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EMA/683954/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Sodium benzoate for the treatment of N-acetylglutamate synthase deficiency

On 18 November 2016, orphan designation (EU/3/16/1788) was granted by the European Commission to Lucane Pharma SA, France, for sodium benzoate for the treatment of N-acetylglutamate synthase deficiency.

What is N-acetylglutamate synthase deficiency?

N-acetylglutamate synthase (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 NAGS, one of the liver enzymes 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 harmful 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 disability 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 less than 0.01 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 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, Carbaglu (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 in nitrogen, to reduce the amount of ammonia formed in the body.

[*]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 28), Norway, Iceland and Liechtenstein. This represents a population of 513,700,000 (Eurostat 2016).

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The sponsor has provided sufficient information to show that sodium benzoate might be of significant benefit for patients with NAGS deficiency because this medicine could be used to treat 'breakthrough hyperammonaemia', when ammonia levels rise suddenly despite ongoing treatment. 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?

Sodium benzoate has been used as an unlicensed treatment for hyperammonaemia.

It works by combining with the amino acid glycine, which contains nitrogen, to form a substance that can be removed from the body by the kidneys. This allows the levels of nitrogen in the body to decrease, reducing the amount of ammonia produced and therefore the damage to the brain and other organs.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, no clinical trials with sodium benzoate in patients with NAGS deficiency had been started. The sponsor presented data from the published literature on the use of sodium benzoate in urea cycle disorders.

At the time of submission, sodium benzoate was not authorised anywhere in the EU for NAGS 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 6 October 216 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:

Contact details of the current sponsor for this orphan designation can be found on EMA website, on the medicine's rare disease designations page.

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	Sodium benzoate	Treatment of N-acetylglutamate synthetase deficiency
Bulgarian	Натриев бензоат	Лечение на N-ацетилглутамат синтетазна недостатъчност
Croatian	Natrijev benzoat	Liječenje nedostatka N-acetil glutamat sintetaze
Czech	Benzoát sodný	Léčba deficitu N-acetylglutamát-syntetázy
Danish	Natriumbenzoat	Behandling af N-acetylglutamat syntetase mangel
Dutch	Natriumbenzoaat	Behandeling van N-acetylglutamaat-synthetase deficiëntie
Estonian	Naatriumbensoaat	N-atsetüülglutamaadi süntetaasi vaeguse ravi
Finnish	Natriumbentsoaatti	N-asetyyliglutamaatti syntetaasin puutostilan hoito
French	Benzoate de sodium	Traitement du déficit en N-acétyl-glutamate synthétase
German	Natriumbenzoat	Behandlung des N-Acetylglutamat-Synthetase-Mangels
Greek	Βενζοϊκό νάτριο	Θεραπεία της ανεπάρκειας N-ακετυλογλουταματικής συνθετάσης
Hungarian	Nátrium benzoát	N-acetilglutamát-szintetáz elégtelenség kezelése
Italian	Benzoato di sodio	Trattamento della deficienza di N-acetilglutamato sintetasi
Latvian	Nātrija benzoāts	N-acetilglutamāta sintāzes deficīta ārstēšana
Lithuanian	Natrio benzoatas	N-acetilglutamato sintetazės trūkumo gydymas
Maltese	Sodium benzoate	Kura ta' nuqqas ta' N-acetylglutamate synthetase
Polish	Benzoesan sodu	Leczenie niedoboru syntetazy N-acetyloglutaminianowej
Portuguese	Benzoato de sódio	Tratamento da deficiência de N-acetilglutamato sintetase
Romanian	Benzoat de sodiu	Tratamentul deficienţei de N-acetilglutamat sintetază
Slovak	Benzoan sodný	Liečba deficitu N-acetylglutamátsyntetázy
Slovenian	Natrijev benzoat	Zdravljenje pomanjkanja encima N-acetilglutamat- sintetaze
Spanish	Benzoato de sodio	Tratamiento de déficit de N-acetilglutamato sintetasa
Swedish	Natriumbensoat	Behandling av N-acetylglutamatsyntetas brist
Norwegian	Natriumbenzoat	Behandling av N-acetylglutamatsyntetase-mangel
Icelandic	Natríumbenzóat	Meðferð við skorti á N-asetýlglútamatsýntetasa

[1] At the time of designation