



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

recombinant fusion protein of circularly-permuted IL-4 and pseudomonas exotoxin A, [IL-4(38-37)-PE38KDEL] for the treatment of glioma

On 3 June 2008, orphan designation (EU/3/08/553) was granted by the European Commission to Gregory Fryer Associates Ltd, United Kingdom, for recombinant fusion protein of circularly-permuted IL-4 and pseudomonas exotoxin A, [IL-4(38-37)-PE38KDEL] for the treatment of glioma.

What is glioma?

Glioma is a type of brain tumour that begins in 'glial' cells (the cells that surround and support nerve cells). Patients with gliomas can suffer from different symptoms, depending on the part of the brain where the tumour develops. Glioma is a life-threatening disease.

What are the methods of treatment available?

Treatment for glioma may combine different methods such as surgery, radiotherapy (treatment with radiation) and chemotherapy (medicines used to treat cancer). Other treatments are used to relieve the disease's symptoms, including corticosteroids that help to reduce pressure within the skull, and medicines that help with the control of seizures (fits). At the time of orphan designation, several medicines were authorised in the European Union for the treatment of glioma and its symptoms. Recombinant fusion protein of circularly-permuted IL-4 and pseudomonas exotoxin A, [IL-4(38-37)-PE38KDEL] could be of benefit in the treatment of glioma because it seems to have less severe side effects and because it accumulates in the area in the brain where the tumour is developing. These assumptions will need to be confirmed at the time of marketing authorisation, to maintain the orphan status of the medicine.

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

Based on the information provided by the sponsor and previous knowledge of the Committee, glioma was considered to affect approximately 1 in 10,000 persons in the European Union, which, at the time of designation, corresponded to about 50,000 persons.

How is this medicinal product expected to act?

Recombinant fusion protein of circularly-permuted IL-4 and pseudomonas exotoxin A, [IL-4(38-37)-PE38KDEL] is made of a bacterial toxin (exotoxin A) attached to interleukin-4 (IL-4). Exotoxin A is a toxic substance produced by the bacterium *Pseudomonas aeruginosa*, and IL-4 is a human protein that binds to a specific protein receptor found at higher levels on the surface of tumour cells compared with normal cells. Because it is attached to IL-4, the exotoxin A is concentrated at the site of the tumour, where it kills the tumour cells, reducing the size of the tumour.

* 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 27), Norway, Iceland and Liechtenstein. This represents a population of 498,000,000 (Eurostat 2006). This estimate is based on available information and calculations presented by the sponsor at the time of the application.

What is the stage of development of this medicinal product?

The effects of recombinant fusion protein of circularly-permuted IL-4 and pseudomonas exotoxin A, [IL-4(38-37)-PE38KDEL] have been evaluated in experimental models. At the time of submission of the application for orphan designation, clinical trials in patients with glioma had been completed.

