



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF

humanised antibody fragment (Ep-CAM)-truncated *Pseudomonas* exotoxin A fusion protein for the treatment of Ep-CAM-positive squamous cell carcinoma of the head and neck

On 20 June 2005, orphan designation (EU/3/05/290) was granted by the European Commission to CanReg (Europe) Limited, Ireland, for humanised antibody fragment (Ep-CAM)-truncated *Pseudomonas* exotoxin A fusion protein for the treatment of Ep-CAM-positive squamous cell carcinoma of the head and neck.

The sponsorship was transferred to Viventia Biotech (EU) Limited, United Kingdom, in November 2005.

What is squamous cell carcinoma of the head and neck?

Head and neck cancer is the name given to a variety of malignant tumours that have their origin in the head and neck region (particularly in the mouth area). This definition excludes tumours that occur within the brain or the eyes. The term malignant defines these tumours as having the potential to infiltrate locally and spread to other parts of the body.

The most common type of malignant tumours in the head and neck region is squamous cell carcinoma. Most of the lining of the mouth, nose and throat is made up of a type of cells known as squamous cells. When a malignancy arises in this type of cells, the tumour is called squamous cell carcinoma. Squamous cell carcinoma is often associated with the use of tobacco and/or heavy consumption of alcohol.

The "Epithelial Cell Adhesion Molecule" (Ep-CAM) is a molecule involved in the interactions between cells that form the layers covering the internal and external surfaces of the body (the so called epithelial cells). Ep-CAM seems also to play a role in the growth of these cells, and its function seems to be increased in those cells that are transformed into cancer cells.

Ep-CAM-positive squamous cell carcinoma of the head and neck is life-threatening.

What are the methods of treatment available?

The main treatment of cancer of the head and neck includes surgery, radiotherapy (using high-dose x-rays or other high-energy rays to kill cancer cells) and chemotherapy (using drugs to kill cancer cells). Other types of treatments include immunotherapy (using drugs that stimulate the body's own immune system to kill cancer cells). Treatment for head and neck cancer is very dependent on the type of cancer, where it has occurred, how large it is and how far it has spread. For many patients, cancer treatment involves a combination of surgery and radiation therapy. Several products were authorised for the condition in the Community at the time of submission of the application for orphan drug designation.

Humanised antibody fragment (Ep-CAM)-truncated *Pseudomonas* exotoxin A fusion protein could be of potential significant benefit for the treatment of Ep-CAM-positive squamous cell carcinoma of the head and neck, because it might improve the long-term outcome of the patients. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

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

According to the information provided by the sponsor, Ep-CAM-positive squamous cell carcinoma of the head and neck was considered to affect not more than 211,000 persons in the European Union.

How is this medicinal product expected to act?

Antibodies are proteins in the body that target and link specific shapes (the so-called antigens) on the surface of various cells. The humanised antibody fragment (Ep-CAM) of the medicinal product recognises and binds to the Ep-CAM cell surface marker on the cancer cell. After the binding, the whole product enters the Ep-CAM positive cell and is activated, then the activated toxin part inhibits protein synthesis and induces cell death.

What is the stage of development of this medicinal product?

The evaluation of the effects of humanised antibody fragment (Ep-CAM)-truncated *Pseudomonas* exotoxin A fusion protein in experimental models is ongoing.

At the time of submission of the application for orphan designation, clinical trials in patients with Ep-CAM-positive squamous cell carcinoma of the head and neck were ongoing.

Humanised antibody fragment (Ep-CAM)-truncated *Pseudomonas* exotoxin A fusion protein was not marketed anywhere worldwide for the treatment Ep-CAM-positive squamous cell carcinoma of the head and neck, at the time of submission. Orphan designation of humanised antibody fragment (Ep-CAM)-truncated *Pseudomonas* exotoxin A fusion protein was granted in the United States in January 2005 for treatment of Ep-CAM-positive squamous cell carcinoma of the head and neck.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 12 May 2005 a positive opinion recommending the grant of the above-mentioned designation.

Opinions on orphan medicinal products designations are based on the following cumulative criteria: (i) the seriousness of the condition, (ii) the existence or not of alternative methods of diagnosis, prevention or treatment and (iii) either the rarity of the condition (considered to affect not more than five in ten thousand persons in the Community) or the insufficient return of development investments.

Designated orphan medicinal products are still investigational products which were considered for designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of the quality, safety and efficacy will be necessary before this product can be granted a marketing authorisation.

For more information:

Sponsor's contact details:

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*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union (EU 25), Norway, Iceland and Lichtenstein. This represents a population of 459,700,000 (Eurostat 2004). This estimate is based on available information and calculations presented by the sponsor at the time of the application.

