komórki pnia izolowane z wątroby	Leczenie zespolu Criglera-Najjara
Portuguese	Células estaminais humanas de tecido hepático heterologo adulto	Tratamento de síndrome de Crigler-Najjar
Romanian	celule stem heterologe extrase din tesut hepatic uman adult	Tratamentul sindromului Crigler Najjar
Slovak	Heterológne kmeňové bunky získané z pečene dospelého človeka	Liečba Crigler-Najjarovho syndrómu
Slovenian	heterologne jetrne zarodne celice pridobljene iz odraslega človeka	Zdravljenje sindroma Crigler-Najjar
Spanish	Células madre humanas extraídas de tejido hepático heterólogo adulto	Tratamiento del síndrome de Crigler-Najjar

Swedish	heterologa vuxna mänskliga leverderiverade stamceller	Behandling av Crigler-Najjar syndrom
Norwegian	Heterologe humane leverstamceller fra voksen	Behandling av Crigler Najjar syndrom
Icelandic	Manna-lifrarstofnfrumur úr fullorðnum	Meðfrð við Crigler-Najjar heilkenni