EMA/COMP/57753/2011 Rev.1
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3, 4-dihydro-4-quinazolinyl} acetic acid for the prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk

First publication	20 April 2011
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Disclaimer

Please note that revisions to the Public Summary of Opinion are purely administrative updates. Therefore, the scientific content of the document reflects the outcome of the Committee for Orphan Medicinal Products (COMP) at the time of designation and is not updated after first publication.

On 15 April 2011, orphan designation (EU/3/11/849) was granted by the European Commission to AiCuris GmbH & Co. KG, Germany, for (S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3, 4-dihydro-4-quinazolinyl} acetic acid for the prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk.

The sponsorship was transferred to Merck Sharp & Dohme Limited, United Kingdom, in March 2013.

What is cytomegalovirus disease?

Cytomegalovirus is a common virus that can cause mild infection such as a sore throat. Most people get infected at some stage during their lifetime but are very often unaware of it. After infection, the virus remains in the body in a 'latent' (inactive) state and only becomes active again if the body's immunity, specifically its cell-mediated immunity, is weakened.

Cell-mediated immunity is a defence mechanism where specialised cells called T-lymphocytes directly neutralise viruses. In people with weakened cell-mediated immunity, such as patients with HIV infection or transplant patients receiving immunosuppressant treatment (medicines that reduce the activity of the immune system), cytomegalovirus can become active again and, this time, cause severe infection.

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Cytomegalovirus disease in patients with impaired cell-mediated immunity is long-term debilitating and life threatening because of the complications it causes, such as inflammation of the lungs, liver and digestive tract, as well as reduced graft survival in transplanted patients.

What is the estimated number of patients at risk of developing the condition?

At the time of designation, the number of patients with impaired cell-mediated immunity at risk of cytomegalovirus disease was estimated to be approximately 3.1 people in 10,000 in the European Union (EU). This is equivalent to a total of around 157,000 people[*], which 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).

What methods of prevention are available?

At the time of designation, several antiviral medicines were authorised in the EU for the prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk (ganciclovir, valganciclovir and valaciclovir). Patients at risk were also closely monitored to detect signs of cytomegalovirus infection as early as possible.

The sponsor has provided sufficient information to show that the medicine '(S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3, 4-dihydro-4-quinazolinyl} acetic acid' might be of significant benefit for patients with impaired cell-mediated immunity at risk of cytomegalovirus disease because it has a different mechanism of action to current treatments, which may bring improved effectiveness against strains of cytomegalovirus resistant to existing antiviral medicines. 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?

During replication, cytomegaloviruses have their DNA packaged into small protein shells. This medicine is thought to block the action of an enzyme in the virus called 'terminase', which is involved in cleaving the DNA strands to fit within the shells. By blocking the enzyme, the medicine is expected to prevent the DNA in the virus from reaching maturity, thereby killing the virus.

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 impaired cell-mediated immunity at risk of cytomegalovirus disease were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk or designated as an orphan medicinal product elsewhere for this condition.

[*]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.
At the time of designation, this represented a population of 507,700,000 (Eurostat 2011).

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 12 January 2011 recommending the granting of this designation.

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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:

