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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Glyceryl tri-(4-phenylbutyrate) for the treatment of argininosuccinic aciduria

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Disclaimer Please note that revisions to the Public Summary of Opinion are purely administrative updates. Therefore, the scientific content of the document reflects the outcome of the Committee for Orphan Medicinal Products (COMP) at the time of designation and is not updated after first publication.	

On 10 June 2010, orphan designation (EU/3/10/736) was granted by the European Commission to Hyperion Therapeutics Limited, United Kingdom, for glyceryl tri-(4-phenylbutyrate) for the treatment of argininosuccinic aciduria.

What is argininosuccinic aciduria?

Argininosuccinic aciduria is one of the inherited disorders known as 'urea cycle disorders', which cause ammonia to accumulate in the blood. Patients with argininosuccinic aciduria lack 'argininosuccinate lyase', one of the liver enzymes that are needed to get rid of excess nitrogen. In the absence of this enzyme, excess nitrogen accumulates in the body in the form of ammonia, which can be toxic 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.

Argininosuccinic aciduria is a long-term debilitating and life-threatening disease that leads to mental retardation and is associated with poor overall survival.

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

At the time of designation, argininosuccinic aciduria affected approximately 0.07 in 10,000 people in the European Union (EU). This was equivalent to a total of around 4,000 people*, and is below the

*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 27), Norway, Iceland and Liechtenstein.
At the time of designation, this represented a population of 506,300,000 (Eurostat 2010).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

threshold 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, no satisfactory methods were authorised in the EU for the treatment of argininosuccinic aciduria. 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.

How is this medicine expected to work?

Glyceryl tri-(4-phenylbutyrate) is a 'prodrug' of phenylbutyrate. It consists of three molecules of phenylbutyrate linked together. After it is swallowed, the medicine is expected to be broken down into phenylbutyrate in the gut. Phenylbutyrate works by being converted into phenylacetate in the body and combining with the amino acid glutamine, 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.

What is the stage of development of this medicine?

The effects of glyceryl tri-(4-phenylbutyrate) have been evaluated in experimental models.

At the time of submission of the application for orphan designation, a study with glyceryl tri-(4-phenylbutyrate) in patients with urea cycle disorders had been completed.

At the time of submission, glyceryl tri-(4-phenylbutyrate) was not authorised anywhere in the EU for argininosuccinic aciduria. Orphan designation of glyceryl tri-(4-phenylbutyrate) had been granted in the United States of America for the maintenance treatment of patients with deficiencies in enzymes of the urea cycle.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 3 February 2010 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:

Hyperion Therapeutics Limited
90 Long Acre, Covent Garden
London WC2E 9RZ
United Kingdom
Tel. +44 650 745 7820
Fax +44 650 745 1021
E-mail: klara.dickinson@hyperiontx.com

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	Glyceryl tri-(4-phenylbutyrate)	Treatment of argininosuccinic aciduria
Bulgarian	Глицерил три-(4-фенилбутират)	Лечение на аргининосукцининова ацидурия
Czech	Glyceryl tri-(4-fenylbutyrát)	Léčba argininosukcinátové acidurie
Danish	Glyceryl tri-(4-fenylbutyrat)	Behandling af argininravsyreuri
Dutch	Glyceryltri-(4-fenylbutyraat)	Behandeling van argininosuccinic aciduria
Estonian	Glütserüül-tri(4-fenüülbutüraat)	Argininosuktsiin-atsiduuria ravi
Finnish	Glyseryyli-tri-(4-fenyylibutyraatti)	Argininosukkinaattiasidurian hoito
French	Glycéryl tri-(4-phénylbutyrate)	Traitement de l'acidurie argininosuccinique
German	Glyceryl-tri-4-phenylbutyrat	Behandlung einer Argininosukzinoazidurie
Greek	4-φαινυλοβουτυρικός τριεστέρας γλυκερίνης	Θεραπεία της αργινοηλεκτρικής οξυουρίας.
Hungarian	Gliceril tri-(4-fenilbutirát)	Argininoszukcinin anuria kezelésére
Italian	Gliceril-tri-(4-fenilbutirrato)	Trattamento dell'aciduria argininosuccinica
Latvian	Gliceril tri-(4-fenilbutirāts)	Arginīna sukcināta acidūrijas ārstēšana
Lithuanian	Gliceril-tri-(4-fenilbutiratas)	Arginino sukcininės acidurijos gydymas
Maltese	Glyceryl tri-(4-phenylbutyrate)	Kura tal-aċidurja arġininosuċċinika
Polish	Tri-(4-fenylomaślan) glicerylu	Leczenie acydurii argininobursztynianowej
Portuguese	Tri-(4-fenilbutirato) de glicerilo	Tratamento da acidúria argininosuccínica
Romanian	Gliceril tri-(4-fenilbutirat)	Tratamentul aciduriei argininosuccinice
Slovak	Glyceryl tri-(4-fenylbutyrát)	Liečba arginínosukcinátovej acidúrie
Slovenian	Gliceril tri-(4-fenilbutirat)	Zdravljenje argininsukcinilne acidurije
Spanish	Gliceril tri-(4-fenilbutirato)	Tratamiento de la aciduria argininsuccínica
Swedish	Glyceryl tri-(4-fenylbutyrat)	behandling av argininbärnstensaciduri
Norwegian	Glyseroltri-(4-fenylbutyrat)	Behandling av argininsuccinaturiravsyreuril
Icelandic	Glýserýl þrí-(4-fenýlbúterat)	Meðferð á arginínósúksíniksýrumigu

[1] At the time of designation