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 human heterologous liver cells (for infusion) for the treatment of ornithine-transcarbamylase deficiency

On 14 September 2007, orphan designation (EU/3/07/470) was granted by the European Commission to Cytonet GmbH & Co. KG, Germany, for human heterologous liver cells (for infusion) for the treatment of ornithine-transcarbamylase deficiency.

What is ornithine-transcarbamylase deficiency?

Ornithine-transcarbamylase deficiency is congenital error of metabolism that causes hyperammonaemia (abnormally high levels of ammonia in the blood). The disease is usually much milder in females than in males, because it is caused by a damaged gene on the X chromosome. As females have two X chromosomes, the normal gene on the other chromosome usually compensates the damage. Males however have only one X chromosome, so if the gene is damaged there is no compensation. As ammonia cannot be eliminated easily, it accumulates in the body. Ammonia is a toxic compound for the brain and leads to neurological damage depending on the duration and degree of hyperammonaemia. The condition is chronically debilitating and life-threatening.

What are the methods of treatment available?

Liver transplantation may be used in these patients. 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 of acute liver failure were authorised in the Community.

Human heterologous liver cells (for infusion) might be of potential significant benefit for the treatment of ornithine-transcarbamylase deficiency 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, ornithine-transcarbamylase deficiency was considered to affect less than 5,000 persons in the European Union.

*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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How is this medicinal product expected to act?
Liver cells differ from other cells in the sense that they are specialised to perform certain specific functions. The heterologous cells come from donors different to the person who will receive the cells. It is planned to isolate and treat these liver cells in such a way that they become able to be used for infusion into patients suffering from ornithine-transcarbamylase deficiency. The mechanism of action is not clear; it is believed that the human heterologous liver cells (for infusion) when administered to the patient, will give support to the liver functions.

What is the stage of development of this medicinal product?
At the time of submission of the application for orphan designation, the evaluation of the effects of human heterologous liver cells (for infusion) in experimental models was ongoing; clinical trials in patients with acute liver failure were also ongoing.

Human heterologous liver cells (for infusion) were not authorised anywhere in the world for acute liver failure, or designated as 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 25 July 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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Translations of the active ingredient and indication in all EU languages and Norwegian and Icelandic

Language	Active Ingredient	Indication
English	Human heterologous liver cells (for infusion)	Treatment of ornithine-transcarbamylase deficiency
Bulgarian	Човешки хетероложни чернодробни клетки (за инфузия)	Лечение на дефицит на орнитин транскарбамилаза
Czech	Lidské heterologní jaterní buňky (k infúzi)	Léčba nedostatku transkarbamylázy ornithinu
Danish	Humane heterologe leverceller (til infusion)	Behandling af ornithin transcarbamylase defekt
Dutch	Humane heterologe levercellen (voor infusie)	Behandeling van ornithine transcarbamylase deficiëntie
Estonian	Inimese heteroloogilised maksarakud (infusiooniks)	Ornitiintranskarbamülaasi puudulikkuse ravi
Finnish	Ihmisen heterologiset maksasolut (infuusiota varten)	Ornitiinitranskarbamylaasin puutoksen hoito
French	Cellules hépatiques humaines hétérologues (pour perfusion)	Traitement du déficit en ornithine transcarbamylase
German	Humane heterologe Leberzellen (zur Infusion)	Behandlung des Ornithintranscarbamylase-Mangels
Greek	Ανθρώπινα ετερόλογα ηπατικά κύτταρα (για έγχυση)	Αγωγή για την έλλειψη της τρανσκαρβαμυλάσης της ορνιθίνης
Hungarian	Humán heterológ májsejtek (infúzióhoz)	Ornitin transzkarbamiláz hiány kezelése
Italian	Cellule epatiche umane eterologhe (per infusione)	Trattamento del deficit di ornitina-transcarbamilasi
Latvian	Cilvēka ksenogēnās aknu šūnas (infūzijai)	Ornitīna transkarbamilāzes nepietiekamības ārstēšana
Lithuanian	Žmonių heterologinės kepenų ląstelės (infuzijai)	Ornitintranskarbamilazės stokos gydymas
Maltese	Ċelluli tal-fwied eterologi umani	Kura ta' defiċjenza ta’ l-Ornithine Transcarbamylase
Polish	Ludzkie heterologiczne komórki wątroby (do infuzji)	Leczenie pacjentów z niedoborem transkarbamylazy ornitynowej
Portuguese	Células hepáticas humanas heterólogas (para perfusão)	Tratamento da deficiência de ornitina-transcarbamilase
Romanian	Hepatocite heterologe umane (pentru perfuzie)	Tratamentul deficitului de ornitin-transcarbamilază
Slovak	Ľudské heterológne hepatocyty (pečeňové bunky) (pre infúziu)	Liečba nedostatku transkarbamylázy ornitínu
Slovenian	Človeške heterologne jetrne celice (za infundiranje)	Zdravljenje pomanjkanja ornitin-transkarbamilaze
Spanish	Células hepáticas heterólogas humanas (para infusión)	Tratamiento de la deficiencia de ornitina transcarbamilasa
Swedish	mänskliga heterologa leverceller (för infusion)	Behandling av brist på ornitintranskarbamylas

Norwegian	Humane heterologe leverceller (til infusjon)	Behandling av ornitintranskarbamylase-mangel
Icelandic	Ósamgena lifrarfrumur úr mönnum (gefið í æð)	Meðferð við skorti á ornitín transkarbamýlasa