Patients' associations contact points:

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**Translations of the active ingredient and indication in all EU languages
and Norwegian and Icelandic**

Language	Active Ingredient	Indication
English	Humanised antibody fragment (Ep-CAM)-truncated <i>Pseudomonas</i> exotoxin A fusion protein	Treatment Ep-CAM-positive squamous cell carcinoma of the head and neck
Czech	Humanizovaný protilátkový fragment (Ep-CAM)- zkrácený pseudomonádový exotoxin A fúzní protein	Léčba Ep-CAM-pozitivního skvamocelulárního karcinomu hlavy a krku
Danish	Humaniseret antistof fragment (EpCAM)-trunkeret <i>Pseudomonas</i> Exotoxin A fusionsprotein	Behandling af Ep-CAM-positiv pladeepitelcarcinom i hoved- og halsregion
Dutch	Gehumaniseerd antilichaam fragment (Ep-CAM)- getrunceerd <i>Pseudomonas</i> exotoxin A fusie proteïne	Behandeling van Ep-CAM-positief plaveiselcelcarcinoma van het hoofd en de nek
Estonian	Ep-CAM spetsiifilise humaniseeritud antikeha fragmendi ja lühendatud <i>Pseudomonas</i> eksotoksiin A liitvalk	Pea- ja kaelapiirkonna Ep-CAM-positiivse sarvestuva lamerakulise vähi ravi
Finnish	Humanisoitu vasta- ainefragmentti (Ep-CAM)- lyhennetty <i>Pseudomonas</i> exotoxin A fuusioproteiini	Ep-CAM-positiivisen levyepiteelisyövän hoito pään ja kaulan alueella
French	Protéine de fusion formée du fragment d'anticorps humanisé (Ep-CAM) liée à l'exotoxine A tronquée de <i>Pseudomonas</i>	Traitement du cancer Ep-CAM-positif squameux de la tête et du cou
German	Humanisiertes Antikörper-fragment (Ep-CAM)-- eine trunkierte Form des <i>Pseudomonas</i> -Exotoxin A Fusionsproteins	Behandlung von Ep-CAM-positivem Plattenepithelkarzinom des Kopf-Hals-Bereiches
Greek	Ανθρωποποιημένο θραύσμα αντισώματος συνδεδεμένο με ακρωτηριασμένη πρωτεΐνη σύντηξης εξωτοξίνης Α της <i>Pseudomonas</i>	Αγωγή Ep-CAM-θετικού καρκίνου κεφαλής και τραχήλου από πλακώδες επιθήλιο
Hungarian	Humanizált ellenanyag fragmens (Ep-CAM) és megcsonkított <i>Pseudomonas</i> exotoxin A fúziós fehérje	Ep-CAM-pozitív fej és a nyak laphámsejt-carcinoma kezelése

Italian	Proteina di fusione del frammento dell'anticorpo umanizzato (Ep-CAM) e dell'endotossina A troncata di <i>Pseudomonas</i>	Trattamento del carcinoma a cellule squamose della testa e del collo Ep-CAM-positivo
Latvian	Humanizēts (Ep-CAM)-saīsināta <i>Pseudomonas</i> eksotoksīna A savienojuma proteīna antivielas fragments	Galvas un kakla Ep-CAM-pozitīvas plakanšūnu karcinomas ārstēšana
Lithuanian	Humanizuotas antikūno fragmentas (Ep-CAM) – sutrumpintas <i>Pseudomonas</i> egzotoksino A susijungimo baltymas	Ep-CAM teigiamos galvos ir kaklo ragėjančių ląstelių karcinomos gydymas
Polish	Humanizowany fragment przeciwciała (Ep-CAM) - białko łączące egzotoksyny A <i>Pseudomonas</i> pozbawione domeny wiązania z komórką	Leczenie płaskokomórkowego Ep-CAM-dodatniego raka skóry głowy i szyi
Portuguese	Proteína de fusão do fragmento de anticorpo humanizado (Ep-CAM) – truncada de exotoxina A da <i>Pseudomonas</i>	Tratamento do carcinoma das células escamosas positivo a Ep-CAM da cabeça e pescoço
Slovak	Humanizovaný protilátkový fragment (EP-CAM)-skrátенý <i>Pseudomonádový</i> exotoxín A, zlúčený proteín	Liečba Ep-CAM-pozitívneho skvamocelulárneho karcinómu hlavy a krku
Slovenian	Humanizirani fragment protitelesa (Ep-CAM) za <i>Pseudomonas</i> eksotoksin A	Zdravljenje Ep-CAM pozitivnih ploščatoceličnih karcinomov glave in vrata
Spanish	Fragmento del anticuerpo humanizado para Ep-CAM asociado la proteína de fusión truncada de la exotoxina A de <i>Pseudomonas</i>	Tratamiento del carcinoma escamoso de cabeza y cuello positivo para Ep-CAM-
Swedish	human antikroppsfragment (Ep-CAM)-trunkerad <i>Pseudomonas</i> exotoxin A fusionsprotein	Behandling av Ep-CAM-positiv skivepitelcancer i huvud-halsregionen
Norwegian	Fusjonsprotein humanisert antistoff fragment (anti Ep-CAM) trunkert <i>Pseudomonas</i> eksotoksin A	Behandling av Ep-CAM-positivt plateepitelkarsinom i hode-halsregionen
Icelandic	Manngert stýft mótefnabrot (Ep-CAM)- <i>Pseudomonas</i> exotoxín A samtengingarprótein.	Meðferð við Ep-CAM-jákvæðu flöguþekjukrabbameini á höfði og hálsi