

2 February 2016
EMA/COMP/861603/2015
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Live attenuated *Listeria monocytogenes* transfected with plasmids encoding the HPV-16E7 protein fused to a truncated fragment of the Lm protein listeriolysin O for the treatment of anal cancer

On 11 January 2016, orphan designation (EU/3/15/1602) was granted by the European Commission to Dr Ulrich Granzer, Germany, for live attenuated *Listeria monocytogenes* transfected with plasmids encoding the HPV-16E7 protein fused to a truncated fragment of the Lm protein listeriolysin O (also known as axalimogene filolisbac) for the treatment of anal cancer.

What is anal cancer?

Anal cancer is a cancer of the tissues of the anus. Bleeding from the anus is often the first sign of the disease. Other symptoms include pain, discomfort and itching and small lumps around the anus, difficulty controlling bowels (faecal incontinence) and ulcers. Sometimes the cancer causes no symptoms.

A number of risk factors are linked to anal cancer, one of them being infection with the human papilloma virus (HPV), the same virus that causes cervical cancer.

Anal cancer is a long-term debilitating disease due to its symptoms such as incontinence, bleeding, itching and non-healing ulcers. This disease is also life threatening and associated with shortened life expectancy.

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

At the time of designation, anal cancer affected approximately 0.4 in 10,000 people in the European Union (EU). This was equivalent to a total of around 21,000 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 512,900,000 (Eurostat 2015).

What treatments are available?

At the time of designation, several medicines were authorised for the treatment of anal cancer in the EU. Treatments for anal cancer included radiotherapy (treatment with radiation) and chemotherapy (medicines to treat cancer).

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with anal cancer because early studies show that it might improve survival in patients whose disease came back after previous standard treatment. 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 medicine works by stimulating the patient's immune system, the body's natural defences, so that it targets and destroys the cancer cells. It is made of live *Listeria monocytogenes* bacteria, which have been attenuated (weakened) so that they do not cause disease in humans. The bacteria have also been modified to produce large amounts of the 'human papilloma virus 16 E7' (HPV-16E7 protein). HPV-16E7 is found at high levels on cells in anal cancer caused by HPV type 16. The HPV-16E7 protein on the bacteria has been attached to a protein called listeriolysin O, which helps it to stimulate the body's immune system.

When the medicine is given, the patient's immune system is expected to learn to treat HPV-16E7 as 'foreign'. This is expected to stimulate an immune response against the cancer cells carrying HPV-16E7 on their surface, resulting in the immune system attacking and destroying the cancer cells.

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 anal cancer were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for anal cancer. Orphan designation of the medicine had been granted in the United States for treatment of HPV-positive associated anal cancer.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 10 December 2015 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 languages¹, Norwegian and Icelandic

Language	Active ingredient	Indication
English	Live attenuated <i>Listeria monocytogenes</i> transfected with plasmids encoding the HPV-16E7 protein fused to a truncated fragment of the Lm protein listeriolysin O	Treatment of anal cancer
Bulgarian	Жива атенюирана бактерия <i>Listeria monocytogenes</i> трансфектирана с плазмиди, кодиращи HPV-16E7 протеин, свързан със скъсен фрагмент на Lm протеина листериолизин O	Лечение на рак на ануса
Croatian	Živa atenuirana <i>Listeria monocytogenes</i> transficirana plazmidom koji kodira za protein HPV-16E7 vezan na skraćeni oblik Lm proteina listeriolizin O	Liječenje karcinoma anusa
Czech	Živé oslabené bakterie <i>Listeria monocytogenes</i> transfekované plazmidy kódujícími protein lidského papilomaviru HPV-16E7 fúzovaný se zkráceným fragmentem Lm proteinu LLO	Léčba análního karcinomu
Danish	Levende svækket <i>Listeria monocytogenes</i> transficeret med plasmid-kodende HPV-16E7-protein sammensmeltet med et forkortet fragment af Lm-proteinet Listeriolysin O	Behandling af analcancer
Dutch	Levende geattenueerde <i>Listeria monocytogenes</i> die getransfecteerd zijn met plasmiden coderend voor HPV-16E7-eiwit gefuseerd aan een getrunceerd fragment van het Lm-eiwit listeriolysine O	Behandeling van anuskanker
Estonian	Elusad nõrgestatud listeriabakterid <i>Listeria monocytogenes</i> , mida on transfekteeritud plasmiididega, mis kodeerivad HPV-16E7 valku sulandunud Lm valgu listeriolüsiin O kärbitud fragmenti	Pärakuvähi ravi
Finnish	Eläviä heikennettyjä <i>Listeria monocytogenes</i> - bakteereja, jotka on transfektoitu plasmideilla. Nämä plasmidit koodittavat HPV-16E7-proteiinia, joka on fuusioitu Lm-proteiini listeriolysiini O:n katkaistuun fragmenttiin	Peräaukon syövän hoito
French	Bactéries <i>Listeria monocytogènes</i> atténuées vivantes transfectées avec des plasmides encodant la protéine HPV-16E7 fusionnée à un fragment tronqué de la protéine listériolysine O Lm	Traitement du cancer de l'anus
German	Lebende, abgeschwächte <i>Listeria monocytogenes</i> -Bakterien, die biotechnologisch verändert wurden mit dem chimären humanen epidermalen Wachstumsfaktor-Rezeptor 2, der an eine verkürzte Form des Lm-Proteins Listeriolysin O fusioniert ist	Behandlung des Analkarzinoms

