18 January 2011
EMA/COMP/636271/2010
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Human heterologous liver cells (for infusion) for the treatment of carbamoyl-phosphate synthase-1 deficiency

On 17 December 2010, orphan designation (EU/3/10/821) was granted by the European Commission to Cytonet GmbH & Co. KG, Germany, for human heterologous liver cells (for infusion) 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 less than 0.02 in 10,000 people in the European Union (EU)*. This is equivalent to a total of fewer than 1,000 people, and is below the threshold 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 506,500,000 (Eurostat 2010).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

What treatments are available?

At the time of designation, phenylbutyrate was 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 sponsor has provided sufficient information to show that human heterologous liver cells (for infusion) might be of significant benefit for patients with carbamoyl-phosphate synthase-1 deficiency because it works in a different way to existing treatment and early studies indicate that it might improve the treatment of patients with this condition. 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?

Human heterologous liver cells (for infusion) are 'somatic cell therapy products'. These are medicines that contain cells or tissues that have been manipulated to change their biological characteristics so that they can be used to cure, diagnose or prevent a disease.

This medicine is made of liver cells from a donor, which have been manipulated and then frozen for long-term storage. When the medicine is injected repeatedly into the portal vein (the vein leading to the liver) of patients with carbamoyl-phosphate synthase-1 deficiency, some of the liver cells it contains are expected to settle in the recipient's liver and start producing the missing liver enzyme, thus helping to alleviate the symptoms of the disease.

What is the stage of development of this medicine?

The effects of human heterologous liver cells (for infusion) have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with the medicine in patients with urea cycle disorders were ongoing.

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 7 October 2010 recommending the granting of this designation.

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:

Cytonet GmbH & Co. KG
Albert-Ludwig-Grimm Strasse 20
D-69469 Weinheim
Germany
Telephone: +49 62 01 25 98 14
Telefax: +49 62 01 25 98 28
E-mail: info@cytonet.de

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	Human heterologous liver cells (for infusion)	Treatment of carbamoyl-phosphate synthase-1 deficiency
Bulgarian	Човешки хетероложни чернодробни клетки (за инфузия)	Лечение на карбамоил-фосфат синтаза- 1 недостатъчност
Czech	Lidské heterologní jaterní buňky (k infúzi)	Léčba deficitu karbamylfosfátusyntásy-1
Danish	Humane heterologe leverceller (til infusion)	Behandling af carbamylfosfat synthetase 1 mangel
Dutch	Humane heterologe levercellen (voor infusie)	Behandeling van carbamoyl- fosfaat synthase -1 deficiëntie
Estonian	Inimese heteroloogilised maksarakud (infusiooniks)	Karbamoüülfosfaadi süntetaas-1 puudulikkuse ravi
Finnish	Ihmisen heterologiset maksasolut (infuusiota varten)	Karbamyylifosfaattisyntetaasin-1 puutoksen hoito
French	Cellules hépatiques humaines hétérologues (pour perfusion)	Traitement du déficit en carbamoyl phosphate synthetase-1
German	Humane heterologe Leberzellen (zur Infusion)	Behandlung eines chronischen Mangels an Carbamylphosphatsynthetase-1
Greek	Ανθρώπινα ετερόλογα ηπατικά κύτταρα (για έγχυση)	Θεραπεία της ανεπάρκειας συνθετάσης φωσφοκαρβαμιδικού οξέος τύπου 1
Hungarian	Humán heterológ májsejtek (infúzióhoz)	Karbamil-foszfát-szintetáz-1 elégtelenség kezelésére
Italian	Cellule epatiche umane eterologhe (per infusione)	Trattamento della carenza di carbamoilfosfato sintetasi-1
Latvian	Cilvēka ksenogēnās aknu šūnas (infūzijai)	Karbamoilfosfāta sintetēzes -1 deficīta ārstēšana
Lithuanian	Žmonių heterologinės kepenų ląstelės (infuzijai)	Karbamoilfosfato sintetazės-1 stokos gydymas
Maltese	Ċelluli tal-fwied eterologi umani	Kura ta' nuqqas ta' carbamoyl-phosphate synthase-1
Polish	Ludzkie heterologiczne komórki wątroby (do infuzji)	Leczenie niedoboru syntetazy karbamoilofosforanowej I
Portuguese	Células hepáticas humanas heterólogas (para perfusão)	Tratamento da deficiência de carbamil fosfato sintetase-1
Romanian	Hepatocite heterologe umane (pentru perfuzie)	Tratamentul deficienţei de carbamoil-fosfat sintetază-1
Slovak	Ľudské heterológne hepatocyty (pečeňové bunky) (pre infúziu)	Liečba nedostatku karbamoylfosfátsyntetázy-1
Slovenian	Človeške heterologne jetrne celice (za infundiranje)	Zdravljenje pomanjkanja karbamil-fosfat-sintetaze-1
Spanish	Células hepáticas heterólogas humanas (para infusión)	Tratamiento del déficit de carbamoilfosfato sintetasa 1

[1] At the time of designation

Swedish	mänskliga heterologa leverceller (för infusion)	behandling av karbamolylfosfatsyntas I-bristsjukdom
Norwegian	Humane heterologe leverceller (til infusjon)	Behandling av karbamoylfosfatsyntetase-1-mangel
Icelandic	Ósamgena lifrarfrumur úr mönnum (gefið í æð)	Meðferð á karbamóýl-fosfat sýnthasa-1 skorti