



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

25 May 2011  
EMA/COMP/275889/2006 Rev.1  
Committee for Orphan Medicinal Products

## Public summary of opinion on orphan designation

### 4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride for the moderate and severe traumatic brain injury

On 28 August 2006, orphan designation (EU/3/06/390) was granted by the European Commission to vasopharm BIOTECH GmbH, Germany, for 4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride for the treatment of moderate and severe traumatic brain injury.

#### **What is moderate and severe traumatic brain injury?**

Traumatic brain injury is brain damage caused by a head injury (in a traffic accident or a fall). The initial injury to the head and brain usually goes on to cause 'secondary' problems, most frequently due to bleeding or swelling of the brain tissue (oedema) increasing the pressure within the skull. Traumatic brain injury is classified as minor, moderate or severe according to the patient's symptoms: patients with moderate injury are lethargic (lacking in energy) or stuporous (unaware of their surroundings), and those with severe injury are comatose (unconscious). People with moderate or severe traumatic brain injury need to be admitted to hospital for observation and examination, in case the condition gets worse.

Moderate and severe traumatic brain injury is chronically debilitating and life threatening.

#### **What is the estimated number of patients?**

At the time of designation, moderate and severe traumatic brain injury affected less than 4 in 10,000 people in the European Union (EU)\*. This is equivalent to a total of fewer than 184,000 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).

---

\*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).



## **What treatments are available?**

Various treatments to reduce pressure within the skull in patients with moderate or severe closed traumatic brain injury, including medicines and surgery were available at the time of submission of the application for orphan drug designation.

4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride, as a new medicine in the treatment of moderate and severe traumatic brain injury, might help to achieve better overall control of the condition in particular by decreasing oedema formation. These benefits 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?**

4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride is an inhibitor of the nitric oxide synthase enzyme (a type of protein). An inhibitor is a substance that tends to nullify the action of another. Nitric oxide is generated in the brain (due to action by nitric oxide synthase) following a brain injury and causes dilatation (widening) of blood vessels and swelling of the brain tissue (oedema). 4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride is expected to act by inhibiting nitric oxide synthase and thus reducing the swelling of the brain following brain injury. This might improve the long-term outcome of the patients.

## **What is the stage of development of this medicine?**

The effects of 4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride were evaluated in experimental models.

At the time of submission of the application for orphan designation, no clinical trials in patients with moderate and severe traumatic brain injury were initiated.

4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride was not authorised anywhere worldwide for moderate and severe traumatic brain injury or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 12 July 2006 recommending the granting of this 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 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:

vasopharm BIOTECH GmbH  
Friedrich-Bergius-Ring 15  
D-97076 Wuerzburg  
Germany  
Telephone: +49 931 35 90 99 0  
Telefax: +49 931 35 90 99 12  
E-mail: [office@vasopharm.com](mailto:office@vasopharm.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<sup>1</sup>, Norwegian and Icelandic

Language	Active Ingredient	Indication
English	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride	Treatment of moderate and severe traumatic brain injury
Czech	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochlorid	Léčba středně závažného až závažného traumatického poranění mozku
Danish	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydrochlorid	Behandling af moderat til svær traumatisk hjerneskade
Dutch	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterine dihydrochloride	Behandeling van matig tot ernstig traumatisch hersenletsel
Estonian	4-amino-(6R,S)-5,6,7,8-tetrahüdrol-L-biopteriinidivesinikkloriid	Mõõduka ja raske traumaatilise ajukahjustuse ravi
Finnish	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopteriinidihydrokloridi	Kohtalaisen ja vaikean traumaattisen aivovaurion hoito
French	dichlorhydrate de 4-amino-(6R,S)-5,6,7,8-tétrahydro-L-bioptérine	Traitement de blessures traumatiques modérées et sévères du cerveau
German	4-Amino-(6R,S)-5,6,7,8-Tetrahydro-L-biopterin dihydrochlorid	Behandlung mittelschwerer und schwerer traumatischer Hirnverletzungen
Greek	4-αμινο-(6R,S)-5,6,7,8-τετραϋδρο-L-διυδροχλωρική βιοπτερίνη	Θεραπεία μέτριας και σοβαρής τραυματικής κάκωσης εγκεφάλου
Hungarian	4-amino-(6R,S)-5,6,7,8-tetrahidro-L-biopterin-dihidroklorid	Középsúlyos vagy súlyos traumás agysérülések kezelése
Italian	4-amino-(6R,S)-5,6,7,8-tetraidro-L-biopterina diidrocloruro	Tattamento delle lesioni cerebrali traumatiche gravi e moderate
Latvian	4-amino-(6R,S)-5,6,7,8-tetrahidro-L-biopterīna dihidrohlorīds	Smadzeņu vidēji smagu un smagu traumatisku bojājumu ārstēšana
Lithuanian	4-amino-(6R,S)-5,6,7,8-tetrahidro-L-biopterino dihidrochloridas	Vidutinio sunkumo ir sunkaus trauminio galvos smegenų pažeidimo gydymas
Polish	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopteryny dichlorowodorek	Leczenie umiarkowanych i ciężkich urazów mózgu

<sup>1</sup> At the time of designation

Language	Active Ingredient	Indication
Portuguese	diidrocloreto de 4-amino-(6R,S)-5,6,7,8-tetraidro-L-biopterina	Tratamento de danos cerebrais traumáticos moderados a graves
Slovak	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterín dihydrochlorid	Liečba stredne závažného až závažného traumatického poranenia mozgu
Slovenian	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihidroklorid	Zdravljenje zmernih in težkih travmatskih možganskih poškodb
Spanish	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterina dihidrocloruro	Tratamiento de lesiones traumáticas cerebrales moderadas y graves
Swedish	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterin dihydroklorid	Behandling av måttlig och svår traumatisk hjärnskada
Norwegian	4-amino-(6R,S)-5,6,7,8-tetrahydro-L-biopterindihydroklorid	Behandling av moderat og alvorlig traumatisk hjerneskode
Icelandic	4-amínó-(6R,S)-5,6,7,8-tetrahýdró-L-bíopterín tvíhýdróklóríð	Meðferð miðlungs- og alvarlegs heilaáverka á heila