¹ At the time of designation

Language	Active ingredient	Indication
Greek	Ζώντες εξασθενημένοι μικροοργανισμοί <i>Listeria monocytogenes</i> επιμολυσμένοι με πλασμίδια που κωδικοποιεί την πρωτεΐνη HPV-16E7 συντηγμένη σε αποκομμένο τεμάχιο της πρωτεΐνης λιστεριολυσίνης O του Lm	Θεραπεία του καρκίνου του πρωκτού
Hungarian	A <i>Listeria monocytogenes</i> listeriolizin O fehérjéjének csonka fragmentjével fuzionált HPV-16E7 fehérjét kódoló plazmidokkal transzfektált élő, attenuált, <i>Listeria monocytogenes</i>	Végbélnyílásrák kezelése
Italian	<i>Listeria monocytogenes</i> viva attenuata trasfettata con plasmidi codificanti la proteina HPV-16E7 fusa a un frammento troncato della listeriolisina O della <i>Listeria monocytogenes</i>	Trattamento del cancro anale
Latvian	Dzīva novājināta <i>Listeria monocytogenes</i> , kurai veikta transfekcija ar plazmīdām, kas kodē HPV-16E7 proteīna savienojumu ar Lm proteīna listeriolizīna O nošķeltu fragmentu	Tūpļa ļaundabīga audzēja ārstēšana
Lithuanian	Gyvos susilpnintos <i>Listeria monocytogenes</i> , transfekuotos su plazmidėmis, koduojančiomis HPV-16E7, baltymą, sulietą su sutrumpintu Lm baltymo listeriolizino O fragmentu	Išangės vėžio gydymas
Maltese	<i>Listeria monocytogenes</i> ħaj u attenwat transfettat bi plasmids li jikkodifikaw il-proteina HPV-16E7 magħquda ma' framment imqassar tal-proteina ta' Lm listeriolysin O	Kura tal-kanċer anali
Polish	Żywe, atenuowane bakterie <i>Listeria monocytogenes</i> transfekowane plazmidami kodującymi białko HPV-16E7 zespolone ze skróconym fragmentem listeriolizyny O białka Lm	Leczenie raka odbytu
Portuguese	<i>Listeria monocytogenes</i> viva atenuada transfetada com plasmídeos que codificam a proteína HPV-16E7 fundida com um fragmento truncado da proteína listeriolisina O da Lm	Tratamento do carcinoma do canal anal
Romanian	Tulpina vie atenuata de <i>Listeria monocytogenes</i> (Lm) transfectată cu plasmidele care codifică proteina HPV-16E7 fuzionată cu un fragment trunchiat al proteinei listeriolizina O a Lm	Tratamentul cancerului anal
Slovak	Živé oslabené baktérie <i>Listeria monocytogenes</i> transfekované plazmidmi kódujúcimi HPV-16E7 proteín zlúčený so skráteným fragmentom Lm proteínu Listeriolyzín O	Liečba análnej rakoviny
Slovenian	Živa, atenuirana <i>Listeria monocytogenes</i> , transficirana s plazmidi z zapisom za fuzijsko beljakovino HPV-16E7, vezano na skrajšani fragment beljakovine Lm listeriolizina O	Zdravljenje analnega raka

Language	Active ingredient	Indication
Spanish	<i>Listeria monocytogenes</i> viva atenuada y transfectada con plásmidos que codifican proteína HPV-16E7 fusionada a un fragmento truncado de listeriolisina O de la Lm	Tratamiento del cáncer de ano
Swedish	Levande försvagade <i>Listeria monocytogenes</i> , transfekterade med plasmider som kodar för HPV-16E7-protein fuserat till ett förkortat fragment av Lm-proteinet Listeriolysin O	Behandling av analcancer
Norwegian	Levende, svekkede <i>Listeria monocytogenes</i> transfektert med plasmider som koder HPV-16E7-protein fusjonert til et beskåret fragment av Lm-proteinet Listeriolysin O	Behandling av analkreft
Icelandic	Lifandi veikluð <i>Listeria monocytogenes</i> , veiruleidd með plasmíðum sem tjá HPV-16E7-prótein sem sameinast stýfðu broti af Lm-próteninu Listeriolysin O	Meðferð við krabbameini í endaparmi