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 genetically modified allogenic (human) tumour cells for the expression of IL-7, GM-CSF, CD80 and CD154, in fixed combination with a DNA-based double stem loop immunomodulator (dSLIM) for the treatment of renal cell carcinoma

On 23 October 2006, orphan designation (EU/3/06/405) was granted by the European Commission to MOLOGEN AG, Germany, for genetically modified allogenic (human) tumour cells for the expression of IL-7, GM-CSF, CD80 and CD154, in fixed combination with a DNA-based double stem loop immunomodulator (dSLIM) for the treatment of renal cell carcinoma.

What is renal cell carcinoma?
Renal cell carcinoma (also called cancer of the kidney or renal adenocarcinoma) is a disease in which cancer (malignant) cells are found in certain tissues of the kidney. Inside each kidney, there are tiny tubules that filter and clean the blood, taking out waste products, and making urine. Renal cell carcinoma is a cancer of the lining of the tubules in the kidney. Renal cell carcinoma accounts for approximately 85% of all kidney cancers. Signs of cancer are difficult to detect in early stages of the disease, and about half of the patients are diagnosed when the disease has spread around the kidney or to distant parts of the body. Renal cell carcinoma is life-threatening.

What is the estimated number of patients affected by the condition?
At the time of designation renal cell carcinoma affected approximately 3.5 in 10,000 people in the European Union (EU)[*]. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP). This is below the threshold for orphan designation which is 5 in 10,000. This is equivalent to a total of around 161,000 people.

What treatments are available?
There are treatments for most patients with renal cell cancer. These may include surgery (taking out the cancer in an operation), chemotherapy (using drugs to kill cancer cells), radiation therapy (using high-dose x-rays or other high-energy rays to kill cancer cells), hormone therapy (using hormones to stop cancer cells from growing), and biological therapy (using the body's immune system to fight cancer). The primary therapies for advanced cancer are biologic agents, such as interleukin-2 and interferon-α. Other anticancer agents were also authorised in the Community for treatment of renal cell carcinoma at the time of submission of the application for orphan designation.

[*]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 Liechtenstein. This represents a population of 459,700,000 (Eurostat 2004).

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Satisfactory argumentation has been submitted by the sponsor to justify the assumption that genetically modified allogenic (human) tumour cells for the expression of IL-7, GM-CSF, CD80 and CD154, in fixed combination with a DNA-based double stem loop immunomodulator (dSLIM) might be of potential significant benefit for the treatment of renal cell carcinoma mainly because this could represent an additional treatment option for patients with renal cell carcinoma, when cancer cells have spread to other parts of the body (metastasis). This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

How is this medicine expected to work?
The medicinal product is a so called tumour vaccine, meaning that it is a treatment aiming at activating the patients' own immune system (the body's natural defence system) against the tumour cells. The product consists of two compounds: the first substance is human renal cell carcinoma cells that have been modified to express specific molecules on their surface so that the immune system can be waken up to recognise, and ultimately to destroy, the tumour cells. These cells are modified in a way that they start producing molecules called IL-7, GM-CSF, CD80 and CD154. IL-7 and GM-CSF are so called cytokines that are important signalling substances for the immune system, while CD80 and CD154 are molecules that support the immune system in its work. The second substance in this combination product is the so called DNA-based double stem loop immunomodulator (dSLIM) that is thought to increase the activation of the immune system against the renal cell carcinoma cells. By activating the immune system of the patients specifically against the renal cell carcinoma cells, this medicinal product is expected to decrease the growth of these tumours.

What is the stage of development of this medicine?
The effects of genetically modified allogenic (human) tumour cells for the expression of IL-7, GM-CSF, CD80 and CD154 were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with renal cell carcinoma were ongoing.

Genetically modified allogenic (human) tumour cells for the expression of IL-7, GM-CSF, CD80 and CD154 was not authorised anywhere worldwide for the treatment of renal cell carcinoma, nor designated as orphan medicinal product elsewhere for this condition, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 6 September 2008 a positive opinion recommending the grant of the above-mentioned 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 Community) 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.

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

Language	Active Ingredient	Indication
English	Genetically modified allogeneic (human) tumour cells for the expression of IL-7, GM-CSF, CD80 and CD154, in fixed combination with a DNA-based double stem loop immunomodulator (dSLIM)	Treatment of renal cell carcinoma
Czech	Geneticky modifikované allogenní (humánní) tumorosní buňky pro expresi IL-7, GM-CSF, CD80 a CD154,kombinované s DNA dvojitě centrálním smyčkovitým imunomodulátorem (dSLIM).	Léčba karcinomu ledvin
Danish	Genetisk modificerede allogene (humane) tumorceller for udtrykkelse af IL-7, GM-CSF, CD80 og CD154, i fast kombination med en DNA-baseret håndvægtsformet immunmodulator (dSLIM) (det er navnet brugt under den regulatoriske klassifikationsprocess)	Behandling af renalcellekarcinom
Dutch	Genetisch gemodifiëerde allogene (humane) tumorcellen voor de expressie van IL-7, GM-CSF, CD80 en CD154, in vaste combinatie met een DNA-gebaseerd, haltervormige immuunmodulator (dSLIM)	Behandeling van niercelcarcinoom
Estonian	IL-7, GM-CSF, CD80 ja CD154 ekspresserivad geneetiliselt modifitseeritud allogeensed (inimese) kasvajarakud, mis on fikseeritud kombinatsioonis DNA-põhise kaksiktüviahelaga immunomodulaatoriga (dSLIM) (see on nimi, mida kasutatakse regulatoorse klassifitseerimise perioodil)	Neeru vähi-ravi
Finnish	Allogeeniset (ihmisen) kasvainsolut, jotka on geneettisesti muunneltu IL-7:n, GM-CSF:n, CD80:n ja CD154:n ilmentymistä varten, yhdistettynä DNA-pohjaiseen kaksoiskantaiseen immunomodulaattoriin (dSLIM)	Munuaiskarsinooman hoito
French	Cellules tumorales allogéniques (humaines) génétiquement modifiées exprimant IL-7, GM-CSF, CD80 et CD154, associées à un immuno-modulateur en boucle à double tige à base d'ADN (dSLIM)	Traitement du carcinome rénal
German	Gentechnisch modifizierte allogene (humane) Tumorzellen für die Expression von IL-7, GM-CSF, CD80 und CD154, in fixer Kombination mit einem DNA-baiserten, handelförmigem Immunmodulator (dSLIM)	Behandlung des Nierenzellkarzinoms