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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 languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	(S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl} acetic acid	Prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity deemed at risk
Bulgarian	(S)-{8-флуоро-2-2[4-(3-метоксифенил)-1-пиперазинил]-3-[2-метокси-5-(трифлуорометил)-фенил]-3,4-дихидро-4-квиназолинил}оцетна киселина.	Превенция на цитомегаловирусно (CMV) заболяване при пациенти с увреден клетъчно-медииран имунитет считани за рискови
Czech	(S)-{8-fluoro-2-2[4-(3-methoxyfenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-fenyl]-3,4-dihydro-4-chinazolinyl}acetát.	Prevence cytomegalovirové (CMV) choroby u pacientů s poruchou buněčné imunity se zvýšeným rizikem
Danish	(S)-{8-fluor-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluormethyl)-phenyl]-3,4-dihydro-4-quinazolinyl}eddikesyre	Forebyggelse af cytomegalovirus (CMV)-sygdom hos risikopatienter med svækket cellemedieret immunitet
Dutch	(S)-{8-fluor-2-2[4-(3-methoxyfenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluormethyl)-fenyl]-3,4-dihydro-4-chinazolinyl}acetaat.	Preventie van cytomegalievirusinfectie bij risicopatiënten met verzwakte cellulaire immuniteit
Estonian	(S)-{8-fluoro-2-2[4-(3-metoksüfenüül)-1-piperasinüül]-3-[2-metoksü-5-(trifluorometüül)-fenüül]-3,4-dihüdro-4-kinasolinüül}äädikhape.	Tsütomegaloviiruse (CMV)-haiguse ennetamine patsientidel, kellel on suurenenud risk rakulise immunsuse häireks.
Finnish	(S)-{8-fluoro-2-2[4-(3-metoksifenyyli)-1-piperatsinyyli]-3-[2-metoksi-5-(trifluorometyyli)-fenyyli]-3,4-dihydro-4-kinatsolinyyli}etikkahappo.	Sytomegalovirussairauden ehkäisy riskipotilailla, joiden soluvälitteinen immuniteetti on heikentynyt
French	Acide (S)-{8-fluoro-2-2[4-(3-méthoxyphényl)-1-pipérazinyl]-3-[2-méthoxy-5-(trifluorométhyl)-phényl]-3,4-dihydro-4-quinazolinyl}-acétique.	Prévention de la maladie due au CMV chez les patients présentant une altération de l'immunité cellulaire
German	(S)-{8-Fluor-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluormethyl)-phenyl]-3,4-dihydro-4-chinazolinyl}essigsäure.	Prävention der CMV-Erkrankung bei gefährdeten Patienten mit gestörter zellvermittelter Immunität
Greek	(S)-{8-φθοριο-2-2[4-(3-μεθοξυφαινυλο)-1-πιπεραζινυλο]-3-[2-μεθοξυ-5-(τριφθοριομεθυλο)-φαινυλο]-3,4-διϋδρο-4-κιναζολινύλο}οξικό οξύ.	Προφύλαξη από τον μεγαλοκυτταροϊό (CMV) σε ασθενείς υψηλού ρίσκου, με διαταραχή της κυτταροεξαρτώμενης ανοσίας
Hungarian	(S)-{8-Fluor-2-2[4-(3-metoxifenil)-1-piperazinil]-3-[2-metoxi-5-(trifluormetil)-fenil]-3,4-dihidro-4-kinazolinil}ecetsav.	Citomegalovírus (CMV) betegség megelőzése csökkent celluláris immunitá rizikója esetén

