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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

N-carbamyl-l-glutamic acid for the treatment of n-acetylglutamate synthetase (NAGS) deficiency

First publication	3 March 2009
Rev.1: administrative update	3 May 2011
Rev.2: withdrawal from the Community Register	3 October 2013
Rev.3: administrative update	22 July 2014

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.

Please note that this orphan designation was withdrawn from the Community Register of designated orphan medicinal products in January 2013 at the end of the period of market exclusivity.

On 18 October 2000, orphan designation (EU/3/00/007) was granted by the European Commission to Orphan Europe SARL, France, for n-carbamyl-l-glutamic acid for the treatment of n-acetylglutamate synthetase (NAGS) deficiency.

What is n-acetylglutamate synthetase (NAGS) deficiency?

Patients with n-acetylglutamate synthetase (NAGS) deficiency lack a vital enzyme called N-acetylglutamate synthetase. N-acetylglutamate synthetase is a protein that catalyzes (enzyme) a chemical reaction that produces a compound called n-acetylglutamate. This is needed in a process known as urea cycle, which clears harmful ammonia substances from the body by transforming them into urea, which can easily be excreted in urine. Patients affected by NAGS deficiency have a defect in the gene that regulates the production of NAGS leading to a less active or less abundant enzyme in the body. As a result ammonia accumulates in these patients. The disease is chronically debilitating and has acute periods of hyperammonaemia (too much ammonia in the blood). Symptoms usually have an

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early onset in childhood and include cerebral oedema (swelling around the brain), seizures and coma. N-acetylglutamate deficiency is life-threatening.

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

At the time of designation, n-acetylglutamate deficiency affected approximately 0.00125 in 10,000 in 10,000 people in the European Union (EU). This was equivalent to a total of around 50 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 submission of application for orphan drug designation, there were no satisfactory treatments authorised in the Community for the treatment of n-acetylglutamate deficiency.

How is this medicine expected to work?

N-carbamyl-l-glutamic acid is structurally similar to n-acetylglutamate, the compound that is produced by NAGS and is missing from patients with the condition. The product is expected to replace the missing compound in patients' body, preventing the accumulation of ammonia and decreasing the symptoms of the disease.

What is the stage of development of this medicine?

The effects of n-carbamyl-l-glutamic acid were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with n-acetylglutamate synthetase deficiency were ongoing.

N-carbamyl-l-glutamic acid was not authorised anywhere worldwide for the treatment of n-acetylglutamate deficiency, at the time of submission. Orphan designation of n-carbamyl-l-glutamic acid was granted in the United States for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 13 September 2000 recommending the granting of this designation.

Update: N-carbamyl-l-glutamic acid (Carbaglu) has been authorised in the EU since 28 January 2003 for treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency.

More information on Carbaglu can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

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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.
At the time of designation, this represented a population of 375,500,000 (Eurostat 2000)

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	N-carbamyl-L-glutamic acid	treatment of N-acetylglutamate synthetase (NAGS) deficiency
Danish	N-carbamyl-L-glutaminsyre	Behandling af N-acetylglutamat syntetase mangel (NAGS)
Dutch	N-carbamyl-L-glutaminezuur	Behandeling van N-acetylglutamaat-synthetase (NAGS) deficiëntie
Finnish	N-karbamyyli-L-glutaamihappo	N-asetyyliglutamaatti syntetaasin (NAGS) puutostilan hoito
French	Acide N-carbamyl-L-glutamique	Traitement du déficit en N-acétyl-glutamate synthétase (NAGS)
German	N-Carbamyl-L-Glutaminsäure	Behandlung des N-Acetylglutamat-Synthetase-Mangels (NAGS)
Greek	Ν-καρβαμυλικό-L-γλουταμινικό οξύ	Θεραπεία της ανεπάρκειας Ν-ακετυλογλουκαματικής συνθετάσης (NAGS)
Italian	Acido N-carbamil-L-glutamico	Trattamento della deficienza di N-acetilglutamato sintetasi (NAGS)
Portuguese	Ácido N-carbamil-L-glutâmico	Tratamento da deficiência de N-acetilglutamato sintetase (NAGS)
Spanish	Ácido N-carbamil-L-glutámico	Tratamiento de déficit de N-acetilglutamato sintetasa (NAGS)
Swedish	N-karbamyl-L-glutaminsyra	Behandling av N-acetylglutamatsyntetas (NAGS) brist.

[1] At the time of designation