At the time of submission, recombinant fusion protein of circularly-permuted IL-4 and pseudomonas exotoxin A, [IL-4(38-37)-PE38KDEL] was not authorised anywhere in the world for glioma. Orphan designation of recombinant fusion protein of circularly-permuted IL-4 and pseudomonas exotoxin A, [IL-4(38-37)-PE38KDEL] had been granted in the United States for the treatment of glioma.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted a positive opinion on 8 April 2008 recommending the granting of the above-mentioned orphan 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 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 a product's quality, safety and efficacy is necessary before it 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	Recombinant fusion protein of circulary-permuted IL-4 and pseudomonas exotoxin A, [IL-4(38-37)-PE38KDEL]	Treatment of glioma
Bulgarian	Рекомбинантен фузионен протеин от кръгово- променен IL-4 и псевдомонасен екзотоксин А [IL-4(38-37)-PE38KDEL]	Лечение на глиома
Czech	Rekombinační spojitý protein cirkulárně-permutovaného IL-4 a Pseudomonas Exotoxinu A [IL-4(38-37)-PE38KDEL]	Léčba gliomů
Danish	Rekombinant fusionsprotein af cirkulært permuteret IL-4 og Pseudomonas Exotoxin A [IL-4(38-37)-PE38KDEL]	Behandling af gliom
Dutch	Recombinant fusie-proteïne van circulair IL-4 en Pseudomonas exotoxine A [IL-4(38-37)-PE38KDEL]	Behandeling van glioma
Estonian	Rekombinantne liitvalk, mis koosneb tsirkulaarselt permuteeritud IL-4-st ja Pseudomonas'e eksotoksiin A-st [IL-4(38-37)-PE38KDEL]	Glioomi ravi
Finnish	Sirkulaarisesti permutoidun IL-4:n ja pseudomonasin eksotoksiini A:n [IL-4(38-37)-PE38KDEL] rekombinantti fuusioproteiini	Gliooman hoito
French	Protéine de fusion recombinante composée d'IL-4 permulée circulairement et d'exotoxine A de Pseudomonas [IL-4(38-37)-PE38KDEL]	Traitement des gliomes
German	Rekombinantes Fusionsprotein aus zirkulär permutiertem IL-4 und Pseudomonas Exotoxin A [IL-4(38-37)-PE38KDEL]	Behandlung von Gliomen
Greek	Ανασυνδυασμένη πρωτεΐνη σύντηξης ιντερλευκίνης 4 (IL-4) που έχει υποστεί κυκλική αναδιάταξη και εξωτοξίνης Α της ψευδομονάδας [IL-4(38-37)-PE38KDEL]	Θεραπεία του γλοιώματος
Hungarian	Cirkulárisan-permutált IL-4 és Pseudomonas Exotoxin A [IL-4(38-37)-PE38KDEL] rekombináns fúziós proteinje	Glioma kezelése
Italian	Proteina ricombinante di fusione di IL-4 permutata circolarmente ed esotossina A di Pseudomonas [IL-4(38-37)-PE38KDEL]	Trattamento del glioma
Latvian	Rekombinēts jauktais proteīns no cirkulāri mainīta IL-4 un pseidomonas eksotoksīna A [IL-4(38-37)-PE38KDEL]	Gliomas ārstēšana

Lithuanian	Rekombinantinis susijungtas baltymas iš cirkuliariai perkeltos IL4 ir Pseudomonas eksotoksino A [IL-4(38-37)-PE38KDEL]	Gliomos gydymas
Maltese	Proteina tal-fużjoni rikombinanti ta' l-IL-4 permutat b' mod ċirkulari u l-esotossina A tal-pseudomonas [IL-4(38-37)-PE38KDEL]	Kura tal-glioma
Polish	Rekombinowane białko fuzyjne spiralnie poskręcanej interleukiny-4 (IL-4) oraz egzotoksyny A wydzielanej przez Pseudomonas [IL-4(38-37)-PE38KDEL]	Leczenie glejaka
Portuguese	Proteína de fusão recombinante constituída por IL-4 circularmente permutada e Exotoxina A de Pseudomonas [IL-4(38-37)-PE38KDEL]	Tratamento do glioma
Romanian	Proteină recombinantă de fuziune compusă din IL-4 permutată circular și exotoxina A a Pseudomonas [IL-4(38-37)-PE38KDEL]	Tratamentul gliomului
Slovak	Rekombinantný spojený proteín cirkulárne-permutovaného IL-4 a Pseudomonas exotoxínu A [IL-4(38-37)-PE38KDEL]	Liečba gliómu
Slovenian	Rekombinantna fuzijska beljakovina ciklično-permutiranega IL-4 in psevdomonasnega eksotoksina A [IL-4(38-37)-PE38KDEL]	Zdravljenje glioma
Spanish	Proteína de fusión recombinante de IL-4 permutada circularmente y exotoxina A de pseudomonas [IL-4(38-37)-PE38KDEL]	Tratamiento del glioma
Swedish	Rekombinant fusionsprotein av cirkulärt permuterat IL-4 och Pseudomonas Exotoxin A [IL-4(38-37)-PE38KDEL]	Behandling av gliom
Norwegian	Rekombinant fusjonsprotein av sirkulært permutert IL-4 og Pseudomonas exotin A [IL-4(38-37)-PE38KDEL]	Behandling av gliom
Icelandic	Raðbrigða samrunaprótein úr hringumröðuðu interleukíni-4 og Pseudomonas-úteitri-A [IL-4(38-37)-PE38KDEL]	Meðhöndlun á glíóma