



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

Document Date: London, 6 October 2009
Doc.Ref.: EMEA/COMP/315304/2005 Rev.1

Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in December 2008 on request of the Sponsor.

Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of tilarginine acetate for the treatment of cardiogenic shock

On 3 November 2005, orphan designation (EU/3/05/330) was granted by the European Commission to Dr Ulrich Granzer, Germany, for tilarginine acetate for the treatment of cardiogenic shock.

What is cardiogenic shock?

Shock is defined by inadequate delivery of oxygen to the tissues. Cardiogenic shock is a form of shock that occurs due to the weakened pumping function of the heart. A sudden decrease in the strength of the heart pump (e.g. due to a heart attack or heart diseases) combined with an inadequate response of the tone of the vascular system (the system composed of arteries and veins, which serves to transport the blood around the body), results in a lowering of the blood pressure. This might lead to a reduction of oxygen brought to the vital body organs, which will ultimately lead to shock and death. Nitric oxide (NO) is a naturally produced substance, released by certain cells such as those which are lining the inside surface of the blood vessels. NO is known to be a powerful substance that can cause widening of blood vessels (vasodilatation) and thus reduces the blood pressure. It is hypothesized that the production of a too high concentration of NO by the body might play an important role in the development of cardiogenic shock process. Cardiogenic shock is a life-threatening condition.

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

At the time of designation, cardiogenic shock affected not more than 4 in 10,000 people in the European Union (EU)*. This is equivalent to a total of not more than 184,000 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 knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

Various products have been authorised for treatment of the condition in countries in the Community at the time of submission of the application for orphan drug designation. Treatment includes medicines to support the blood pressure and stimulate the heart to contract more forcefully. In addition, other measures have been used such as revascularisation and temporary supporting devices. Satisfactory argumentation has been submitted by the sponsor to justify the assumption that the medicinal product might be of potential significant benefit for the treatment of cardiogenic shock because it might act in a different way and thereby it might improve the long-term outcome of the patients. The assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

*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 Lichtenstein. This represents a population of 459,700,000 (Eurostat 2004).

How is this medicine expected to work?

Tilarginine acetate is expected to block (inhibit) the production of nitric oxide (NO) in the vessel wall. If NO is generated during myocardial infarction (heart attack) or other heart diseases, it would lead to the vasodilatation and thus to a reduction of the blood pressure contributing to the generation of the cardiogenic shock. Tilarginine acetate is expected to prevent such vasodilatation and further drop of blood pressure and might thus interfere in the intensification of the cardiogenic shock.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, clinical trials in patients with cardiogenic shock were ongoing.

The medicinal product was not authorised anywhere worldwide for cardiogenic shock, at the time of submission. Orphan designation of tilarginine acetate was granted in United States for treatment of cardiogenic shock following complicating acute myocardial infarction.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 9 September 2005 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	Tilarginine acetate	Treatment of cardiogenic shock
Czech	Tilarginin acetát	Léčba kardiogenního šoku
Danish	Tilarginin acetat	Behandling af kardiogent shock
Dutch	Tilarginine-acetaat	Behandeling van cardiogene shock
Estonian	Tilarginiinatsetaat	Kardiogeense šoki ravi
Finnish	Tilarginiiniasettaatti	Kardiogeenisen sokin hoito
French	Acétate de tilarginine	Traitement du choc cardiogénique
German	Tilargininacetat	Behandlung des kardiogenen Schocks
Greek	Οξική τιλαργινίνη	Θεραπεία καρδιογενούς καταπληξίας
Hungarian	Tilarginin acetát	Cardiogen shock kezelése
Italian	Acetato di Tilarginina	Trattamento dello shock cardiogenico
Latvian	Tilarginīna acetāts	Kardiogēnā šoka ārstēšana
Lithuanian	Tilarginino acetatas	Kardiogeninio šoko gydymas
Polish	Tilargininy octan	Leczenie wstrząsu kardiogenego
Portuguese	Acetato de tilarginina	Tratamento do choque cardiogénico
Slovak	Tilarginín acetát	Liečba kardiogénneho šoku
Slovenian	Tilarginin acetat	Zdravljenje kardiogenega šoka
Spanish	Acetato de tilarginina	Tratamiento del shock cardiogénico
Swedish	Tilargininacetat	Behandling av kardiogen chock
Norwegian	Tilargininacetat	Behandling av kardiogent sjokk
Icelandic	Tilarginín acetat	Meðferð við hjartalosti