13 April 2015
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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

5-(2,6-Difluoro-phenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinoline-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyrylamino]-propionylamino}-4-oxo-pentanoic acid methyl ester for the treatment of neonatal brain injury

First publication	26 October 2009
Rev.1: transfer of sponsorship	11 March 2010
Rev.2: administrative update	27 May 2011
Rev.2: withdrawal from the Community Register	13 April 2015

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Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in March 2015 on request of the Sponsor.

On 23 October 2006, orphan designation (EU/3/06/403) was granted by the European Commission to Theraptosis, France, for 5-(2,6-Difluoro-phenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinoline-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyrylamino]-propionylamino}-4-oxo-pentanoic acid methyl ester for the treatment of neonatal brain injury.

The sponsorship was transferred to Chiesi Farmaceutici S.P.A., Italy, in February 2010.

What is neonatal brain injury?

Neonatal brain injury refers to damage to certain parts of the developing brain. This damage can occur early in pregnancy when the brain is forming, during the birth process or after birth in the first few days to weeks of life. In many cases, the exact cause of the brain damage is not known. The severity of the injury varies widely, from very mild and subtle to very profound. In its severe form, it leads to damage in one or more parts of the brain that control muscle tone and motor activity (movement) and

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then is called cerebral palsy. These infants are usually slow to reach developmental milestones such as rolling over, sitting, crawling, and walking.

Another possible sign of neonatal brain injury is known as neonatal seizures. These occur within 28 days of birth but often no typical convulsions are detected. Instead, for example their eyes appear to be looking in different directions; or they may have lip smacking or periods of no breathing.

Neonatal brain injury is a life-threatening and chronically debilitating condition.

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

At the time of designation, neonatal brain injury affected less than 1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 47,000 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?

No satisfactory methods exist that were authorised at the time of application.

How is this medicine expected to work?

5-(2,6-Difluoro-phenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinoline-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyrylamino]-propionylamino}-4-oxo-pentanoic acid methyl ester has been shown to inhibit the function of a cell molecule, called caspase-2. The latter is one of a series of specific enzymes (a type of protein) involved in the "programmed death" of cells. By inhibiting this enzyme, the proposed medicinal product aims to prevent the process of programmed brain cell (neuronal) death, associated with neonatal brain injury. The goal of this treatment is to limit long-term adverse (negative) consequences to proper brain functioning.

What is the stage of development of this medicine?

The evaluation of the effects of 5-(2,6-Difluoro-phenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinoline-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyrylamino]-propionylamino}-4-oxo-pentanoic acid methyl ester in experimental models is ongoing.

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

5-(2,6-Difluoro-phenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinoline-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyrylamino]-propionylamino}-4-oxo-pentanoic acid methyl ester was not authorised anywhere worldwide for neonatal 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 6 September 2006 recommending the granting of this designation.

*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 25), Norway, Iceland and Liechtenstein.
At the time of designation, this represented a population of 468,900,000 (Eurostat 2006).

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 European Union) 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	5-(2,6-Difluoro-phenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinoline-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyrylamino]-propionylamino}-4-oxo-pentanoic acid methyl ester	Treatment of neonatal brain injury
Bulgarian	5-(2,6-Дифлуоро-фенокси)-3(R,S)-{2(S)-[2(S)-(3-метоксикарбонил-2(S)-{3-метил-2(S)-[(хинолон-2-карбонил)-амино]-бутириламино}-пропиониламино)-3-метил-бутириламино]-пропиониламино}-4-оксо-пентаноева киселина метил естер	Лечение на неонатална мозъчна увреда
Czech	Metyl ester kyseliny 5-(2,6-difluoro-fenoxy)-3(R,S)-{2(S)-[2(S)-(3-metoxykarbonyl-2(S)-{3-metyl-2(S)-[(chinolin-2-karbonyl)-amino]-butyrylamino}-propionylamino)-3-metyl-butyrylamino]-propionylamino}-4-oxo-valerové	Léčba perinatálního poškození mozku
Danish	5-(2,6-difluoro-phenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinolin-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyroylamino]-propionylamino}-4-oxo-pentansyremethylester	Behandling af neonatal hjerneskade
Dutch	5-(2,6-difluor-fenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinoline-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyrylamino]-propionylamino}-4-oxopentaanzuur methylester	Behandeling van neonatale hersenbeschadiging
Estonian	5-(2,6-difluorofenoksü)-3(R,S)-{2(S)-[2(S)-(3-metoksüülkarbonüül-2(S)-{3-metüül-2(S)-[(kvinoliin-2-karbonüül)-amino]-butürüülamino}-propionüülamino)-3-metüülbuturüülamino]-propionüülamino}-4-oksopentaanhappe metüülester	Neonataalse ajukahjustuse ravi
Finnish	5-(2,6-difluorifenoksi)-3(R,S)-{2(S)-[2(S)-(3-metoksikarbonyyli-2(S)-{3-metyyli-2(S)-[(kinoliini-2-karbonyyli)-amino]-butyryyliamino}-propionyyliamino)-3-metyyli-butyryyliamino]-propionyyliamino}-4-oksopentaanihappometyyliesteri	Vastasyntyneen lapsen aivovaurion hoito

