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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Synthetic double-stranded siRNA oligonucleotide directed against claudin-5 complexed with polyethyleneimine (prior to administration of doxorubicin) for the treatment of glioma

On 8 November 2012, orphan designation (EU/3/12/1065) was granted by the European Commission to Avena Therapeutics Ltd, Ireland, for synthetic double-stranded siRNA oligonucleotide directed against claudin-5 complexed with polyethyleneimine (prior to administration of doxorubicin) for the treatment glioma.

What is glioma?

Glioma is a type of brain tumour that affects the 'glial' cells (the cells that surround and support the nerve cells). Patients with glioma can have severe symptoms, but the types of symptoms experienced depend on where the tumour develops in the brain. Symptoms can include headaches, nausea (feeling sick), loss of appetite, vomiting, and changes in personality, mood, mental capacity and concentration. About a fifth of patients with glioma have seizures (fits) for months or years before the disease is diagnosed.

Glioma is a long-term debilitating and life-threatening disease because of the severe damage to the brain and is associated with poor long-term survival.

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

At the time of designation, glioma affected less than 2.2 in 10,000 people in the European Union (EU)[*]. This is equivalent to a total of fewer than 111,000 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 27), Norway, Iceland and Liechtenstein. This represents a population of 506,300,000 (Eurostat 2011).

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What treatments are available?

At the time of designation, several medicines were authorised for the treatment of glioma in the EU. Treatments for glioma included surgery, radiotherapy (treatment with radiation), and chemotherapy (medicines to treat cancer) to improve survival. Patients also received treatments for the symptoms of glioma, including corticosteroids to reduce pressure within the skull and medicines to prevent seizures.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients on the basis of studies in experimental models showing that the medicine might prolong survival and reduce tumour size. 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?

This medicine is expected to be given before the anticancer medicine doxorubicin. The medicine makes the blood-brain barrier more permeable, allowing sufficient amounts of doxorubicin to pass into the brain so that it can only work against the cancer cells in glioma.

The medicine is made up of a small strand of synthetic genetic material, called 'small interfering RNA' (siRNA), which interferes with the functioning of certain genes. The siRNA in the medicine is designed to target the gene for the protein claudin-5 at the blood-brain barrier, thereby blocking its production. Claudin-5 is responsible for the tight junctions between the cells in the barrier. By blocking claudin-5, the medicine is expected to increase the permeability of the blood brain barrier, allowing doxorubicin to reach the glioma cells in the brain.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, the evaluation of the effects of the medicinal product in experimental models was ongoing.

At the time of submission, no clinical trials with the medicinal product in patients with glioma had been started.

At the time of submission, the medicinal product was not authorised anywhere in the EU for glioma 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 2012 recommending the granting of this designation.

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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:

