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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19 for treatment in haematopoietic stem cell transplantation

On 27 June 2016, orphan designation (EU/3/16/1674) was granted by the European Commission to QRC Consultants Ltd, United Kingdom, for allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19 (also called BPX-501) for treatment in haematopoietic stem cell transplantation.

What is haematopoietic stem cell transplantation?

Haematopoietic stem cell transplantation involves a patient receiving stem cells (cells that can develop into different types of cell) to help the bone marrow produce healthy blood cells. It can be used to treat serious diseases of the blood and immune system. A stem cell transplant in which the patient receives cells from a healthy donor is called an allogeneic transplant. Before receiving the transplant, the patient's own bone marrow is cleared of cells. The patient then receives the donor stem cells, which multiply and develop into healthy blood cells.

Haematopoietic stem cell transplantation can be a debilitating and life-threatening procedure due to the risk of severe infections and developing graft-versus-host disease (when the transplanted cells recognise the patient's body as 'foreign' and attack the patient's organs leading to organ damage).

What is the estimated number of patients receiving haematopoietic stem cell transplants?

At the time of designation, approximately 1 in 10,000 people in the European Union (EU) have haematopoietic stem cell transplants per year. This was equivalent to a total of around 51,000 people per year*, 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 513,700,000 (Eurostat 2016).

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What treatments are available?

At the time of designation, several medicines were authorised in the EU for patients undergoing haematopoietic stem cell transplants. These included medicines to help restore the immune system, such as immunoglobulin replacement therapy, and to reduce the risk of infections, such as antiviral and antifungal medicines. Medicines that suppress the immune system, such as ciclosporin and corticosteroids were used for the treatment of graft-versus-host disease.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients undergoing haematopoietic stem cell transplantation because early studies showed that its use resulted in fewer admissions to hospital, less time spent in hospital, fewer infections and improved survival when used on top of standard of care. 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?

For many patients who require haematopoietic stem cell transplantation, it is often difficult to find a fully matched donor. When the donor is partly matched to the patient (e.g. a close relative), the risk of the patient developing graft-versus-host disease is increased.

This medicine is made of T lymphocytes or T cells, a type of white blood cell, extracted from a donor who is partly matched to the patient. These T cells are genetically modified to include a 'suicide gene'. The patient first receives the transplant which has had the donor's T cells removed. Afterwards the modified T cells are given. The suicide gene in the T cells is switched off. These cells are expected to help the patient to fight off viral infections while their immune system is being restored with the transplanted stem cells.

However, the transplanted T cells can cause graft-versus-host disease. If the patient develops graft-versus-host disease, a medicine called rimiducid is given to switch on the suicide gene in the T cells. This causes the T cells to die, thus preventing further development 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 undergoing haematopoietic stem cell transplantation were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for use in haematopoietic stem cell transplantation. This medicine in combination with rimiducid has been designated as an orphan medicinal product in the United States for 'replacement T-cell therapy for the treatment of immunodeficiency and graft versus host disease after allogeneic hematopoietic stem cell transplant'.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 19 May 2016 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, 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	Allogeneic donor-derived ex-vivo expanded T lymphocytes transduced with a retroviral vector containing inducible caspase 9 and truncated CD19	Treatment in haematopoietic stem cell transplantation
Bulgarian	Алогенни донорски Т-лимфоцити, разширени ex-vivo, трансдуцирани с ретровирусен вектор съдържащ индуцируема каспаза 9 и скъсен CD19	Лечение при трансплантация на хемопоетични стволови клетки
Croatian	Alogeni od donora dobiveni ex-vivo ekspandirani T limfociti zaraženi retrovirusnim vektorom koji sadrži inducibilnu kaspazu 9 i okrnjen CD19	Liječenje u transplantaciji hematopoetskih matičnih stanica
Czech	Allogenní ex vivo expandované dárcovské T lymfocyty transdukované retrovirovým vektorem obsahujícím kaspásu 9 a zkrácený CD 19	Léčba transplantace hemopoetickými zárodečnými buňkami
Danish	Allogeneisk donor-deriveret ex-vivo ekspanderede T lymfocytter transduceret med en retroviral vektor, som indeholder inducerbar caspase 9 og trunkeret CD19	Behandling i hæmatopoietisk stamcelletransplantation
Dutch	Allogenene donor-afgeleide ex-vivo geëxpandeerde T lymfocyten getransduceerd met een retrovirale vector welke induceerbaar caspase 9 and getrunceerd CD19 bevat	Behandeling in haematopoiëtische stemceltransplantatie
Estonian	Ex-vivo paljundatud allogeensed doonorist lähtuvad T-lümfotsüüdid, mida on transdutseeritud indutseeritavat kaspaas-9 ja lühendatud CD19 sisaldava retroviirusvektoriga	Kasutamiseks hematopoeetiliste tüvirakkude transplantatsiooni ravis.
Finnish	Allogeniset luovuttajaperäiset ex-vivo monistetut T-lymfosyytit, joihin on siirretty retroviraalinen vektori, joka sisältää indusoitavan kaspaasi 9:n ja typistetyn CD 19	Hoito hematopoeettisen kantasolusiirron yhteydessä
French	Lymphocytes T, de croissance ex-vivo, allogéniques, dérivés de donneur transduits avec un vecteur rétroviral contenant caspase 9 inductible et CD 19 tronqué	Traitement dans la greffe de moëlle osseuse
German	Allogene Spender-T-Lymphozyten, ex-vivo vermehrt, transduziert mit einem retroviralen Vektor der eine induzierbare Caspase 9 und ein gekuerztes CD19 enthält	Behandlung in hämatopoetischer Stammzelltransplantation
Greek	Τ λεμφοκύτταρα προερχόμενα από αλλογενή δότη και ανεπτυγμένα ex-vivo μεταγωγημένα με ένα ρετροϊικό φορέα που περιέχει διεγέρσιμο κασπάσης 9 και κολοβωμένη CD19	θεραπεία σε μεταμόσχευση αρχέγονων αιμοποιητικών κυττάρων

