

10 November 2014
EMA/COMP/557455/2014
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrrolo[2,1-f][1,2,4]triazine-5-carbonitrile for the treatment of pemphigus

On 15 October 2014, orphan designation (EU/3/14/1335) was granted by the European Commission to Almirall S.A., Spain, for (S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrrolo[2,1-f][1,2,4]triazine-5-carbonitrile for the treatment of pemphigus.

What is pemphigus?

Pemphigus is a group of autoimmune diseases characterised by widespread blistering and erosion of the skin and mucous membranes (the linings of internal organs). 'Autoimmune' means that the disease is caused by the immune system attacking the body's own cells.

In pemphigus, the autoimmune response produces antibodies that attack desmoglein, a protein which acts as a 'glue' attaching together the cells of the epidermis (the outer layer of the skin). As a result skin cells separate from each other, causing blisters that turn into sores. In some cases these blisters can cover large areas of the skin.

Pemphigus is a long-term debilitating and life-threatening disease because of the long-term blistering which can lead to dehydration and infection.

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

At the time of designation, pemphigus affected approximately 3.27 in 10,000 people in the European Union (EU). This was equivalent to a total of around 167,000 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 511,100,000 (Eurostat 2014).

What treatments are available?

At the time of designation, prednisolone (a steroid) and azathioprine (a medicine that reduces the activity of the immune system) were authorised in the EU to treat pemphigus.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with pemphigus because early studies in experimental models show that it may improve the skin damage seen in this condition. 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?

This medicine is a small molecule that blocks the effects of an enzyme called PI3K-delta. PI3K-delta activates B-cells, a type of white blood cells involved in autoimmune mechanisms. In patients with pemphigus, this activation of B-cells results in the production of antibodies against desmoglein. By blocking the activation of B-cells, this medicine is expected to prevent desmoglein from being attacked, thereby reducing the blistering seen in people with this condition.

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, no clinical trials with the medicine in patients with pemphigus had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for pemphigus or designated as an orphan medicinal product elsewhere for this condition

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 4 September 2014 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:

Almirall S.A.
Ronda General Mitre, 151
08022 Barcelona
Spain
Tel. +34 93 291 31 90
Fax +34 93 291 35 31
E-mail: global.regulatory@almirall.com

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	(S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-5-carbonitrile	Treatment of pemphigus
Bulgarian	(S)-2-(1-((6-амино-5-цианопиримидин-4-ил)амино)етил)-4-оксо-3-фенил-3,4-дихидропироло[2,1-f][1,2,4]триазин-5-карбонитрил	Лечение на пемфигус
Croatian	(S)-2-(1-((6-amino-5-cijanopirimidin-4-il)amino)etil)-4-okso-3-fenil-3,4-dihidropirololo[2,1-f][1,2,4]triazin-5-karbonitril	Liječenje pemfigusa
Czech	(S)-2-(1-((6-amino-5-kyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-fenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-5-karbonitril	Léčba pemfigu
Danish	(S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-5-carbonitril	Behandling af pemphigus
Dutch	(S)-2-(1-((6-amino-5-cyanopyrimidine-4-yl)amino)ethyl)-4-oxo-3-fenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-5-carbonitril	Behandeling van pemphigus
Estonian	(S)-2-(1-((6-amino-5-tsüanopürimidiin-4-üül)amino)etüül)-4-okso-3-fenüül-3,4-dihüdropürrolo[2,1-f][1,2,4]triisiin-5-karbonitriil	Pemfiguse ravi
Finnish	(S)-2-(1-((6-amino-5-syanopyrimidiini-4-yyli)amino)etyyli)-4-okso-3-fenyyli-3,4-dihydropyrrolo[2,1-f][1,2,4]triatsiini-5-karbonitriili	Pemfiguksen hoito
French	(S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)éthyl)-4-oxo-3-phényl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-5-carbonitrile	Traitement du pemphigus
German	(S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-5-carbonitril	Behandlung des Pemphigus
Greek	(S)-2-(1-((6-αμινο-5-κυανοπυριμιδινο-4-υλ)αμινο)αιθυλ)-4-οξο-3-φαινυλ-3,4-διυδροπυρρολο[2,1-f][1,2,4]τριαζινο-5-καρβονιτρίλιο	Θεραπεία της πέμφιγας
Hungarian	(S)-2-(1-((6-amino-5-cianopirimidin-4-il)-amino)-etil)-4-oxo-3-fenil-3,4-dihidropirrololo[2,1-f][1,2,4]triazin-5-karbonitril	Pemphigus kezelése
Italian	(S)-2-(1-((6-amino-5-ciano pirimidina-4-il)amino)etil)-4-osso-3-fenil-3,4-diidropirrololo[2,1-f][1,2,4]triazina-5-carbonitrile	Trattamento del pemfigo
Latvian	(S)-2-(1-((6-amino-5-ciānpirimidīn-4-il)amino)etil)-4-okso-3-fenil-3,4-dihidropirololo[2,1-f][1,2,4]triazīna-5-karbonitrils	Pemfigusa (pemphigus) ārstēšana

¹ At the time of designation

Language	Active ingredient	Indication
Lithuanian	(S)-2-(1-((6-amino-5-cianopirimidin-4-il)amino)etil)-4-okso-3-fenil-3,4-dihidropirol[2,1-f][1,2,4]triazino-5-karbonitrilas	Pūslinės (pemphigus) gydymas
Maltese	(S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-5-carbonitrile	Kura ta' Pemfigus
Polish	(S)-2-(1-((6-amino-5-cyjanopirymidyn-4-ylo)amino)etyl)-4-okso-3-fenyl-3,4-dihidropirol[2,1-f][1,2,4]triazyno-5-karbonitryl	Leczenie pęcherzycy
Portuguese	(S)-2-(1-((6-amino-5-cianopirimidina-4-il)amino)etil)-4-oxo-3-fenil-3,4-dihidropirrol[2,1-f][1,2,4]triazina-5-carbonitrila	Tratamento do pênfigo
Romanian	(S)-2-(1-((6-amino-5-cianopirimidin-4-il)amino)etil)-4-oxo-3-fenil-3,4-dihidropirol[2,1-f][1,2,4]triazin-5-carbonitril	Tratamentul pemfigusului
Slovak	(S)-2-(1-((6-amino-5-kyanopyrimidín-4-yl)amino)etyl)-4-oxo-3-fenyl-3,4-dihydropyrol[2,1-f][1,2,4]triazín-5-karbonitril	Liečba pemfigu
Slovenian	(S)-2-(1-((6-amino-5-cianopirimidin-4-il)amino)etil)-4-okso-3-fenil-3,4-dihidropirol[2,1-f][1,2,4]triazin-5-karbonitril	Zdravljenje pemfigusa
Spanish	(S)-2-(1-((6-amino-5-cianopirimidina-4-il)amino)etil)-4-oxo-3-fenil-3,4-dihidropirrol[2,1-f][1,2,4]triazina-5-carbonitrilo	Tratamiento del pénfigo
Swedish	(S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)etyl)-4-oxo-3-fenyl-3,4-dihydropyrrol[2,1-f][1,2,4]triazin-5-carbonitril	Behandling av pemfigus
Norwegian	(S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)etyl)-4-okso-3-fenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazin-5-karbonitril	Behandling av pemfigus
Icelandic	(S)-2-(1-((6-amínó-5cýanópýrimídín-4-ý)amínó)etýl)-4-oxó-3-fenýl-3,4-díhýdrópýrróló[2,1-f][1,2,4]tríazín-5-karbónitríl	Meðferð við blöðrusótt