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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Human heterologous liver cells (for infusion) for the treatment of citrullinaemia type 1

On 17 December 2010, orphan designation (EU/3/10/818) was granted by the European Commission to Cytonet GmbH & Co. KG, Germany, for human heterologous liver cells (for infusion) for the treatment of citrullinaemia type 1.

What is citrullinaemia type 1?

Citrullinaemia type 1 is one of the inherited disorders known as 'urea cycle disorders', which cause ammonia to accumulate in the blood. Patients with citrullinaemia type 1 lack 'argininosuccinate 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.

Citrullinaemia type 1 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, citrullinaemia type 1 affected less than 0.03 in 10,000 people in the European Union (EU)*. This is equivalent to a total of fewer than 1,500 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).

What treatments are available?

At the time of designation, phenylbutyrate was authorised in the EU for the treatment of some urea cycle disorders, including citrullinaemia type 1. In addition, patients were advised to control their

*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).

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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 citrullinaemia type 1 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 citrullinaemia type 1, 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 citrullinaemia type 1 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:

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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	Human heterologous liver cells (for infusion)	Treatment of citrullinaemia type 1
Bulgarian	Човешки хетероложни чернодробни клетки (за инфузия)	Лечение на цитрилинемия тип 1
Czech	Lidské heterologní jaterní buňky (k infúzi)	Léčba citrulinémie typu 1
Danish	Humane heterologe leverceller (til infusion)	Behandling af citrullinæmi type 1
Dutch	Humane heterologe levercellen (voor infusie)	Behandeling van citrullinemia type1
Estonian	Inimese heteroloogilised maksarakud (infusiooniks)	1.tüüpi tsitrullineemia ravi
Finnish	Ihmisen heterologiset maksasolut (infuusiota varten)	1-Tyypin sitrullinemian hoito
French	Cellules hépatiques humaines hétérologues (pour perfusion)	Traitement de la citrullinémie de type 1
German	Humane heterologe Leberzellen (zur Infusion)	Behandlung einer Citrullinämie Typ 1
Greek	Ανθρώπινα ετερόλογα ηπατικά κύτταρα (για έγχυση)	Θεραπεία της κιτρουλιναιμίας τύπου 1.
Hungarian	Humán heterológ májsejtek (infúzióhoz)	1-es típusú citrullinaemia kezelésére
Italian	Cellule epatiche umane eterologhe (per infusione)	Trattamento della citrullinemia di tipo 1
Latvian	Cilvēka ksenogēnās aknu šūnas (infūzijai)	1. tipa citrulinēmijas ārstēšana
Lithuanian	Žmonių heterologinės kepenų ląstelės (infuzijai)	Citrulinemijos 1 tipo gydymas
Maltese	Ċelluli tal-fwied eterologi umani	Kura taċ-ċitrullinemija tat-tip 1
Polish	Ludzkie heterologiczne komórki wątroby (do infuzji)	Leczenie cytrulinemii typu 1
Portuguese	Células hepáticas humanas heterólogas (para perfusão)	Tratamento da citrulimémia Tipo 1
Romanian	Hepatocite heterologe umane (pentru perfuzie)	Tratamentul citrulinemiei de tip 1
Slovak	Ľudské heterológne hepatocyty (pečeňové bunky) (pre infúziu)	Liečba citrulinémie 1. typu
Slovenian	Človeške heterologne jetrne celice (za infundiranje)	Zdravljenje citrulinemije tipa 1
Spanish	Células hepáticas heterólogas humanas (para infusión)	Tratamitento de la citrulinemia de tipo 1
Swedish	mänskliga heterologa leverceller (för infusion)	behandling av citrullinemi typ 1
Norwegian	Humane heterologe leverceller (til infusjon)	Behandling av citrullinemi type 1
Icelandic	Ósamgena lifrarfrumur úr mönnum (gefið í æð)	Meðferð á cítrúllíndreyra gerð 1

[1] At the time of designation