[1] At the time of transfer of sponsorship

Language	Active Ingredient	Indication
French	Ester méthylique de l'acide 5-(2,6-difluoro-phénoxy)-3(R,S)-{2(S)-[2(S)-(3-méthoxycarbonyl-2(S)-{3-méthyl-2(S)-[(quinoléine-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-méthyl-butyrylamino]-propionylamino}-4-oxo-pentanoïque	Traitement des lésions cérébrales néonatales
German	5-(2,6-Difluorophenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinoline-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyrylamino]-propionylamino}-4-oxo-Pentansäuremethylester	Behandlung von neonataler Hirnschädigung
Greek	Μεθυλικός εστέρας του 5-(2,6-διφθορο-φαινοξυ)-3(R,S)-{2(S)-[2(S)-(3-μεθοξυκαρβονυλ-2(S)-{3-μεθυλ-2(S)-[(κινολινο-2-καρβονυλ)-αμινο]-βουτυρυλαμινο}-προπιονυλαμινο)-3-μεθυλο-βουτυρυλαμινο]-προπιονυλαμινο}-4-οξο-πεντανοϊκού οξέος	Θεραπεία περιγεννητικής εγκεφαλικής βλάβης
Hungarian	5-(2,6-difluor-fenoxi)-3(R,S)-{2(S)-[2(S)-(3-metoxikarbonil-2(S)-{3-metil-2(S)-[(kinolin-2-karbonil)-amino]-butirilamino}-propionilamino)-3-metil-butirilamino]-propionilamino}-4-oxo-pentánsav-metilészter	Újszülöttkori agykárosodás kezelése
Italian	Estere metilico dell'acido 5-(2,6-difluorofenossi)-3(R,S)-{2(S)-[2(S)-(3-metossicarbonil-2(S)-{3-metil-2(S)-[(chinolina-2-carbonil)-ammino]-butirilammino}-propionilammino)-3-metil-butirilammino]-propionilammino}-4-oxopentanoico	Trattamento del danno cerebrale neonatale
Latvian	5-(2,6-difluor-fenoksi)-3(R,S)-{2(S)-[2(S)-(3-metoksikarbonil-2(S)-{3-metil-2(S)-[(hinolīn-2-karbonila)-amīn]-butirilamīn}-propionilamīn)-3-metil-butirilamīn]-propionilamīn}-4-okso-pentānskābes metilesters	Neonatāla galvas smadzeņu bojājuma ārstēšana
Lithuanian	5-(2,6-Difluoro-fenoksi)-3(R,S)-{2(S)-[2(S)-(3-metoksikarbonil-2(S)-{3-metil-2(S)-[(kvinolin-2-karbonil)-amino]-butirilamino}-propionilamino)-3-metil-butirilamino]-propionilamino}-4-okso-pentanoinės rūgšties metilo esteris	Neonatalinio galvos smegenų pažeidimo gydymas

