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Public summary of opinion on orphan designation

Autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor for the treatment of diffuse large B-cell lymphoma

On 17 July 2017, orphan designation (EU/3/17/1890) was granted by the European Commission to Celgene Europe Limited, United Kingdom, for autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor (also known as JCAR017) for the treatment of diffuse large B-cell lymphoma.

What is diffuse large B-cell lymphoma?

Diffuse large B-cell lymphoma is a type of blood cancer and the most common form of a group of blood cancers known as non-Hodgkin lymphomas.

Diffuse large B-cell lymphoma affects a type of white blood cell called B lymphocytes, or B cells. In patients with this cancer, the B cells multiply too quickly and live for too long, so there are too many of them in the lymph nodes. The first sign of the disease is usually a lump in the neck, under the arm or in the groin area, which is caused by an enlarged lymph node. Patients with diffuse large B-cell lymphoma may also have fever, tiredness, night sweats or weight loss that have no obvious cause.

Although some people with diffuse large B-cell lymphoma can be cured, it remains a serious and life-threatening disease, particularly when the disease is diagnosed late or has come back after treatment.

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

At the time of designation, diffuse large B-cell lymphoma affected approximately 4.3 in 10,000 people in the European Union (EU). This was equivalent to a total of around 222,000 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).

What treatments are available?

At the time of designation, several medicines were authorised for the treatment of diffuse large B-cell lymphoma in the EU. The main treatment was chemotherapy (medicines to treat cancer) usually in

[*]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).

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combination with medicines called monoclonal antibodies and sometimes with radiotherapy (treatment with radiation). Autologous haematopoietic (blood) stem-cell transplantation was also used in patients at risk of the disease coming back after treatment. This is a procedure where the patient's bone marrow is replaced with the patient's own stem cells to form new bone marrow that produces healthy blood cells.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with diffuse large B-cell lymphoma based on preliminary results showing that this medicine worked in patients who did not respond to previous treatments or whose disease came back after it. 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 B cells in patients with diffuse large B-cell lymphoma produce a protein on their surface called CD19. To make this medicine, certain T cells (a different type of white blood cells that are part of the body's natural defences) called CD4+ and CD8+ are taken from the patient. The cells are then modified in the laboratory by a virus that carries a gene into the cells which allows them to target CD19. The modified T cells are grown to increase their numbers before being given back to the patient. Once the modified T cells are returned to the patient, they are expected to recognise CD19 on the cancerous B cells, allowing the T cells to target and kill them.

The virus used in this medicine ('lentivirus') is modified in order not to cause disease in humans.

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 diffuse large B-cell lymphoma were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for diffuse large B-cell lymphoma. Orphan designation of the medicine had been granted in the United States for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 15 June 2017 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:

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 languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor	Treatment of diffuse large B-cell lymphoma
Bulgarian	Автоложни CD4+ и CD8+ Т-клетки, експресиращи специфичен химерен CD19 антигенен рецептор	Лечение на дифузен В-едроклетъчен лимфом
Croatian	Autologne T stanice tipa CD4+ i CD8+ s ekspresijom CD19 specifičnog kimeričnog antigenskog receptora	Liječenje difuznog limfoma velikih B-stanica
Czech	Autologní CD4 a CD8 pozitivní T-lymfocyty exprimující specifický chimérický antigenní receptor CD19	Léčba velkobuněčného difuzního B-lymfomu
Danish	Autologe CD4+ og CD8+ T-celler, der udtrykker CD19-specifik kimær antigenreceptor	Behandling af diffust storcellet B-celle lymfom
Dutch	Autologe CD4+ en CD8+ T-cellen die een CD19-specifieke chimere antigeenreceptor tot expressie brengen	Behandeling van diffuus grootcellig B-cel-lymfoom
Estonian	Autoloogsed CD4+ CD8+ T-rakud, millel avaldub CD19 kimäärne antigeeniretseptor	Diffuusse suure β-rakulise lümfoomi ravi
Finnish	Autologiset CD4+ ja CD8+-T-solut, jotka ilmentävät CD19:lle spesifistä kimeeristä antigeenireseptoria	Diffuusin suurisoluisen B-solulymfooman hoito
French	Lymphocytes T CD4+ CD8+ autologues exprimant le récepteur antigénique chimérique (CAR) anti-CD19	Traitement du lymphome diffus à grandes cellules B
German	Autologe CD4+ und CD8+ T-Zellen, die einen CD19-spezifischen, chimären Antigen-Rezeptor exprimieren	Behandlung des diffusen großzelligen B-Zell-Lymphoms
Greek	Αυτόλογα CD4+ και CD8+ Τ-κύτταρα που εκφράζουν εναν χιμαιρικό αντιγονικό υποδοχέα εναντι του CD19	Θεραπεία του διάχυτου μεγαλοκυτταρικού λεμφώματος Β-κυττάρου (DLBCL)
Hungarian	CD19 speciális kiméra antigén receptort expresszáló autológ CD4+ és CD8+ T-sejtek.	Diffúz nagy B-sejtes lymphoma kezelése
Italian	Cellule autologhe T CD4+ e CD8+che esprimono il recettore chimerico specifico per l'antigene CD19	Terapia del Linfoma non-Hodgkin diffuso a grandi cellule di tipo B (DLBCL)
Latvian	Autologas CD4+ un CD8+ T šūnas, kas ekspresē CD19 specifiska himēriska antigēna receptoru	Difūzas lielo B šūnu limfomas ārstēšana
Lithuanian	Autologinės CD4+ ir CD8+ T ląstelės, ekspresuojančios CD19-specifinį chimerinio antigeno receptorių	Difuzinės stambiųjų B ląstelių limfomos gydymas

[1] At the time of designation

Language	Active ingredient	Indication
Maltese	Celluli T CD4+ u CD8+ awtologi li jesprimu riċettatur ta' antiġen kimeriku speċifiku għal CD19	Kura tal-limfoma taċ-ċelluli tat-tip B kbar mxerrda
Polish	Autologiczne komórki T CD4+ i CD8+ eksprymujące specyficzne dla CD19chimeryczne receptory antygenowe	Leczenie rozlanego chłoniaka z dużych limfocytów B
Portuguese	Células T CD4+ e CD8+ autólogas que exprimem o recetor quimérico do antigénio específico para CD19	Tratamento do linfoma difuso de grandes células B
Romanian	Limfocite T CD4+ și CD8+ autologe care exprimă receptorul chimeric specific pentru antigenul CD19	Tratamentul limfomului difuz cu celule B mari
Slovak	Autológne CD4+ a CD8+ T-lymfocyty exprimujúce CD19-špecifický chimérický antigénny receptor	Liečba difúzneho veľkobunkového lymfómu z buniek B
Slovenian	Avtologne celice T tipa CD4+ in CD8+, ki izražajo CD19 specifičen himerni antigenski receptor	Zdravljenje razširjenega limfoma velikih B celic
Spanish	Células T autólogas CD4+ y CD8+ que expresan un receptor de antígeno quimérico específico de CD19	Tratamiento del linfoma difuso de células B grandes
Swedish	Autologa CD4+ och CD8+ T-celler som uttrycker CD19-specifik chimär antigenreceptor	Behandling av diffusa storcelliga B-cells lymfom
Norwegian	Autologe CD4+ og CD8+ T-celler som uttrykker en CD19-spesifikk kimær antigenreseptor	Behandling av diffust storcellet B-celle lymfom
Icelandic	Samgena CD4+ og CD8+ T-frumur sem tjá CD19-sértækan blendingsmótefnavakaviðtaka	Til meðferðar á dreifðu stórfrumu B frumu eitlakrabbameini