[1] At the time of designation

Language	Active ingredient	Indication
Italian	Acido (S)-{8-fluoro-2-2[4-(3-metossifenil)-1-piperazinil]-3-[2-metossi-5-(trifluorometil)-fenil]-3,4-diidro-4-chinazolinil} acetico.	Prevenzione della malattia da citomegalovirus (CMV) nei pazienti a rischio, con deficit dell'immunità cellulo-mediata
Latvian	(S)-{8-fluor-2-2[4-(3-metoksifenil)-1-piperazinil]-3-[2-metoksi-5-(trifluormetil)-fenil]-3,4-dihidro-4-kvinazolinil}etiķskābe.	Citomegalovīrusa (CMV) infekcijas profilakse riska grupas slimniekiem ar šūnu imunitātes traucējumiem
Lithuanian	(S)-{8-fluor-2-2-[4-(3-metoksifenil)-1-piperazinil]-3-[2-metoksi-5-(trifluorometil)-fenil]-3,4-dihidro-4-kvinazolinil} acto rūgštis	Citomegalo viruso (CMV) sukeltos ligos prevencija pacientams su susilpnėjusiu netiesioginiu ląsteliniu imunitetu
Maltese	(S)-{8-fluoro-2-2[4-(3-methoxyphenyl)-1-piperazinyl]-3-[2-methoxy-5-(trifluoromethyl)-phenyl]-3,4-dihydro-4-quinazolinyl}acetic acid.	Prevenzjoni ta' mard ikkawżat mill-citomegalovirus (CMV) f'pazjenti b'riskju li għandhom dgħjufija ta' l-immunità permezz taċ-ċelloli
Polish	Kwas (S)-{8-fluoro-2-2[4-(3-metoksyfenylo)-1-piperazynylo]-3-[2-metoksy-5-(trifluorometylo)-fenylo]-3,4-dihydro-4-chinazolinylo}octowy.	Zapobieganie cytomegalii (CMV) u chorych zwiększonego ryzyka z obniżoną odpornoscią typu komórkowego
Portuguese	Ácido (S)-{8-fluoro-2-2[4-(3-metoxifenil)-1-piperazinil]-3-[2-metoxi-5-(trifluorometil)-fenil]-3,4-di-hidro-4-quinazolinil} acético.	Prevenção da doença por citomegalovírus (CMV) em doentes com alteração da imunidade mediada por células
Romanian	Acid (S)-{8-fluoro-2-2[4-(3-metoxifenil)-1-piperazinil]-3-[2-metoxi-5-(trifluorometil)-fenil]-3,4-dihidro-4-chinazolinil}acetic.	Prevenirea bolii produsă de citomegalovirus (CMV) la pacienţii cu imunitate mediată celular deficitară consideraţi cu risc
Slovak	Kyselina (S)-{8-fluoro-2-2[4-(3-metoxyfenyl)-1-piperazinyl]-3-[2-metoxy-5-(trifluorometyl)-fenyl]-3,4-dihydro-4-chinazolinyl}octová.	Prevencia cytomegalovírusovej choroby (CMV) u pacientov s rizikom porušenej bunkovej imunity
Slovenian	(S)-{8-fluoro-2-2[4-(3-metoksifenil)-1-piperazinil]-3-[2-metoksi-5-(trifluorometil)-fenil]-3,4-dihidro-4-kinazolinil}ocetna kislina.	Preprečitev okužbe s citomegalovirusom (CMV) pri bolnikih s sumom zvečanega tveganja zaradi oslabljene celične imunosti
Spanish	Ácido (S)-{8-fluoro-2-2[4-(3-metoxifenil)-1-piperazinil]-3-[2-metoxi-5-(trifluorometil)-fenil]-3,4-dihidro-4-quinazolinil} acético.	Prevención de la enfermedad por citomegalovirus (CMV) en pacientes con deterioro de la inmunidad mediada por células considerados de riesgo
Swedish	(S)-{8-fluor-2-2[4-(3-metoxifenyl)-1-piperazinyl]-3-[2-metoxi-5-(trifluorometyl)-fenyl]-3,4-dihydro-4-kinazolinyl}ättiksyra.	Förebyggande av cytomegalovirus (CMV) sjukdom hos riskpatienter med nedsatt cellmedierad immunitet
Norwegian	(S)-{8-fluoro-2-2[4-(3-metoksyfenyl)-1-piperazinyl]-3-[2-metoksy-5-(trifluorometyl)-fenyl]-3,4-dihydro-4-kinazolinyl}eddiksyre.	Forebygging av cytomegalovirus (CMV)-sykdom hos pasienter med nedsatt cellemediert immunitet og som har antatt øket risiko

Language	Active ingredient	Indication
Icelandic	(S)-{8-flúoró-2-2[4-(3-metoxýfenýl)-1-píperaszínýl]-3-[2-metoxý-5-(triflúórómetýl)-fenýl]-3,4-díhýdró-4-kvínazólínýl}ediksýra.	Fyrirbyggjandi meðferð við cýtómegalóveiru (CMV) sjúkdómi hjá sjúklingum með skert frumubundið ónæmi og teljast í áhættu