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 consisting of the extracellular portion of CD95 fused to the Fc part of a human IgG1 molecule for the prevention of graft versus host disease

On 31 October 2006, orphan designation (EU/3/06/411) was granted by the European Commission to Apogenix GmbH, Germany, for recombinant fusion protein consisting of the extracellular portion of CD95 fused to the Fc part of a human IgG1 molecule for the prevention of graft versus host disease.

What is graft versus host disease?
Graft-versus-host disease (GvHD) is a complication of bone marrow transplant. The bone marrow is the spongy tissue inside the large bones in the body that makes blood cells and platelets (components that help the blood to clot). Bone marrow transplants are used for diseases such as leukaemia.
In GvHD, the cells in the transplanted bone marrow react against the patients' organs, such as the stomach, gut, skin and liver, leading to organ damage. GvHD may happen in the short term, or later after transplantation, in which case a wider range of organs can be involved. GvHD is a serious, life-threatening disease.

What is the estimated number of patients at risk of developing the condition?
At the time of designation the population at risk of developing graft versus host disease was approximately 0.2 in 10,000 people in the European Union (EU)[*]. This is equivalent to a total of around 10,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

What methods of prevention are available?
Current methods for preventing GvHD aim to reduce the activity of the immune system (the body's natural defences). These methods work by targeting cells that divide often, such as the immune system cells.
Satisfactory argumentation has been submitted by the sponsor to justify the assumption that recombinant fusion protein consisting of the extracellular portion of CD95 fused to the Fc part of a human IgG1 molecule might be of potential significant benefit for the prevention of graft versus host disease, mainly because it has a new mechanism of action. 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?
Antibodies are proteins of the immune system that can bind to specific structures and help the body fight infections and other diseases. IgG1 is one type of antibody and CD95 is a protein that is located

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

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on some cells of the immune system. This medicinal product is an artificially engineered antibody-like compound where parts of CD95 and IgG1 proteins have been coupled together (fusion protein). It is thought to act by blocking the immune cells from attacking healthy tissues of the patient, thus preventing graft versus host disease.

What is the stage of development of this medicine?
The effects of recombinant fusion protein consisting of the extracellular portion of CD95 fused to the Fc part of a human IgG1 molecule were evaluated in experimental models.
At the time of submission of the application for orphan designation, no clinical trials in patients at risk of graft versus host disease were initiated.

Recombinant fusion protein consisting of the extracellular portion of CD95 fused to the Fc part of a human IgG1 molecule was not authorised anywhere worldwide for the prevention of graft versus host disease, 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 2006 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 official EU languages, Norwegian and Icelandic

Language	Active Ingredient	Indication
English	Recombinant fusion protein consisting of the extracellular portion of CD95 fused to the Fc part of a human IgG1 molecule	Prevention of Graft-versus-Host disease
Czech	Rekombinantní fúzní protein s extracelulárním CD95 fúzovaným k Fc fragmentu IgG1.	Prevence onemocnění štěpu proti hostiteli
Danish	Rekombinant fusionsprotein bestående af den ekstracellulære del af CD95 bundet til Fc delen af et humant IgG1 molekyle	Forebyggelse af graft versus host reaktion
Dutch	Recombinant fusie proteïne omvattende het extracellulair deel van CD95 gefuseerd aan het Fc fragment van humaan IgG1	Preventie van graft versus host ziekte
Estonian	Rekombinantne liitproteiin, mis koosneb CD95 ekstratsellulaarsest osast, mis on liitunud inimese IgG1 molekuli Fc osaga v	Graft versus host haiguse preventsioon
Finnish	Rekombinanttitekniikalla tuotettu fuusioproteiini, jossa on CD95:n ekstrasellulaariosa yhdistettynä ihmisen IgG1-molekyylin Fc-osaan	Käänteishyljintäreaktion esto
French	Protéine de fusion de la partie extracellulaire du CD95 et de la partie Fc de l'IgG1 humaine	Prévention de la réaction du greffon contre l'hôte
German	Rekombinantes Fusionsprotein bestehend aus dem extrazellulären Fragment von CD95 fusioniert mit dem Fc Fragment des humanen IgG1 Moleküls	Prävention der Graft-versus-Host-Reaktion
Greek	Ανασυνδυασμένη πρωτεϊνη σύντηξης αποτελούμενη από το εξωκυτταρικό τμήμα του CD95 και το τμήμα Fc του μορίου ανθρώπινης ανοσοσφαιρίνης IgG1	Πρόληψη της αντίδρασης του μοσχεύματος
Hungarian	Humán IgG1molekula F_c részéhez kötött CD95 extracelluláris részét tartalmazó rekombináns fúziós fehérje	Graft-versus-host betegség megelőzése
Italian	Proteina ricombinante di fusione, composta dalla porzione extracellulare del CD95 fusa al frammento Fc di IgG1 umana	Prevenzione della reazione del trapianto contro l'ospite
Latvian	Rekombinantās fūzijas proteīns, kas sastāv no CD95 ārpusšūnu devas savienojumā ar cilvēka IgG1 molekulas daļu	Saimnieka-transplantāta slimības novēršana
Lithuanian	Rekombinantinis sulietas baltymas, susidedantis iš ekstra-ląstelinio CD95 fragmento, sulieto su žmogaus IgG1 Fc fragmentu.	Transplantato atmetimo ligos prevencija
Polish	Rekombinowane białko fuzyjne złożone z części zewnątrzkomórkowej CD95 połączonej z częścią Fc cząsteczki ludzkiej IgG1	Zapobieganie chorobie przeszczep przeciw gospodarzowi
Portuguese	Proteína de fusão recombinante composta pela parte extracelular do CD95 fundida com a parte Fc da IgG1 humana	Prevenção da doença do enxerto contra o hospedeiro
Slovak	Rekombinantný fúzny proteín zložený z	Prevencia reakcie štepu proti

	extracelulárnej časti CD95 spojenej s časťou Fc ľudskej IgG1 molekuly	hostiteľovi
Slovenian	Rekombinantni fuzijski protein, sestavljen iz ekstracelularnega dela CD95 in Fc segmenta humanega IgG1	Preprečevanje zavrnitvene reakcije pri presaditvi
Spanish	Proteína recombinante de fusión constituída por la fracción extracelular del receptor CD95 fusionada a la fracción Fc de la molécula humana de IgG1	Prevención de la enfermedad de injerto contra huésped
Swedish	Rekombinant fusionsprotein består av extracellulär del av CD95 fusionerad till Fc delen av männsklig IgG1 molekyl	Förebyggande av graft-värd host reaktion
Norwegian	Rekombinant fusjonsprotein bestående av ekstracellulær del av CD95 kombinert med Fc-delen av humant IgG1 molekyl	Forebygging av graft-versus-host -reaksjon
Icelandic	Tengiprótein framleitt með samruna erfðatækni og samanstendur af utanfrumuhluta CD95 tengt við Fc hluta manna IgG1 sameindar	Forvörn gegn hýsilssótt