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EMA/COMP/449116/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Sodium benzoate for the treatment of carbamoyl-phosphate synthase-1 deficiency

On 14 July 2016, orphan designation (EU/3/16/1706) was granted by the European Commission to Lucane Pharma SA, France, for sodium benzoate 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-1, 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, often leading to death. However, some affected individuals may reach adulthood prior to diagnosis.

Carbamoyl-phosphate synthase-1 deficiency is a long-term debilitating and life-threatening disease that leads to altered brain function 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 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 5,000 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).

*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).

What treatments are available?

At the time of designation, sodium phenylbutyrate (Ammonaps, Pheburane) and glycerol phenylbutyrate (Ravicti) were 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. Liver transplantation was used to manage the condition in some people.

The sponsor has provided sufficient information to show that sodium benzoate might be of significant benefit for patients with carbamoyl-phosphate synthase-1 deficiency because its use together with currently authorised treatments may lead to improved effects. 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 (high levels of ammonia in the blood).

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 carbamoyl-phosphate synthase-1 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 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 16 June 2016 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:

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 languages¹, Norwegian and Icelandic

Language	Active ingredient	Indication
English	Sodium benzoate	Treatment of carbamoyl-phosphate synthase-1 deficiency
Bulgarian	Натриев бензоат	Лечение на карбамоил-фосфат синтаза-1 недостатъчност
Croatian	Natrijev benzoat	Liječenje nedostatka karbamoil fosfat sintetaze 1
Czech	Benzoát sodný	Léčba deficitu karbamylfosfátusyntázy-1
Danish	Natriumbenzoat	Behandling af carbamylfosfat synthetase 1 mangel
Dutch	Natriumbenzoat	Behandeling van carbamoyl-fosfaat synthase-1 deficiëntie
Estonian	Naatriumbensoaat	Karbamoüülfosfaadi süntetaas-1 puudulikkuse ravi
Finnish	Natriumbentsoatti	Karbamyylifosfaattisyntetaasi-1 puutoksen hoito
French	Benzoate de sodium	Traitement du déficit en carbamoyl phosphate synthetase-1
German	Natriumbenzoat	Behandlung eines chronischen Mangels an Carbamylphosphatsynthetase-1
Greek	Βενζοϊκό νάτριο	Θεραπεία της ανεπάρκειας συνθετάσης φωσφοκαρβαμιδικού οξέος τύπου 1
Hungarian	Nátrium benzoát	Karbamil-foszfát-szintetáz-1 elégtelenség kezelésére
Italian	Benzoato di sodio	Trattamento della carenza di carbamoilfosfato sintetasi-1
Latvian	Nātrija benzoāts	Karbamoilfosfāta sintetāzes-1 deficīta ārstēšana
Lithuanian	Natrio benzoatas	Karbamoilfosfato sintetazės-1 stokos gydymas
Maltese	Sodium benzoate	Kura ta' nuqqas ta' carbamoyl-phosphate synthase-1
Polish	Benzoesan sodu	Leczenie niedoboru syntetazy karbamoilofosforanowej 1
Portuguese	Benzoato de sódio	Tratamento da deficiência de carbamil fosfato sintetase-1
Romanian	Benzoat de sodiu	Tratamentul deficienței de carbamoil-fosfat sintetază-1
Slovak	Benzoan sodný	Liečba nedostatku karbamoylfosfátsyntetázy-1
Slovenian	Natrijev benzoat	Zdravljenje pomanjkanja karbamil-fosfat-sintetaze-1
Spanish	Benzoato de sodio	Tratamiento del déficit de carbamoilfosfato sintetasa 1
Swedish	Natriumbenzoat	Behandling av karbamolylfosfatsyntas 1-bristsjukdom
Norwegian	Natriumbenzoat	Behandling av karbamoylfosfatsyntetase-1-mangel
Icelandic	Natríumbenzóat	Meðferð á karbamóýl-fosfat sýnthasa-1 skorti

¹ At the time of designation