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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Glyceryl tri-(4-phenylbutyrate) for the treatment of ornithine carbamoyltransferase deficiency

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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/3/10/734) was granted by the European Commission to Hyperion Therapeutics Limited, United Kingdom, for glyceryl tri-(4-phenylbutyrate) for the treatment of ornithine carbamoyltransferase deficiency.

What is ornithine carbamoyltransferase deficiency?

Ornithine carbamoyltransferase deficiency is one of the inherited disorders known as 'urea cycle disorders', which cause ammonia to accumulate in the blood. Patients with ornithine carbamoyltransferase deficiency lack 'ornithine carbamoyltransferase', 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.

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

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

At the time of designation, ornithine carbamoyltransferase deficiency affected approximately 0.14 in 10,000 people in the European Union (EU). This was equivalent to a total of around 7,000 people[*], and is below the 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 ornithine carbamoyltransferase deficiency. 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 ornithine carbamoyltransferase deficiency 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 ornithine carbamoyltransferase deficiency. 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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[*]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).

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:

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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 ornithine carbamoyltransferase deficiency
Bulgarian	Глицерил три-(4-фенилбутират)	Лечение на орнитин карбомоилтрансферазна недостатъчност
Czech	Glyceryl tri-(4-fenylbutyrát)	Léčba deficitu ornitinu transkarbamylázy
Danish	Glyceryl tri-(4-fenylbutyrat)	Behandling af ornitincarbamyltransferase mangel
Dutch	Glyceryltri-(4-fenylbutyraat)	Behandeling van carbamoyltransferase deficiëntie
Estonian	Glütserüül-tri(4-fenüülbutüraat)	Ornitiini karbamoüültransferraasi puudulikkuse ravi
Finnish	Glyseryyli-tri-(4-fenyylibutyraatti)	Ornitiinitranskarbamylaasin puutoksen hoito
French	Glycéryl tri-(4-phénylbutyrate)	Traitement du deficit en ornithine transcarbamoyl transférase
German	Glyceryl-tri-4-phenylbutyrat	Behandlung eines chronischen Mangels an Ornithintranscarbamylase
Greek	4-φαινυλοβουτυρικός τριεστέρας γλυκερίνης	Θεραπεία της ανεπάρκειας της τρανσκαρβαμυλάσης της ορνιθίνης
Hungarian	Gliceril tri-(4-fenilbutirát)	Ornitin-karbamoyltranszferáz elégtelenség kezelésére
Italian	Gliceril-tri-(4-fenilbutirrato)	Trattamento della carenza di ornitina transcarbamilasi
Latvian	Gliceril tri-(4-fenilbutirāts)	Ornitīna transkarbamilāzes deficīta ārstēšana
Lithuanian	Gliceril-tri-(4-fenilbutiratas)	Ornitino transkarbamoilazės stokos gydymas
Maltese	Glyceryl tri-(4-phenylbutyrate)	Kura ta' nuqqas ta' ornithine carbamoyltransferase
Polish	Tri-(4-fenylomaślan) glicerylu	Leczenie niedoboru carbamoilotransferazy ornitynowej
Portuguese	Tri-(4-fenilbutirato) de glicerilo	Tratamento da deficiência de ornitina transcarbamilase
Romanian	Gliceril-tri-(4-fenilbutirat)	Tratamentul deficienţei de ornitincarbamoil transferază
Slovak	Glyceryl tri-(4-fenylbutyrát)	Liečba nedostatku ornitínkarbamoyltransferázy
Slovenian	Gliceril tri-(4-fenilbutirat)	Zdravljenje pomanjkanja ornitin-transkarbamilaze
Spanish	Gliceril tri-(4-fenilbutirato)	Tratamiento del déficit de ornitina transcarbamilasa
Swedish	Glyceryl tri-(4-fenylbutyrat)	Behandling ornitinkarbamoyltransferasbristsjukdom
Norwegian	Glyseroltri-(4-fenylbutyrat)	Behandling av ornitinkarbamoyltransferase-mangel
Icelandic	Glýserýl þrí-(4-fenýlbúterat)	Meðferð á ornithín transkarbmóýl transferasa skorti

[1] At the time of designation