Language	Active Ingredient	Indication
Maltese	5-(2,6-Difluoro-phenoxy)-3(R,S)-{2(S)-[2(S)-(3-methoxycarbonyl-2(S)-{3-methyl-2(S)-[(quinoline-2-carbonyl)-amino]-butyrylamino}-propionylamino)-3-methyl-butyrylamino]-propionylamino}-4-oxo-pentanoic acid methyl ester	Kura ta' korriment fil-moħħ fi trabi tat-twelid
Polish	Ester metylowy kwasu 5-(2,6-difluorofenoksy)-3(R,S)-{2(S)-[2(S)-(3-metoksykarbonylo-2(S)-{3-metylo-2(S)-[(chinolino-2-karbonylo)amino]butyryloamino}propionyloamino)-3-metylobutyryloamino]propionyloamino}-4-oksopentanowego	Leczenie urazu mózu u noworodka
Portuguese	Éster metílico do ácido 5-(2,6-difluoro-fenoxi)-3(R,S)-{2(S)-[2(S)-(3-metoxicarbonil-2(S)-{3-metil-2(S)-[(quinolina-2-carbonil)-amino]-butirilamino}-propionilamino)-3-metil-butirilamino]-propionilamino}-4-oxo-pentanóico	Tratamento da lesão cerebral neonatal
Romanian	5-(2,6-difluoro-fenoxi)-3(R,S)-{2(S)-[2(S)-(3-metoxicarbonil-2(S)-{3-metil-2(S)-[(chinolin-2-carbonil)-amino]-butirilamino}-propionilamino)-3-metil-butirilamino]-propionilamino}-4-oxo-pentanoic acid metil ester	Tratamentul leziunilor cerebrale neonatale
Slovak	Metylester kyseliny 5-(2,6-difluór-fenoxy)-3(R,S)-{2(S)-[2(S)-(3-metoxykarbonyl-2(S)-{3-metyl-2(S)-[(chinolín-2-karbonyl)-amino]-butyrylamino}-propionylamino)-3-metyl-butyrylamino]-propionylamino}-4-oxo-pentánovej	Liečba poškodenia mozgu novorodencov
Slovenian	Metil ester 5-(2,6-Difluoro-fenoksi)-3(R,S)-{2(S)-[2(S)-(3-metoksikarbonil-2(S)-{3-metil-2(S)-[(kinolin-2-karbonil)-amino]-butirilamino}-propionilamino)-3-metil-butirilamino]-propionilamino}-4-okso-pentanojske kisline	Zdravljenje neonatalne poškodbe možganov
Spanish	Éster metílico del ácido 5-(2,6-difluoro-fenoxi)-3(R,S)-{2(S)-[2(S)-(3-metoxicarbonil-2(S)-{3-metil-2(S)-[(quinolina-2-carbonil)-amino]-butirilamino}-propionilamino)-3-metil-butirilamino]-propionilamino}-4-oxo-pentanoico	Tratamiento de lesión cerebral neonatal
Swedish	5-(2,6-difluorfenoxi)-3(R,S)-{2(S)-[2(S)-(3-metoxikarbonyl-2(S)-{3-metyl-2(S)-[(kinolin-2-karbonyl)-amino]-butylamino}-propylamino)-3-metylbutylamino]-propionylamino}-4-oxopentansyra, metylester	Behandling av neonatal hjärnskada

Language	Active Ingredient	Indication
Norwegian	5-(2,6-Difluoro-fenoksy)-3(R,S)-{2(S)-[2(S)-(3-metoksycarbonyl-2(S)-{3-metyl-2(S)-[(kinolin-2-karbonyl)-amino]-butyrylamino}-propionylamino)-3-metyl-butyrylamino]-propionylamino}-4-okso-pentansyremetylester	Behandling av hjerneskade hos nyfødte
Icelandic	5-(2,6-tvíflúoró-fenoxý)-3(R,S)-{2(S)-[2(S)-(3-metoxýkarbónýl-2(S)-{3-metýl-2(S)-[(kínólín-2-karbónýl)-amínó]-bútýrýlamínó}-própíónýlamínó)-3-metýl-bútýrýlamínó]-própíónýlamínó}-4-oxó-pentansýrumetýlester	Meðferð nýbura heilaskaða