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Public summary of opinion on orphan designation

Sodium benzoate, sodium phenylacetate for the treatment of hyperargininaemia

On 28 June 2019, orphan designation EU/3/19/2179 was granted by the European Commission to Dipharma B.V., The Netherlands, for sodium benzoate, sodium phenylacetate for the treatment of hyperargininaemia.

What is hyperargininaemia?

Hyperargininaemia is one of the inherited disorders known as 'urea-cycle disorders', which cause ammonia to accumulate in the blood. Patients with hyperargininaemia lack arginase type I, 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 years of life and include developmental delay, stiffness especially in the legs, vomiting and seizures (fits).

Hyperargininaemia is a long-term debilitating and life-threatening disease that leads to learning disabilities and is associated with poor overall survival.

What is the estimated number of patients affected by the condition?

At the time of designation, hyperargininaemia 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, Ravicti (glycerol phenylbutyrate) was authorised in the EU for the treatment of urea cycle disorders including hyperargininaemia. Patients were also 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 518,400,000 (Eurostat 2019).

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The sponsor has provided sufficient information to show that sodium benzoate, sodium phenylacetate might be of significant benefit for patients with hyperargininaemia. 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 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 benzoate and sodium phenylacetate, which work by combining with glycine and glutamine, respectively, two amino acids (the building blocks of proteins) that 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 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 sodium benzoate, sodium phenylacetate have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with sodium benzoate, sodium phenylacetate in patients with hyperargininaemia had finished.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of hyperargininaemia.

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 brand name Ammonul) for the treatment of acute hyperammonaemia and associated encephalopathy (brain disorder) 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 23 May 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.

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 hyperargininaemia
Bulgarian	Натриев бензоат, натриев фенилацетат	Лечение на хипераргининемия
Croatian	Natrijev benzoate, natrijev fenilacetat	Liječenje hiperargininemije
Czech	Natrium-benzoát, natrium-fenylacetát	Léčba hyperargininémie
Danish	Natriumbenzoat, natriumphenylacetat	Behandling af hyperargininæmi
Dutch	Natriumbenzoaat, natriumfenylacetaat	Behandeling van hyperargininemia
Estonian	Naatriumbensoaat, naatriumfenüülatsetaat	Hüperargininеemia ravi
Finnish	Natriumbentsoaatti, natriumfenyyliasetaatti	Hyperargininemian hoito
French	Benzoate de sodium, phénylacétate de sodium	Traitement des hyperargininémies
German	Natriumbenzoat, natriumphenylacetat	Behandlung einer Hyperargininämie
Greek	Βενζοϊκό νάτριο,φαινυλοξικό νάτριο	Θεραπεία της υπεραργινιναιμίας
Hungarian	Nátrium-benzoát, natrium fenilacetát	Hyperargininaemia kezelésére
Italian	Benzoato di sodio, fenilacetato di sodio	Trattamento dell'iperargininemia
Latvian	Nātrija benzoāts/nātrija fenilacetāts	Hiperarginīnēmijas ārstēšana
Lithuanian	Natrio benzoatas, natrio fenilacetatas	Hiperargininemijos gydymas
Maltese	Benżoat tas-sodju, fenilaċetat tas-sodju	Kura ta' l-iperarġininemija
Polish	Benzoesan sodu, octan fenylu sodu	Leczenie hyperargininemii
Portuguese	Benzoato de sódio, fenilacetato de sódio	Tratamento da hiperargininémia
Romanian	Benzoat de sodiu, fenilacetat de sodiu	Tratamentul hiperargininemiei
Slovak	Nátriumbenzoát, fenylacetát sodný	Liečba hyperargininémie
Slovenian	Natrijev benzoate, natrijev fenilacetat	Zdravljenje hiperargininemije
Spanish	Benzoate de sodio, fenilacetato de sodio	Tratamiento de la hiperargininemia
Swedish	Natriumbensoat, natriumfenylacetat	Behandling av hyperargininemi
Norwegian	Natriumbenzoat, natriumfenylacetat	Behandling av hyperargininemi
Icelandic	Natríumbensóat, natríumfenýlasetat	Meðferð á hýperargíníndreyra

[1] At the time of designation