[1] At the time of designation

Language	Active ingredient	Indication
Hungarian	Indukálható kaszpáz 9-et és csonkított CD19-et tartalmazó retrovirális vektorral transzdukált, allogén donortól származó ex-vivo expandált T limfociták	Hematopoietikus őssejt-transzplantáció esetén alkalmazandó
Italian	Lymphocytes T da donatore allogeneico expansi ex –vivo, trasdotti con un vettore retrovirale contenente caspasi inducibile 9 and CD19 troncato	Trattamento nel trapianto di cellule staminali ematopoietiche
Latvian	Allogēni no donora iegūti *ex-vivo* pavairoti T limfocīti, kas transducēti ar retrovīrusa vektoru, kas satur inducējamu kaspāzi 9 un saīsinātu CD19	Ārstēšanai hematopoētisko cilmes šūnu transplantācijā
Lithuanian	Alogeniniai iš donoro išskirti ir *ex vivo* pagausinti T limfocitai, transdukuoti su retro viruso vektoriumi, turinčiu indukuojamąją kaspazę 9 ir sutrumpintą CD19	Taikoma hematopoetinių kamieninių ląstelių transplantacijų gydyme
Maltese	Limfoċiti T alloġeniċi mnissla min donaturi, mwassa' *ex vivo*, trasformati permezz ta' vettur retrovirali li fih *caspase* 9 induċibbli u CD19 imqassar	Kura fi trapjant ta' ċelloli staminali ematopojetiċi
Polish	Allogeniczne limfocyty T uzyskane od dawcy, namnożone ex vivo i transdukowane retrowiralnym nośnikiem zawierającym indukowalną Kaspazę 9 oraz skrócone białko CD19	Leczenie w przebiegu przeszczepu hematopoetycznych komórek macierzystych
Portuguese	Linfócitos T derivados de dador alogénico expandidos *ex-vivo* e transduzidos com um vetor retroviral contendo a caspase 9 induzível e CD19 truncada	Tratamento em transplantes de células estaminais hematopoiéticas
Romanian	Celule T alogenice provenite de la donator si expandate ex vivo transduse cu un vector retroviral ce conţne caspaza 9 inductibilă şi CD19 truncat	Tratament în transplantul de celule stem hematopoetice
Slovak	Darcovské alogénne ex-vivo expandované T lymfocyty transdukované s retrovirálnym vektorom obsahujúcim indukovateľnú kaspázu 9 a skrátený CD19	Liečba pri transplantácii hematopoietických kmeňových buniek
Slovenian	T limfociti alogenski dajalcev, ekspandirani ex vivo in transducirani z retrovirusnim vektorjem, ki vsebujej inducibilno kaspazo 9 in skrajšan CD 19	Zdravljenje pritransplantaciji hematopoetskih matičnih celic
Spanish	Linfocitos T ex vivo derivados de donante alogénico transducidos con un vector retroviral conteniendo la caspase 9 inducible y CD-19 truncado	Tratamiento en el trasplante de células madre hematopoyéticas
Swedish	Ex-vivo expanderade allogena T-lymfocyter från donator, transducerade med en retroviral vector innehållande inducerbar caspase 9 och trunkerad CD19	Behandling vid hematopoetisk stamcellstransplantation
Norwegian	Allogen donor deriverte ex-vivo ekspanderte T-lymfocytter transdusert med en retroviral vektor inneholdende induserbart kaspase 9 og trunkert CD19	Behandling ved hematopoetisk stamcelletransplantasjon

Language	Active ingredient	Indication
Icelandic	Ósamgena gjafatengd ex vivo útví kkað T-eitilfrumur transduced með retrovíral ferju sem inniheldur virkjanlega caspace 9 og truncadet CD19	Meðferð á stofnfrumublóðfrumu ígræðslu