Greek	Γενετικά τροποποιημένα αλλογενή (ανθρώπινα) νεοπλασματικά κύτταρα για την έκφραση των IL-7, GM-CSF, CD80 και CD154, σε συνδυασμό με ανοσορρυθμιστή διπλού στελέχους-θηλιάς με βάση το DNA (dSLIM)	Θεραπεία του νεφροκυτταρικού καρκινώματος
Hungarian	IL-7, GM-CSF, CD80 és CD154 expressziójára genetikailag módosított allogen (humán) tumorsejt fix kombinációban DNS alapú súlyzó alakú immunmodulátorral (dSLIM)	Vesekarcinoma kezelése
Italian	Cellule tumorali allogeniche (umane), geneticamente modificate per l'espressione di IL-7, GM-CSF, CD80 e CD154, in combinazione con un immunomodulatore a doppio stem-loop (dSLIM) basato su DNA	Trattamento del carcinoma renale
Latvian	Ģenētiski modificētas alogēnas (cilvēka) tumora šūnas IL-7, GM-CSF, CD80 un CD154 ekspresijai fiksētā kombinācijā ar DNS bāzes dubultcilmes cilpas imūnmodulatorulatoru (dSLIM) (šis ir nosaukums, ko izmanto regulatīvā klasifikācijas procesa laikā)	Nieru karcinomas ārstēšana
Lithuanian	Genetiškai modifikuotos alogeninės (žmogaus) auglio ląstelės,naudojamos IL-7, GM-CSF, CD80 ir CD154 ekspresijai fiksuotoje kompozicijoje su DNR dvigubos kilpos struktūros imunomoduliatoriumi (dSLIM) (šis pavadinimas naudojamas reguliacijos procesų klasifikacijoje)	Inkstų adenokarcinomos gydymas
Polish	Genetycznie modyfikowane, allogeniczne (ludzkie) komórki nowotworowe z ekspresją IL-7, GM_CSF, CD80 i CD154 w stałym, połączeniu z opartym na DNA dwutrzonowym immunomodulatorem pętlowym (dSLIM)	Leczenie raka nerki
Portuguese	Células (humanas) com tumor alogénico geneticamente modificadas para a expressão de IL-7, GM-CSF, CD80 e CD154, em combinação fixa com um imunomodulador em forma de anel de hélice dupla baseado em ADN (dSLIM)	Tratamento do carcinoma das células renais
Slovak	Geneticky modifikované alogénne (ľudské) nádorové bunky pre expresiu IL-7, GM-CSF, CD80 a CD154, vo fixnej kombinácii s imunomodulátorom na báze DNA tvaru činky (dSLIM) (názov používaný počas registračného hodnotiaceho procesu)	Liečba karcinómu obličky
Slovenian	Alogene (humane) tumorske celice, genetsko spremenjene za ekspresijo genov IL-7, GM-CSF, CD80 ter CD154, kombinirane z imunskim modulatorjem (dSLIM) vezanim na matični zanki dvovijačne DNK.	Zdravljenje raka ledvičnih celic
Spanish	Células tumorales alogénicas (humanas) modificadas genéticamente para la expresión de IL-7, GM-CSF, CD80 y CD154, en combinación fija con un estimulador immunitario de doble bucle basado en ADN	Tratamiento de carcinoma de células renales

Swedish	Genetiskt manupelerade allogena (männskliga) tumörceller för expression av IL-7, GM-CSF, CD80 och CD154, i fast kombination med en DNA-baserad, hantelformad immunomodulator (dSLIM)	Behandling av njurcellscancer
Norwegian	Genetisk modifiserte allogene (humane) tumorceller for ekspresjon av IL-7, GM-CSF, CD80 og CD154, kombinert med en DNA-basert, manualformet immunmodulator (dSLIM)	Behandling av nyrecellekarsinom
Icelandic	Ósamgena (manna) æxlisfrumur erfðabreyttar til að tjá IL-7, GM-CSF, CD80 og CD154 í föstu hlutfalli við DNA byggðan tvístofna lykkjulaga ónæmisbreyti (dSLIM)	Meðferð á nýrnafrumukrabbameini