European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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Please note that this product was withdrawn from the Community Register of Orphan Medicinal Products in September 2008 on request of the sponsor.

Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH for the treatment of myasthenia gravis

On 28 August 2006, orphan designation (EU/3/06/398) was granted by the European Commission to Debioclinic SA, France, for H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH for the treatment of myasthenia gravis.

What is myasthenia gravis?

Myasthenia gravis is caused by the immune system (the body's natural defence system) producing abnormal antibodies (proteins of the immune system that can recognise and bind to specific structures). These antibodies bind to, link and block specific proteins called acetylcholine receptors on the surface of muscle cells. These receptors are needed for the nervous system to be able to control motion, which it does by releasing the signalling molecule acetylcholine. When acetylcholine binds to its receptor it causes the muscle to contract. Myasthenia gravis is characterized by painless muscle weakness. The symptoms typically worsen towards the end of the day and after exercise. When the diaphragm, the muscle that assists breathing, becomes weak, myasthenic crisis can occur and emergency hospitalisation is required. Myasthenia gravis is a so-called autoimmune disease. Myasthenia gravis is chronically debilitating and life-threatening.

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

At the time of designation myasthenia gravis affected less than 2 in 10,000 people in the European Union (EU) [*]. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP). This is below the threshold for orphan designation which is 5 in 10,000. This is equivalent to a total of around 92,000 people.

What treatments are available?

Acetylcholine is broken down in the body by enzymes (proteins that can trigger chemical reactions) called cholinesterases. This action can be blocked by so-called anticholinesterase therapies. This type of medicine can control myasthenia in some patients but others need additional treatment. Surgical removal of an organ of the immune system, the thymus gland (thymectomy) is performed in some patients. Medicines that weaken the immune system are often used in patients with disabling weakness, especially those who cannot have, or fail to respond to thymectomy. When rapid

[*]Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union (EU 25), Norway, Iceland and Liechtenstein. This represents a population of 459,700,000 (Eurostat 2004).

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improvement is needed, for example in case of severe weakness causing breathing or swallowing problems, patients can undergo plasma exchange, which removes antibodies from the blood. Another option is an infusion of intravenous immunoglobulin (a mix of antibodies). Satisfactory argumentation has been submitted by the sponsor to justify the assumption that H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH might be of potential significant benefit for the treatment of myasthenia gravis, mainly due to its new mechanism of action possibly leading to improved treatment of myasthenia gravis. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

How is this medicine expected to work?
Auto-immune disease is a disease which is caused by the body own's defence system attacking normal tissue. In myasthenia gravis, the immune system attacks acetylcholine receptors on the surface of muscle cells so that they can not work properly. This medicinal product is a short protein (peptide) that works on the immune system. Although the way it works is not fully known, it is thought to reduce the activity of the immune system and thus improve the muscle function and decrease the symptoms in myasthenia gravis patients.

What is the stage of development of this medicine?
The evaluation of the effects of the medicinal product in experimental models is ongoing.
At the time of submission of the application for orphan designation, no clinical trials in patients with myasthenia gravis were initiated.

H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH was not authorised anywhere worldwide for the treatment of myasthenia gravis, nor designated as orphan medicinal product elsewhere for this condition, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 12 July 2006 a positive opinion recommending the grant of the above-mentioned 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 Community) 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.

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Translations of the active ingredient and indication in all EU languages and Norwegian and Icelandic

Language	Active Ingredient	Indication
English	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Treatment of myasthenia gravis
Czech	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Léčba myasthenie gravis
Danish	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Behandling af myasthenia gravis
Dutch	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Behandeling van myasthenia gravis
Estonian	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Myasthenia Gravise ravi
Finnish	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Myasthenia graviksen hoito
French	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Traitement de la myasthénie
German	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Behandlung der Myasthenia Gravis
Greek	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Θεραπεία της βαρειάς μυασθένειας
Hungarian	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Myasthenia gravis kezelése
Italian	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Trattamento della miastenia grave
Latvian	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Myasthenia gravis ārstēšanai
Lithuanian	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-	Didžiosios miastenijos gydymas

	Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	
Polish	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Leczenie miastenii gravis
Portuguese	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Tratamento da miastenia gravis
Slovak	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Liečba myasthenie gravis
Slovenian	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Zdravljenje miastenije gravis
Spanish	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Tratamiento de la miastenia gravis
Swedish	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Behandling av myasthenia gravis
Norwegian	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Behandling av myasthenia gravis
Icelandic	H-Val-Ile-Val-Lys-Leu-Ile-Pro-Ser-Thr-Ser-Ser-Ala-Val-Asp-Thr-Pro-Tyr-Leu-Asp-Ile-Thr-Tyr-His-Phe-Val-Ala-Gln-Arg-Leu-Pro-Leu-OH	Meðferð við vöðvaslensfári