10 May 2017
EMA/208155/2017
Committee for Orphan Medicinal Products

# Public summary of opinion on orphan designation

## Autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains for the treatment of multiple myeloma

On 20 April 2017, orphan designation (EU/3/17/1863) was granted by the European Commission to bluebird bio France, France, for autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains for the treatment of multiple myeloma.

### What is multiple myeloma?

Multiple myeloma (also called plasma cell myeloma) is a cancer of a type of white blood cell called plasma cells. Plasma cells originate in the bone marrow, the spongy tissue inside the large bones in the body. In multiple myeloma, the division of plasma cells becomes out of control, resulting in abnormal, immature plasma cells multiplying and filling up the bone marrow. This interferes with production of normal white blood cells, red blood cells and platelets (components that help the blood to clot), leading to complications such as anaemia (low red blood cell counts), bone pain and fractures, raised blood calcium levels and kidney disease.

Multiple myeloma is a debilitating and life-threatening disease particularly because it disrupts the normal functioning of the bone marrow, damages the bones and causes kidney failure.

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

At the time of designation, multiple myeloma affected approximately 3.6 in 10,000 people in the European Union (EU). This was equivalent to a total of around 186,000 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).

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## What treatments are available?

At the time of designation, several medicines were authorised for multiple myeloma in the EU. The main treatment for multiple myeloma was chemotherapy (medicines to treat cancer) usually combined with corticosteroids to reduce the activity of the immune system, the body's natural defences. Where chemotherapy did not work, some patients received a stem-cell transplant (a procedure where the patient's bone marrow is replaced with stem cells to form new bone marrow that produces healthy blood cells). Radiotherapy (using radiation to kill cancer cells) was used to treat pain due to bone damage and prevent further damage.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with multiple myeloma because early studies indicated that patients whose disease came back after previous treatment responded to treatment with this medicine. 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 abnormal immature plasma cells in patients with multiple myeloma produce a protein on their surface called B-cell maturation antigen (BCMA).

This medicine is made up of T cells (a type of white blood cell) which are taken from the patient. The T cells are modified in the laboratory with a virus that carries a gene into the T cells so that they can recognise and attach to BCMA. The T cells are then given back to the patient, where they are expected to attach to BCMA on the cancer cells and kill them, and to activate other T cells.

The type of 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 multiple myeloma were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for multiple myeloma. 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 March 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 T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains | Treatment of multiple myeloma |
| Bulgarian | Автоложна, обогатена с Т лимфоцити популация от клетки, трансдуцирани с лентивирусен вектор, кодиращ химерен антигенен рецептор, насочен към човешкия антиген на матурация на В клетки с 4-1BB и CD3-зета вътреклетъчни сигнални домейни | Лечение на мултиплен миелом |
| Croatian | Populacija stanica obogaćena autolognim T limfocitima transducirana lentivirusnim vektorom koji kodira kimerični antigenski receptor usmjeren na antigen sazrijevanja humanih B stanica sa 4-1BB i CD3-zeta intracelularnim domenama signalizacije | Liječenje multiplog mijeloma |
| Czech | Autologní T lymfocyty obohacená populace obsahující buňky transdukované s lentivirálním vektorem kódující chimerický antigenní receptor k antigenu 4-1BB humánních B-lymfocytů a CD-3 zeta intracelulární signální domény | Léčba mnohočetného myelomu |
| Danish | Autolog T lymfocyt-beriget cellepopulation, transduceret med en lentiviral vektor, der koder en kimær antigenreceptor rettet mod humant B-celle modningsantigen med 4-1BB og CD3-zeta intracellulære signaleringsdomæner | Behandling af multipelt myelom |
| Dutch | Autologe T-lymfocyt-verrijkte populatie van cellen die getransduceerd zijn met een lentivirale vector welke een chimere antigeenreceptor codeert die zich richt op humaan B-cel maturatie-antigeen met 4-1BB en CD3-zeta intracellulaire signaleringsdomeinen | Behandeling van multipel myeloom |
| Estonian | Autoloogsed T-lümfotsüütidega rikastatud rakupopulatsioon, mida on transdutseeritud lentiviraalse vektoriga, mis kodeerib kimäärset antikeha retseptorit suunatud inimese B-rakkude küpsemise antigeenile koos 4-1BB ja CD3-tseeta rakusiseste signaaldomeenidega rakke sisaldav | Multiibelse müeloomi ravi |
| Finnish | Autologiset T-lymfosyyttirikastetut solut, joihin on siirretty lentivirusvektori, joka koodaa ihmisen B-solun maturaatioantigeeniin kohdistuvaa kimeeristä antigeenireseptoria, jossa on 4-1BB:n ja CD3-zetan solunsisäiset signaalinvälitysdomeenit | Multippeli myelooman hoito |