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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	Synthetic double-stranded siRNA oligonucleotide directed against claudin-5 complexed with polyethyleneimine (prior to administration of doxorubicin)	Treatment of glioma
Bulgarian	Синтетичен двойноспирален siРНК олигонуклеотид, насочен срещу клаудин-5 в комплекс с полиетиленимин (преди приложение на доксорубицин)	Лечение на глиома
Czech	Syntetický dvouřetězcový siRNA oligonukleotid namířený proti claudinu-5 v komplexu s polyethyleneiminem (před podáním doxorubicinu)	Léčba gliomů
Danish	Syntetisk dobbeltstrenget siRNA oligonukleotid rettet mod claudin-5, i kompleks med polyethyleneimin (forud for doxorubicin administration)	Behandling af gliom
Dutch	Synthetisch dubbelstrengig siRNA oligonucleotide gericht tegen claudine-5 gecomplexeerd met polyethyleneïmine (voorafgaand tot toediening van doxorubicine)	Behandeling van glioma
Estonian	Sünteetilise kaheahelalise siRNA oligonukleotiid suunatud klaudiin-5 polüetüleeneneimiini kompleski vastu (enne doksorubitsiini manustamist)	Glioomi ravi
Finnish	Synteettinen, kaksijuosteinen siRNA oligonukleotidi, joka on kohdennettu polyetyleeni-iminiin yhdistettyä klaudiini-5:ttä vastaan (annettavaksi ennen doksorubisiinia)	Glioman hoito
French	Aggregat de double-brin si-ARN dirige contre la Claudine-5 et de polyéthyléneimine (avant administration de doxorubicine)	Traitement des gliomes
German	Synthetisches doppelsträngiges siRNA Oligonukleotid gegen Claudin-5, komplexiert mit Polyethyleneimine (Vor einer Verabreichung von Doxorubicin)	Behandlung von Gliomen
Greek	Συνθετικό δίκλωνο ολιγονουκλεοτίδιο siRNA που έναντι της κλωντίνης-5 συμπλεγμένο με πολυαιυλενεϊμίνη (πριν από τη χορήγηση δοξορουμπικίνης)	Θεραπεία του γλοιώματος
Hungarian	Claudin-5-re ható polietilénimin és szintetikus kettős-láncú siRNS oligonukleotid komplex (doxorubicin kezelés előtt)	Glioma kezelése
Italian	Oligonucleotide sintetico siRNA a doppia catena diretto contro la Claudina 5 complessato con polietileneimina (prima della somministrazione di doxorubicina)	Trattamento del glioma
Latvian	Sintētisks dubultķēžu siRNS oligonukleotīds vērsts pret klaudīna-5 kompleksu ar polietilēnimīnu (pirms doksirubicīna ievades)	Gliomas ārstēšana

[1] At the time of designation

Language	Active ingredient	Indication
Lithuanian	Sintetinis dvigrandis siRNR oligonukleotidas nukreiptas prieš klaudiną – 5 prijungtas prie polietilenemino (prieš doksorubicino paskyrimą)	Gliomos gydymas
Maltese	Oligonukleotide sintetiku tas-siRNA b'katina doppja dirett kontra claudin-5 magħqud ma' polyethyleneimine (qabel ma jiġi amministrat doxorubicin)	Kura tal-glioma
Polish	Kompleks syntetycznego dwuniciowego oligonukleotydu siRNA przeciw klaudynie 5 i polietylenoiminy (przed podaniem doksorubicyny)	Leczenie glejaka
Portuguese	Oligonucleotídeo sintético siRNA de cadeia dupla dirigido contra a claudina-5 complexada com polietilenoimina (antes da administração de doxorubicina)	Tratamento do glioma
Romanian	Oligonucleotid sintetic ARNsi dublu catenar directionat impotriva claudin-5 complexat cu polietilenimina (inainte de administrarea de doxorubicina)	Tratamentul gliomului
Slovak	Syntetický dvojvláknový oligonukleotid siDNA zameraný proti klaudínu-5 v komplexe s polyetylénimínom (pred podaním doxorubicínu)	Liečba gliómu
Slovenian	Sintetični dvojno-verižni siRNK oligonukleotid usmerjen proti klavdinu-5, povezanim z polietileneiminom (pred dajanjem doksorubicina)	Zdravljenje glioma
Spanish	Oligonucleotideo sintetico siARN bicatenario dirijido contra la Claudina -5 complejado con polietilenoimina (antes de la administración de doxorubicina)	Tratamiento del glioma
Swedish	Syntestisk dubbelsträngad siRNA oligonukleotid riktad mot claudin-5 i komplex med polyetylenimin (före administrering av doxorubicin)	Behandling av gliom
Norwegian	Syntetisk dobbelttrådet siRNA oligonukleotid rettet mot claudin-5 i kompleks med polyetylenimin (før administrering av doksorubicin)	Behandling av gliom
Icelandic	Tilbúið tví-strengja siRNA ólígónúkleótíð sem beinist gegn claudín-5 samsett með pólýethýleneímíni (fyrir gjöf doxórúbícíns)	Meðferð á glíóma