



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Public summary of opinion on orphan designation

(16E)-14-Methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene-citric acid for the treatment of glioma

On 17 October 2019, orphan designation EU/3/19/2202 was granted by the European Commission to Clinical Network Services (NL) B.V., Netherlands, for (16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene-citric acid (also known as zotiraciclib) for the treatment of glioma.

What is glioma?

Glioma is a 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 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 one-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 it 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 approximately 2.6 in 10,000 people in the European Union (EU). This was equivalent to a total of around 135,000 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 518,400,000 (Eurostat 2019).



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). Patients also received treatments for the symptoms of glioma, including corticosteroids to reduce pressure inside 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 with glioma. Early studies showed that, when the medicine is given with temozolomide (a medicine for glioma), a control of the cancer progression and reduction of the cancer size was observed in some patients whose glioma did not respond to standard treatment. 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?

The medicine blocks the activity of several enzymes, primarily an enzyme called cyclin-dependent kinase 9 (CDK9). By blocking these enzymes, the medicine causes a reduction in the level of key proteins called MYC that glioma cells need to survive, thus causing their death. This is expected to slow down the progression of the disease.

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, clinical trials with the medicine in patients with glioma were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of glioma or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 12 September 2019, 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](#).

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	(16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene–citric acid	Treatment of glioma
Bulgarian	(16E)-14-метил-20-окса-5,7,14,26-тетрааза-тетрацикло[19.3.1.1(2,6).1(8,12)]хептакоса-1(25),2(26),3,5,8(27),9,11,16,21,23-декаен-лимонена киселина	Лечение на глиома
Croatian	(16E)-14-metil-20-oksa-5,7,14,26-tetraaza-tetraciklo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8(27),9,11,16,21,23-dekaen-limunska kiselina	Liječenje glioma
Czech	(16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyklo[19.3.1.1(2,6).1(8,12)]heptakosa-1(25),2(26),3,5,8(27),9,11,16,21,23-dekan citrát	Léčba gliomů
Danish	(16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene–citric-syre	Behandling af gliom
Dutch	16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene–citric zuur	Behandeling van glioma
Estonian	(16E)-14-metüül-20-oksa-5,7,14,26-tetraasa-tetratsüklo[19.3.1.1(2,6).1(8,12)]heptakosa-1(25),2(26),3,5,8(27),9,11,16,21,23-dekaeen–tsitraat	Glioomi ravi
Finnish	(16E)-14-metyyli-20-oksa-5,7,14,26-tetraatsa-tetrasyklo[19.3.1.1(2,6).1(8,12)]heptakosa-1(25),2(26),3,5,8(27),9,11,16,21,23-dekaeeni–sitruunahappo	Gliooman hoito
French	(16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene–citric acide	Traitement des gliomes
German	(16E)-14-methyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene–Zitronensäure	Behandlung von Gliomen
Greek	(16E)-14-μεθυλ-20-οξα-5,7,14,26-τετρααζα-τετρακυκλο[19.3.1.1(2,6).1(8,12)]επτακοσα-1(25),2(26),3,5,8(27),9,11,16,21,23-δεκαενο-κιτρικό οξύ	Θεραπεία του γλοιώματος
Hungarian	(16E)-14-metil-20-oxa-5,7,14,26-tetraaza-tetraciklo[19.3.1.1(2,6).1(8,12)]heptakoza-1(25),2(26),3,5,8(27),9,11,16,21,23-dekaén–citromsav	Glioma kezelése

¹ At the time of designation

Language	Active ingredient	Indication
Italian	(16E)-14-metil-20-ossa-5,7,14,26-tetraaza-tetraciclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene-acido citrico	Trattamento del glioma
Latvian	(16E)-14-metil-20-oksa-5,7,14,26-tetraaza-tetraciklo[19.3.1.1(2,6).1(8,12)]heptakoza-1(25),2(26),3,5,8(27),9,11,16,21,23-decēn-citronskābe	Gliomas ārstēšana
Lithuanian	(16E)-14-metil-20-oksa-5,7,14,26-tetraaza-tetraciklo[19.3.1.1(2,6).1(8,12)]heptakoza-1(25),2(26),3,5,8(27),9,11,16,21,23-dekaeno-citrinos rūgštis	Gliomos gydymas
Maltese	(16E)-14-metil-20-ossa-5,7,14,26-tetraaža-tetraċiklo[19.3.1.1(2,6).1(8,12)]jettakoža-1(25),2(26),3,5,8(27),9,11,16,21,23-deċen-aċidu ċitriku	Kura tal-glioma
Polish	kwas (16E)-14-metylo-20-oksa-5,7,14,26-tetraaza-tetracyklo[19.3.1.1(2,6).1(8,12)]heptakoza-1(25),2(26),3,5,8(27),9,11,16,21,23-dekan-cytrynowy	Leczenie glejaka
Portuguese	Ácido (16E)-14-metil-20-oxa-5,7,14,26-tetraaza-tetraciclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaeno-cítrico	Tratamento do glioma
Romanian	Acid (16E)-14-metil-20-oxa-5,7,14,26-tetraaza-tetraciclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaen-citric	Tratamentul gliomului
Slovak	(16E)-14-metyl-20-oxa-5,7,14,26-tetraaza-tetracyklo[19.3.1.1(2,6).1(8,12)]heptakosa-1(25),2(26),3,5,8(27),9,11,16,21,23-dekaén-citrónová kyselina	Liečba gliómu
Slovenian	(16E)-14-metil-20-oksa-5,7,14,26-tetraaza-tetraciklo[19.3.1.1(2,6).1(8,12)]heptakoza-1(25),2(26),3,5,8(27),9,11,16,21,23-dekaen-citronska kislina	Zdravljenje glioma
Spanish	Acido citrico (16E)-14-metil-20-oxa-5,7,14,26-tetraaza-tetraciclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene	Tratamiento del glioma
Swedish	(16E)-14-metyl-20-oxa-5,7,14,26-tetraaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptakosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaen-citronsyra	Behandling av gliom
Norwegian	(16E)-14-metyl-20-oksa-5,7,14,26-tetraaza-tetrasyklo[19.3.1.1(2,6).1(8,12)]heptakosa-1(25),2(26),3,5,8(27),9,11,16,21,23-dekaen-sitronsyre	Behandling av gliom
Icelandic	(16E)-14-metýl-20-oxa-5,7,14,26-tetraaza-tetracykló[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaen-sítrónusýra	Meðferð á glíóma