[1] At the time of designation

| Language | Active ingredient | Indication |
|---|---|---|
| French | Population enrichie en lymphocytes T autologues transduites avec un vecteur lentiviral codant un récepteur d'antigène chimérique qui cible l'antigène de maturation des lymphocytes B humains avec les domaines de signalement intracellulaire 4-1BB et CD3-zeta | Traitement du myélome multiple |
| German | Autologe Zellpopulation angereichert mit T-Lymphozyten, mit einem lentiviralen Vektor transduziert der für einen chimären Antigen-Rezeptor kodiert, der gegen das humane B-Zellen-Maturationsantigen mit den intrazellulären Signaldomänen 4-1BB und CD3-zeta gerichtet ist | Behandlung des multiplen Myeloms |
| Greek | Πληθυσμός αυτόλογων κυττάρων εμπλουτισμένος με Τ λεμφοκύτταρα καιδιαμολυσμένος με λεντι-ιικό φορέα που κωδικοποιεί ένα χιμαιρικό υποδοχέα αντιγόνου κατά του ανθρώπινου αντιγόνου ωρίμανσης Β κυττάτων με ενδοκυτταρικές περιοχές σήμανσης 4-1ΒΒ και CD3-ζ | Θεραπεία πολλαπλού μυελώματος |
| Hungarian | Humán B-sejt maturációs antigént célzó kimér antigén receptort kódoló lentivirális vektorral transzdukált, autológ T-limfocitával gazdagított sejtpopuláció, 4-1BB és CD3-zeta intracelluláris jeladó doménekkel | Myeloma multiplex kezelése |
| Italian | Popolazione arricchita con linfociti T autologhi trasdotti con un vettore lentivirale che codifica per un recettore antigenico chimerico diretto contro l'antigene di maturazione delle cellule B umano con domini di segnalazione intracellulare 4-1BB e CD3-zeta | Trattamento del mieloma multiplo |
| Latvian | Ar autologiem T limfocītiem bagātināta šūnu populācija, kas transducēta ar lentivīrusa vektoru, kurš kodē himērisku antigēna receptoru, kas vērsts pret cilvēka B šūnu nobriešanas antigēnu, ar 4-1BB un CD3-zeta intracelulārajiem signālceļu domēniem | Multiplās mielomas ārstēšana |
| Lithuanian | Autologiniais T limfocitais praturtintas ląstelių klonas, transdukuotas lentivirusiniu vektoriumi, koduojančiu chimerinį antigeno receptorių, nukreiptą į žmogaus B ląstelių brendimo antigeną su 4-1BB ir CD3-zeta tarpląsteliniais signaliniais domenais | Dauginės mielomos gydymas |
| Maltese | Popolazzjoni awtologa arrikita b'limfoċiti-T ta' ċelluli transdotti b'vettur lentivirali b'ikkowdjar ta' riċettur ta' antiġen kimeriku li fil-mira tiegħu għandu l-antiġen ta' maturazzjoni taċ-ċellula B umana b'dominji ta' senjalazzjoni intraċellulari 4-1BB u CD3-zeta | Kura tal-mjeloma multipla |

| Language | Active ingredient | Indication |
|---|---|---|
| Polish | Populacja krwinek autologicznych wzbogacona w limfocyty T, obejmująca komórki transdukowane wektorem lentiwirusowym zawierającym sekwencję kodującą chimeryczną formę receptora antygenowego skierowanego przeciwko antygenowi dojrzewania limfocytów B, zawierającą wewnątrzkomórkowe domeny sygnałowe 4-1BB i CD3-zeta | Leczenie szpiczaka mnogiego |
| Portuguese | População de linfócitos T autólogos enriquecidos que contém células transduzidas com um vetor lentiviral, codificante de um recetor antigénico quimérico, tendo como alvo o antigénio de maturação de células B humanas com domínios de sinalização intracelular 4-1BB e CD3-zeta | Tratamento do mieloma múltiplo |
| Romanian | Populație îmbogățită de limfocite T autologe transduse cu un vector lentiviral care codifică receptorul antigenului chimeric care vizează antigenul de maturizare a limfocitelor B umane cu domenii de semnalizare intracelulare 4-1BB și CD3-zeta | Tratamentul mielomului multiplu |
| Slovak | Populácia buniek obohatená autológnymi T-lymfocytmi transdukovanými lentivirálnym vektorom kódujúcim antigénový receptor zacielený na ľudský antigén dozrievania B bunky s intracelulárnymi signálnymi doménami 4-1BB a CD3-zeta | Liečba mnohopočetného myelómu |
| Slovenian | Z avtolognimi limfociti T obogatena populacija celic ki kodira antigen dozorevanja humanih celic B, usmerjen proti himernemu antigenskemu receptorju intracelularnih domen signalizacije 4-1BB in CD3-zeta | Zdravljenje multiplega mieloma |
| Spanish | Población enriquecida con linfocitos T autólogos que contiene células transducidas con un vector lentivírico que codifica un receptor de antígenos quimérico selectivo para el antígeno de maduración de los linfocitos B humanos con dominios de señalización intracelular 4-1BB y CD3-zeta | Tratamiento del mieloma múltiple |
| Swedish | Autolog T-lymfocytberikad population som innehåller en lentiviral vektor som kodar en chimär antigenreceptor riktad mot human-B-cellsmognadsantigen med 4-1BB och CD3-zeta intracellulära signaleringsdomäner | Behandling av multipelt myelom |
| Norwegian | Autolog T-lymfocyttberiket populasjon av celler transdusert med en lentiviral vektor som koder for en kimær antigenreseptor rettet mot humant B-cellemodningsantigen med 4-1BB og CD3-zeta intracellulære signaleringsdomener | Behandling av myelomatose |

| Language | Active ingredient | Indication |
|---|---|---|
| Icelandic | Hópur auðgaður samgena T-eitilfrumum, en hann inniheldur frumur þar sem erfðaefni eru flutt á milli hægveiru vigra sem kóðar blendingsmótefnavaka-viðtaka sem markstýrt er á þroskamótefnavaka B-frumu úr mönnum með 4-1BB og CD3-zeta merkjasvæði inni í frumum | Meðferð við mergfrumuæxli |