2 August 2019
EMADOC-628903358-941

Public summary of opinion on orphan designation

Sodium benzoate, sodium phenylacetate for the treatment of citrullinaemia type 1

On 29 May 2019, orphan designation (EU/3/19/2165) was granted by the European Commission to Dipharma B.V., the Netherlands, for sodium benzoate, sodium phenylacetate for the treatment of citrullinaemia type 1.

What is citrullinaemia type 1?

Citrullinaemia type 1 is one of the inherited disorders known as 'urea-cycle disorders', which cause ammonia to accumulate in the blood. Patients with citrullinaemia type 1 lack argininosuccinate synthase, 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 can appear in the first few days of life or later in life. Early life symptoms include lethargy (lack of energy), vomiting, loss of appetite, seizures (fits) and coma, often leading to death.

Citrullinaemia type 1 is a long-term debilitating and life-threatening disease that leads to altered brain function and is associated with poor overall survival.

What is the estimated number of patients affected by citrullinaemia type 1?

At the time of designation, citrullinaemia type 1 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 518,400,000 (Eurostat 2019).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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 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 citrullinaemia type 1. 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 citrullinaemia type 1 had finished.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of citrullinaemia type 1.

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 citrullinaemia type 1
Bulgarian	Натриев бензоат, натриев фенилацетат	Лечение на цитрилинемия тип 1
Croatian	Natrijev benzoate, natrijev fenilacetat	Liječenje citrulinemije tipa 1
Czech	Natrium-benzoát, natrium-fenylacetát	Léčba citrulinémie typu 1
Danish	Natriumbenzoat, natriumphenylacetat	Behandling af citrullinæmi type 1
Dutch	Natriumbenzoaat, natriumfenylacetaat	Behandeling van citrullinemia type1
Estonian	Naatriumbensoaat, naatriumfenüülatsetaat	1.tüüpi tsitrullineemia ravi
Finnish	Natriumbentsoaatti, natriumfenyyliasetaatti	1-Tyypin sitrullinemian hoito
French	Benzoate de sodium, phénylacétate de sodium	Traitement de la citrullinémie de type 1
German	Natriumbenzoat, natriumphenylacetat	Behandlung einer Citrullinämie Typ 1
Greek	Βενζοϊκό νάτριο,φαινυλοξικό νάτριο	Θεραπεία της κιτρουλιναιμίας τύπου 1.
Hungarian	Nátrium-benzoát, natrium fenilacetát	1-es típusú citrullinaemia kezelésére
Italian	Benzoato di sodio, fenilacetato di sodio	Trattamento della citrullinemia di tipo 1
Latvian	Nātrija benzoāts/nātrija fenilacetāts	1. tipa citrulinēmijas ārstēšana
Lithuanian	Natrio benzoatas, natrio fenilacetatas	Citrulinemijos 1 tipo gydymas
Maltese	Benżoat tas-sodju, fenilaċetat tas-sodju	Kura taċ-ċitrullinemija tat-tip 1
Polish	Benzoesan sodu, octan fenylu sodu	Leczenie cytrulinemii typu 1
Portuguese	Benzoato de sódio, fenilacetato de sódio	Tratamento da citrulimémia Tipo 1
Romanian	Benzoat de sodiu, fenilacetat de sodiu	Tratamentul citrulinemiei de tip 1
Slovak	Nátriumbenzoát, fenylacetát sodný	Liečba citrulinémie 1. typu
Slovenian	Natrijev benzoate, natrijev fenilacetat	Zdravljenje citrulinemije tipa 1
Spanish	Benzoate de sodio, fenilacetato de sodio	Tratamitento de la citrulinemia de tipo 1
Swedish	Natriumbensoat, natriumfenylacetat	Behandling av citrullinemi typ 1
Norwegian	Natriumbenzoat, natriumfenylacetat	Behandling av citrullinemi type 1
Icelandic	Natríumbensóat, natríumfenýlasetat	Meðferð á cítrúllíndreyra gerð 1

[1] At the time of designation