



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Public summary of opinion on orphan designation 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio]butadiene for the treatment of non-traumatic subarachnoid haemorrhage

On 12 October 2017, orphan designation (EU/3/17/1935) was granted by the European Commission to Edvince AB, Sweden, for 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio]butadiene (also known as U0126) for the treatment of non-traumatic subarachnoid haemorrhage.

What is non-traumatic subarachnoid haemorrhage?

Non-traumatic subarachnoid haemorrhage is a form of stroke that occurs due to bleeding into the subarachnoid space (the space between two membranes that surround the brain) without previous trauma. Most times it occurs when part of the wall of a blood vessel in the brain that has weakened and expanded over time (a cerebral aneurysm) subsequently bursts, causing bleeding into the subarachnoid space and damaging the brain tissue. In addition, blood vessels near the site of the aneurysm go into spasm (vasospasm) reducing blood supply to the brain and therefore the supply of oxygen and essential nutrients to brain cells.

Aneurysms in the brain are considered to be acquired (they are not present at birth but develop over a lifetime). However, evidence indicates that genetic factors make some people more likely to develop them.

Non-traumatic subarachnoid haemorrhage is life threatening and can be debilitating because it could lead to oxygen shortage in the brain cells and thus to impairment of brain functions.

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

At the time of designation, non-traumatic subarachnoid haemorrhage affected approximately 1 in 10,000 persons in the European Union (EU). This was equivalent to a total of around 52,000 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 on the basis of data from the European Union (EU 28), Norway, Iceland and Liechtenstein. This represents a population of 515,700,000 (Eurostat 2017).



What treatments are available?

At the time of designation, nimodipine was authorised in the EU for the prevention and treatment of complications due to vasospasm following subarachnoid haemorrhage.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with non-traumatic subarachnoid haemorrhage with laboratory studies indicating an improvement in vasospasm and the brain's control of movement. 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?

When injected into the brain, this medicine is expected to block the action of proteins called mitogen-activated protein kinase kinases (MEK1 and MEK2) in blood vessels, which are thought to cause the muscles in the blood vessel wall to contract and narrow. The medicine would thus help to overcome the effects of vasospasm. By preventing or reversing vasospasm, the medicine is expected to help avoid oxygen shortage to the brain cells and thus the impairment of brain functions such as control of movement.

What is the stage of development of this medicine?

The effects of the medicine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, no clinical trials with the medicine in patients with non-traumatic subarachnoid haemorrhage had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for non-traumatic subarachnoid haemorrhage or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 5 October 2017 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:

Contact details of the current sponsor for this orphan designation can be found on EMA website, on the medicine's [rare disease designations page](#).

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 languages¹, Norwegian and Icelandic

| Language | Active ingredient | Indication |
|------------|---|--|
| English | 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio]butadiene | Treatment of non-traumatic subarachnoid haemorrhage |
| Bulgarian | 1,4-диамино-2,3-дициано-1,4-бис[2-аминофенилтио]бутадиен | Лечение на нетравматичен субарахноидален кръвоизлив |
| Croatian | 1,4-diamino-2,3-diciano-1,4-bis[2-aminofeniltio]butadien | Liječenje netraumatskog subarahnoidalnog krvarenja |
| Czech | 1,4-diamino-2,3-dikýano-1,4-bis[2-aminofenylthio]butadien | Léčbě ne traumatického subarachnoidálního krvácení |
| Danish | 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylthio]butadien | Behandling af ikke traumatisk subaraknoidalblødning |
| Dutch | 1,4-diamino-2,3-dicyano-1,4-bis[2-aminofenylthio]butadien | Behandeling van niet-traumatische subarachnoidale bloeding |
| Estonian | 1,4-diamino-2,3-ditsüano-1,4-bis[2-aminofenüültio]butadien | Mittetraumaatilise subarahnoidaalse hemorraagia ravi |
| Finnish | 1,4-diamino-2,3-disýano-1,4-bis[2-aminofenyyilitio]butadieni | Lukinkalvonalaisen ei-traumaattisen verenvuodon hoito |
| French | 1,4-diamino-2,3-dicyano-1,4-bis[2-aminophénylthio]butadiène | Traitement de l'hémorragie sous-arachnoïdienne non-traumatique |
| German | 1,4-Diamino-2,3-dicyano-1,4-bis[2-aminophenylthio]butadien | Behandlung von nicht traumatischer Subarachnoidalblutungen |
| Greek | 1,4-διамиνο-2,3-δικυανο-1,4-δισ[2-αμινοφαινυλθειο]βουταδιένιο | θεραπεία της μη-τραυματικής υπαραχνοειδούς αιμορραγίας |
| Hungarian | 1,4-diamino-2,3-diciano-1,4-bisz[2-aminofeniltio]-butadién | Nem traumás szubarachnoid vérzés kezelése |
| Italian | 1,4-diammino-2,3-diciano-1,4-bis[2-aminofeniltio]butadiene | Tattamento dell'emorragia subaracnoidea non traumatica |
| Latvian | 1,4-diamino-2,3-diciano-1,4-bis[2-aminofeniltio]butadiēns | Netraumatiska subarahnoidāla asinsizplūduma ārstēšana |
| Lithuanian | 1,4-diamino-2,3-diciano-1,4-bis[2-aminofeniltio]butadienas | Netrauminio subarachnoidinio kraujavimo gydymas |
| Maltese | 1,4-diammino-2,3-diċġjan-1,4-bis[2-amminofeniltijo]butadjen | Kura ta' emorragija subaraknojde mhux trawmatika |
| Polish | 1,4-dwuamino-2,3-dwucyjano-1,4-bis[2-aminofenyltio]butadien | Leczenie nie urazowego krwotoku podpajęczynówkowego |
| Portuguese | 1,4-diamino-2,3-diciano-1,4-bis[2-aminofeniltio]butadieno | Tratamento de hemorragia subaracnoidea não traumática |
| Romanian | 1,4-diamino-2,3-diciano-1,4-bis[2-aminofeniltio]butadienă | Tratamentul hemoragiei subarahnoidiene non-traumatice |
| Slovak | 1,4-diamino-2,3-dikýano-1,4-bis[2-aminofenyltio]butadién | Liečba netraumatického subarachnoidálneho krvácania |

¹ At the time of designation

| Language | Active ingredient | Indication |
|-----------|---|--|
| Slovenian | 1,4-diamino-2,3-diciano-1,4-bis[2-aminofeniltio]butadien | Zdravljenje netravnatske subarahnoidne krvavitve |
| Spanish | 1,4-diamino-2,3-diciano-1,4-bis[2-aminofeniltio]butadieno | Tratamiento de la hemorragia subaracnoidea no traumática |
| Swedish | 1,4-diamin-2,3-dicyan-1,4-bis(2-aminfenyltio)butadien | Behandling av icke-traumatisk subaraknoidalblödning |
| Norwegian | 1,4-diamino-2,3-dicyano-1,4-bis[2-aminofenyltio]butadien | Behandling av ikke-traumatisk subaraknoidalblødning |
| Icelandic | 1,4-díamínó-2,3-dícýanó-1,4-bis[2-amínófenýltíó]bútadíen | Meðferð við innanskúmsblæðingu án áverka |