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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Glyceryl tri-(4-phenylbutyrate) for the treatment of citrullinaemia type 1

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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/3/10/735) was granted by the European Commission to Hyperion Therapeutics Limited, United Kingdom, for glyceryl tri-(4-phenylbutyrate) 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 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.

Citrullinaemia type 1 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, citrullinaemia type 1 affected approximately 0.24 in 10,000 people in the European Union (EU). This was equivalent to a total of around 12,000 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

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, phenylbutyrate was authorised in the EU for the treatment of some urea cycle disorders, including citrullinaemia type 1. This medicine was available as tablets and granules. 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.

The sponsor has provided sufficient information to show that glyceryl tri-(4-phenylbutyrate) might be of significant benefit for patients with citrullinaemia type 1 because the medicine would be available as an oil that has almost no taste or smell. This is expected to make the medicine easier for patients to take, because it is more palatable than phenylbutyrate tablets or granules. 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?

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 citrullinaemia type 1. 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 citrullinaemia type 1
Bulgarian	Глицерил три-(4-фенилбутират)	Лечение на цитрилинемия тип 1
Czech	Glyceryl tri-(4-fenylbutyrát)	Léčba citrulinémie typu 1
Danish	Glyceryl tri-(4-fenylbutyrat)	Behandling af citrullinæmi type 1
Dutch	Glyceryltri-(4-fenylbutyraat)	Behandeling van citrullinemia type1
Estonian	Glütserüül-tri(4-fenüülbutüraat)	1.tüüpi tsitrullineemia ravi
Finnish	Glyseryyli-tri-(4-fenyylibutyraatti)	1-Tyypin sitrullinemian hoito
French	Glycéryl tri-(4-phénylbutyrate)	Traitement de la citrullinémie de type 1
German	Glyceryl-tri-4-phenylbutyrat	Behandlung einer Citrullinämie Typ 1
Greek	4-φαινυλοβουτυρικός τριεστέρας γλυκερίνης	Θεραπεία της κιτρουλιναιμίας τύπου 1.
Hungarian	Gliceril tri-(4-fenilbutirát)	1-es típusú citrullinaemia kezelésére
Italian	Gliceril-tri-(4-fenilbutirrato)	Trattamento della citrullinemia di tipo 1
Latvian	Gliceril tri-(4-fenilbutirāts)	1. tipa citrulinēmijas ārstēšana
Lithuanian	Gliceril-tri-(4-fenilbutiratas)	Citrulinemijos 1 tipo gydymas
Maltese	Glyceryl tri-(4-phenylbutyrate)	Kura taċ-ċitrullinemija tat-tip 1
Polish	Tri-(4-fenylomaślan) glicerylu	Leczenie cytrulinemii typu 1
Portuguese	Tri-(4-fenilbutirato) de glicerilo	Tratamento da citrulimémia Tipo 1
Romanian	Gliceril-tri-(4-fenilbutirat)	Tratamentul citrulinemiei de tip 1
Slovak	Glyceryl tri-(4-fenylbutyrát)	Liečba citrulinémie 1. typu
Slovenian	Gliceril tri-(4-fenilbutirat)	Zdravljenje citrulinemije tipa 1
Spanish	Gliceril tri-(4-fenilbutirato)	Tratamitento de la citrulinemia de tipo 1
Swedish	Glyceryl tri-(4-fenylbutyrat)	behandling av citrullinemi typ 1
Norwegian	Glyseroltri-(4-fenylbutyrat)	Behandling av citrullinemi type 1
Icelandic	Glýserýl þrí-(4-fenýlbúterat)	Meðferð á cítrúllíndreyra gerð 1

[1] At the time of designation