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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Heterologous human adult liver-derived stem cells for the treatment of carbamoyl-phosphate synthase-1 deficiency

On 5 March 2012, orphan designation (EU/3/12/971) was granted by the European Commission to Fresenius Medical Care Deutschland GmbH, Germany, for heterologous human adult liver-derived stem cells for the treatment of carbamoyl-phosphate synthase-1 deficiency.

What is carbamoyl-phosphate synthase-1 deficiency?

Carbamoyl-phosphate synthase-1 deficiency is one of the inherited disorders known as 'urea cycle disorders', which cause ammonia to accumulate in the blood. Patients with carbamoyl-phosphate synthase-1 deficiency lack 'carbamoyl-phosphate synthase', one of the liver enzymes that are needed to get rid of excess nitrogen. In the absence of this enzyme, excess nitrogen accumulates in the body in the form of ammonia, which can be toxic at high levels, especially to the brain. Symptoms of the disease usually appear in the first few days of life and include lethargy (lack of energy), vomiting, loss of appetite, seizures (fits) and coma.

Carbamoyl-phosphate synthase-1 deficiency is a long-term debilitating and life-threatening disease that leads to mental retardation and is associated with a high mortality rate.

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

At the time of designation, carbamoyl-phosphate synthase-1 deficiency affected approximately 0.003 in 10,000 people in the European Union (EU)*. This is equivalent to a total of around 150 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 27), Norway, Iceland and Liechtenstein. This represents a population of 506,300,000 (Eurostat 2011).

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What treatments are available?

At the time of designation, sodium phenylbutyrate, sodium phenylacetate and sodium benzoate were authorised in the EU for the treatment of some urea cycle disorders, including carbamoyl-phosphate synthase-1 deficiency. In addition, patients were advised to control their dietary intake of proteins, which are rich in nitrogen, to reduce the amount of ammonia formed in the body. The only cure for the disease was liver transplantation.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with carbamoyl-phosphate synthase-1 deficiency because early studies show that it might improve the treatment of patients by re-establishing a normally functioning urea cycle. This assumption 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 is made up of stem cells derived from the liver of an adult donor ('heterologous'). Stem cells can develop into different types of cell. When implanted into the liver of a patient, it is believed that these heterologous liver-derived stem cells will develop into mature, healthy liver cells that can produce the carbamoyl-phosphate synthase enzyme. The new cells are thereby expected to restore the normal urea cycle and to relieve the symptoms of the disease.

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 heterologous human adult liver-derived stem cells in experimental models was ongoing.

At the time of submission, no clinical trials with the medicine in patients with carbamoyl-phosphate synthase-1 deficiency had been started.

At the time of submission, this medicine was not authorised anywhere in the EU for carbamoyl-phosphate synthase-1 deficiency 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.

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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:

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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 substance	Indication
English	Heterologous human adult liver-derived stem cells	Treatment of carbamoyl-phosphate synthase-1 deficiency
Bulgarian	Хетероложни човешки стволови клетки, получени от черен дроб на възрастен	Лечение на карбамоил-фосфат синтетаза 1 недостатъчност
Czech	Heterologní zralé jaterní lidské kmenové buňky	Léčba deficitu karbamoylfosfát syntetázy-1
Danish	Humane heterologe leverstamceller fra voksne	Behandling af carbamoylfosfat syntetase-1 defekt
Dutch	Uit hepatisch weefsel afgeleide heterologe humaan adulte stamcellen	Behandeling van carbamoylfosfaat synthase-1 deficiëntie
Estonian	Heteroloogilised täiskasvanud inimese maksast pärinevad tüvirakud	Karbamoüülfosfaadi süntetaas-1 puudulikkuse ravi
Finnish	Heterologisia, aikuisen ihmisen maksaperäisiä kantasoluja	Karbamyylifosfaattisyntetaasi-1:n puutoksen hoito
French	Cellules souches hétérologues extraites de foie adulte humain	Traitement du déficit en carbamoyl-phosphate synthétase-1
German	Aus Lebergewebe isolierte, heterologe adulte humane Stammzellen	Behandlung des Carbamoylphosphat-Synthetase-1-Mangels
Greek	Ανθρώπινα ετερόλογα βλαστικά κύτταρα προερχόμενα από ήπαρ ενηλίκου	Θεραπεία της ανεπάρκειας της συνθετάσης 1 του φωσφορικού-καρβαμοϋλίου
Hungarian	Heterológ humán felnőtt máj eredetű őssejt	Carbamoyl-phosphate synthetase-1 hiány kezelése
Italian	Cellule staminali eterologhe di fegato umano adulto	Trattamento del deficit di carbamil-fosfato sintetasi-1
Latvian	Heterologas pieaugušā cilvēka aknu cilmes šūnas	Karbamila-fosfāta sintetāzes-1 trūkuma ārstēšana
Lithuanian	Heterologinės suaugusiojo žmogaus kepenų kamieninės ląstelės	Karbamoilfosfato sintetazės-1 stokos gydymas
Maltese	Ċelloli Staminali Eterologi tal-Fwied ta' Adult Uman	Kura ta’ nuqqas ta’ Carbamoyl-phosphate synthetase-1
Polish	Ludzkie heterologiczne komórki macierzyste izolowane z wątroby osoby dorosłej	Leczenie niedoboru syntetazy karbamoilofosforanowej1
Portuguese	Células Progenitoras Heterólogas Derivadas do Fígado de Humanos Adultos	Tratamento da deficiência da Carbamoil-fosfato sintetase-1
Romanian	Celule stem heterologe extrase din ţesut hepatic uman adult	Tratamentul deficitului de carbamil-fosfat-sintetază-1
Slovak	Heterológne kmeňové bunky získané z	Liečba deficitu karbamoylfosfátsyntetázy-1

[1] At the time of designation

Language	Active substance	Indication
	pečene dospelého človeka	
Slovenian	Heterološke matične celice, pridobljene iz jeter odraslega človeka	Zdravljenje pomanjkanja karbamoil-fosfat sintetaze-1
Spanish	Células madre heterólogas extraídas de tejido hepático humano adulto	Tratamiento de la deficiencia de carbamil-fosfato sintetasa-1
Swedish	Humana heterologa vuxna leverderiverade stamceller	Behandling av brist på karmabylfostatsyntetas-1
Norwegian	Humane heterologe leverstamceller fra voksne	Behandling av mangel på karbamoylfosfat syntetase I
Icelandic	Fullorðinsmanna ósamgena lifrarstofnfrumur	Meðferð á karbamóýl-fosfat sýnthasa-1 skorti