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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Heterologous human adult liver-derived progenitor cells for the treatment of N-acetylglutamate synthetase (NAGS) deficiency

On 17 July 2013, orphan designation (EU/3/13/1165) was granted by the European Commission to Promethera Biosciences, Belgium, for heterologous human adult liver-derived progenitor cells for the treatment of N-acetylglutamate synthetase (NAGS) deficiency.

What is N-acetylglutamate synthetase (NAGS) deficiency?

N-acetylglutamate synthetase (NAGS) deficiency is one of the inherited disorders known as 'urea cycle disorders', which cause ammonia to accumulate in the blood. Patients with this disorder lack 'N-acetylglutamate synthetase', one of the liver enzymes that are needed to get rid of excess nitrogen. In the absence of this liver 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.

NAGS 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, NAGS deficiency affected approximately 0.01 in 10,000 people in the European Union (EU). This was equivalent to a total of around 500 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).

What treatments are available?

At the time of designation, carglumic acid was authorised in the EU for the treatment of NAGS deficiency. In addition, patients were advised to control their dietary intake of proteins, which are rich

[*]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 509,000,000 (Eurostat 2013).

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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 heterologous human adult liver-derived progenitor cells might be of significant benefit for patients with NAGS deficiency because early studies in experimental models show that it might lead to healthy liver cells that can produce the N-acetylglutamate synthetase enzyme, thereby improving 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?

This medicine is an advanced therapy medicine that belongs to the group called '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. The medicine is made up of progenitor (immature) cells derived from the liver of an adult donor ('heterologous'). When implanted into the liver of a patient, it is believed that these heterologous liver-derived progenitor cells will develop into mature, healthy liver cells that can produce the N-acetylglutamate synthetase enzyme. The new cells are thereby expected to reduce the accumulation of ammonia and to relieve the symptoms of the disease.

What is the stage of development of this medicine?

The effects of heterologous human adult liver-derived progenitor cells 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, the medicine was not authorised anywhere in the EU for NAGS deficiency. Orphan designation of the medicine had been granted in the United States for urea cycle disorders.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 13 June 2013 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 ingredient	Indication
English	Heterologous human adult liver-derived progenitor cells	Treatment of N-acetylglutamate synthetase (NAGS) deficiency
Bulgarian	Хетероложни човешки прогенитorни клетки, получени от черен дроб на възрастен	Лечение на N-ацетилглутамат синтетазна недостатъчност
Czech	Heterologní progenitorové buňky získané z jater dospělého člověka	Léčba deficitu N-acetylglutamát-syntetázy
Croatian	Heterologne progenitorske stanice izolirane iz jetre odraslog čovjeka	Liječenje nedostatka N-acetil glutamat sintetaze
Danish	Heterologe humane leverderiverede progenitorceller fra voksne	Behandling af N-acetylglutamat syntetase mangel (NAGS)
Dutch	Uit de adulte lever afgeleide heterologe humane progenitorcellen	Behandeling van N-acetylglutamaat-synthetase (NAGS) deficiëntie
Estonian	Heteroloogilised täiskasvanud inimese maksast pärinevad eellasrakud	N-atsetüülglutamaadi süntetaasi vaeguse (NAGS) ravi
Finnish	Heterologiset aikuisen ihmisen maksaperäiset progenitorisolut	N-asetyyliglutamaatti syntetaasin (NAGS) puutostilan hoito
French	Cellules progénitrices hétérologues dérivées du foie adulte humain	Traitement du déficit en N-acétyl-glutamate synthétase (NAGS)
German	Aus der adulten Leber abgeleitete heterologe Vorläuferzellen	Behandlung des N-Acetylglutamat-Synthetase-Mangels (NAGS)
Greek	Ανθρώπινα ετερόλογα προγονικά κύτταρα προερχόμενα από ήπαρ ενηλίκου	Θεραπεία της ανεπάρκειας N-ακετυλογλουκαματικής συνθετάσης (NAGS)
Hungarian	Heterológ humán felnőttek májából származó progenitor sejtek	N-acetilglutamát-szintetáz (NAGS) elégtelenség kezelése
Italian	Cellule progenitrici eterologhe di fegato umano adulto	Trattamento della deficienza di N-acetilglutamato sintetasi (NAGS)
Latvian	Heterologas pieauguša cilvēka aknu priekšgājēju šūnas	N-acetilglutamāta sintāzes deficīta ārstēšana
Lithuanian	Heterologinės pirminės ląstelės, išskirtos iš suaugusio žmogaus kepenų	N-acetilglutamato sintetazės trūkumo gydymas
Maltese	Ċelloli proġenituri eteroloġi mnisslin minn fwied adult uman	Kura ta' nuqqas ta' N-acetylglutamate synthetase (NAGS)
Polish	Ludzkie heterologiczne komórki progenitorowe izolowane z wątroby osoby dorosłej	Leczenie niedoboru syntetazy N-acetyloglutaminianowej
Portuguese	Células progenitoras heterólogas derivadas do fígado de adultos humanos	Tratamento da deficiência de N-acetilglutamato sintetase (NAGS)
Romanian	Celule progenitoare heterologe umane derivate din celule hepatice adulte	Tratamentul deficienţei de N-acetilglutamat sintetază

[1] At the time of designation

Language	Active ingredient	Indication
Slovak	Heterológne progenitorové bunky derivované z pečene dospelého človeka	Liečba deficitu N-acetylglutamátsyntetázy
Slovenian	Heterologne progenitorne celice pridobljene iz jeter odraslih oseb	Zdravljenje pomanjkanja encima N-acetilglutamat- sintetaze (NAGS)
Spanish	Células progenitoras heterólogas extraídas de hígado humano adulto	Tratamiento de déficit de N-acetilglutamato sintetasa (NAGS)
Swedish	Humana heterologa leverderiverade progenitorceller från vuxna	Behandling av N-acetylglutamatsyntetas (NAGS) brist
Norwegian	Heterologe leverderiverte progenitorceller fra voksne	Behandling av N-acetylglutamatsyntetase-mangel
Icelandic	Ósamgena lifrarforstigsfrumur úr fullorðnum	Meðferð við skorti á N-asetýlglútamatsýntetasa