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Public summary of opinion on orphan designation

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

On 29 May 2019, orphan designation (EU/3/19/2166) was granted by the European Commission to Dipharma B.V., Netherlands, for sodium benzoate, sodium phenylacetate 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 carbamoyl-phosphate synthase-1 deficiency?

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 5,200 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 518,400,000 (Eurostat 2019).

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What treatments are available?

At the time of application for orphan designation, Ravicti (glycerol phenylbutyrate) was authorised in the EU to manage urea cycle disorders, when the diseases cannot be managed by changes in diet alone. Ammonaps and Pheburane (sodium phenylbutyrate) were also authorised to treat patients with urea-cycle disorders.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with carbamoyl-phosphate synthase-1 deficiency. Data from the scientific literature have shown that the medicine can improve patients 'survival when used in emergency situations to treat acute hyperammonaemia (sudden rise of blood ammonia levels), which can occur despite ongoing long-term treatment with the authorised medicines.

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?

The medicine is made up of two substances, sodium phenylbutyrate and sodium benzoate, which work by combining with glycine and glutamine, two amino acids (the building blocks of proteins) which contain nitrogen. The combination products are then removed through the urine. This can lower the amount of nitrogen in the body and so reduce the amount of waste ammonia produced. By reducing the amount of ammonia in the body, the medicine is expected to reduce its harmful effects on the brain.

What is the stage of development of this medicine?

The effects of the medicine 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 carbamoyl-phosphate synthase-1 deficiency had finished.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of carbamoyl-phosphate synthase-1 deficiency.

In the United States, orphan designation of the medicine had been granted for the treatment of acute hyperammonaemia. At the time of submission, the medicine was authorised in this country (under the name Ammonul) for the treatment of acute hyperammonaemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 29 April 2019, 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 languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Sodium benzoate, sodium phenylacetate	Treatment of carbamoyl-phosphate synthase-1 deficiency
Bulgarian	Натриев бензоат, натриев фенилацетат	Лечение на карбамоил-фосфат синтаза-1 недостатъчност
Croatian	Natrijev benzoate, natrijev fenilacetat	Liječenje nedostatka karbamoil fosfat sintetaze 1
Czech	Natrium-benzoát, natrium-fenylacetát	Léčba deficitu karbamylfosfátusyntásy-1
Danish	Natriumbenzoat, natriumphenylacetat	Behandling af carbamylfosfat synthetase 1 mangel
Dutch	Natriumbenzoaat, natriumfenylacetaat	Behandeling van carbamoyl-fosfaat synthase-1 deficiëntie
Estonian	Naatriumbensoaat, naatriumfenüülatsetaat	Karbamoüülfosfaadi süntetaas-1 puudulikkuse ravi
Finnish	Natriumbentsoaatti, natriumfenyyliasetaatti	Karbamyylifosfaattisyntetaasi-1 puutoksen hoito
French	Benzoate de sodium, phénylacétate de sodium	Traitement du déficit en carbamoyl phosphate synthetase-1
German	Natriumbenzoat, natriumphenylacetat	Behandlung eines chronischen Mangels an Carbamylphosphatsynthetase-1
Greek	Βενζοϊκό νάτριο,φαινυλοξικό νάτριο	Θεραπεία της ανεπάρκειας συνθετάσης φωσφοκαρβαμιδικού οξέος τύπου 1
Hungarian	Nátrium-benzoát, natrium fenilacetát	Karbamil-foszfát-szintetáz-1 elégtelenség kezelésére
Italian	Benzoato di sodio, fenilacetato di sodio	Trattamento della carenza di carbamoilfosfato sintetasi-1
Latvian	Nātrija benzoāts/nātrija fenilacetāts	Karbamoilfosfāta sintetāzes-1 deficīta ārstēšana
Lithuanian	Natrio benzoatas, natrio fenilacetatas	Karbamoilfosfato sintetazės-1 stokos gydymas
Maltese	Benżoat tas-sodju, fenilaċetat tas-sodju	Kura ta' nuqqas ta' carbamoyl-phosphate synthase-1
Polish	Benzoesan sodu, octan fenylu sodu	Leczenie niedoboru syntetazy karbamoilofosforanowej 1
Portuguese	Benzoato de sódio, fenilacetato de sódio	Tratamento da deficiência de carbamil fosfato sintetase-1
Romanian	Benzoat de sodiu, fenilacetat de sodiu	Tratamentul deficienţei de carbamoil-fosfat sintetază-1
Slovak	Nátriumbenzoát, fenylacetát sodný	Liečba nedostatku karbamoylfosfátsyntetázy-1

[1] At the time of designation

Language	Active ingredient	Indication
Slovenian	Natrijev benzoate, natrijev fenilacetat	Zdravljenje pomanjkanja karbamil-fosfat-sintetaze-1
Spanish	Benzoate de sodio, fenilacetato de sodio	Tratamiento del déficit de carbamoilfosfato sintetasa 1
Swedish	Natriumbensoat, natriumfenylacetat	Behandling av karbamolylfosfatsyntas 1-bristsjukdom
Norwegian	Natriumbenzoat, natriumfenylacetat	Behandling av karbamoylfosfatsyntetase-1-mangel
Icelandic	Natríumbensóat, natríumfenýlasetat	Meðferð á karbamóýl-fosfat sýnthasa-1 skorti