



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

23 September 2014  
EMA/COMP/457064/2014  
Committee for Orphan Medicinal Products

## Public summary of opinion on orphan designation

4-{{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}}-3-methoxy-benzoic acid for the treatment of acute myeloid leukaemia

On 22 August 2014, orphan designation (EU/3/14/1328) was granted by the European Commission to Roche Registration Limited, United Kingdom, for 4-{{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}}-3-methoxy-benzoic acid for the treatment of acute myeloid leukaemia.

### What is acute myeloid leukaemia?

Acute myeloid leukaemia (AML) is a cancer of the white blood cells (cells that fight against infections). In patients with AML, the bone marrow (the spongy tissue inside the large bones, where blood cells are produced) produces large numbers of abnormal, immature white blood cells. These abnormal cells quickly build up in large numbers in the bone marrow and are found in the blood.

AML is a long-term debilitating and life-threatening disease because these abnormal immature cells take the place of the normal white blood cells, causing bleeding episodes, blood clots and reducing the patient's ability to fight infections.

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

At the time of designation, AML affected approximately 1.2 in 10,000 people in the European Union (EU). This was equivalent to a total of around 61,000 people<sup>\*</sup>, 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).

### What treatments are available?

Treatment for AML is complex and depends on a number of factors including the extent of the disease, whether it has been treated before, and the patient's age, symptoms and general state of health. At

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<sup>\*</sup>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).



the time of designation, the main treatments for AML were chemotherapy (medicines to treat cancer) and haematopoietic (blood) stem-cell transplantation (a complex procedure where the patient receives stem cells from a matched donor to help restore the bone marrow).

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with AML because results of early studies showed improvements in patients with previously untreated and advanced disease. 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 works by blocking the action of a protein known as MDM2. MDM2 normally regulates the action of a cancer-suppressing protein called p53 which prevents cancer by promoting cell death and repair.

In many cancers MDM2 is overactive, leading to reduced p53 activity. By attaching to MDM2 and blocking its action, this medicine is expected to increase the activity of p53 and restore the body's ability to prevent the growth of 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 AML were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for AML. Orphan designation of the medicine had been granted in the United States for the treatment of this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 10 July 2014 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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AL7 1TW  
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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<sup>1</sup>, Norwegian and Icelandic

Language	Active ingredient	Indication
English	4-{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxybenzoic acid	Treatment of acute myeloid leukaemia
Bulgarian	4-{[(2R,3S,4R,5S)-4-(4-хлоро-2-флуоро-фенил)-3-(3-хлоро-2-флуоро-фенил)-4-циано-5-(2,2-диметил-пропил)-пирролидин-2-карбонил]-амино}-3-метоксибензоена киселина	Лечение на остра миелоидна левкемия
Croatian	4-{[(2R,3S,4R,5S)-4-(4-kloro-2-fluoro-fenil)-3-(3-kloro-2-fluoro-fenil)-4-cijano-5-(2,2-dimetil-propil)-pirolidin-2-karbonil]-amino}-3-metoksi-benzoatna kiselina	Liječenje akutne mijeloične leukemije
Czech	4-{[(2R,3S,4R,5S)-4-(4-chloro-2-fluorofenyl)-3-(3-chloro-2-fluorofenyl)-4-kyano-5-(2,2-dimethylpropyl)-pyrrolidin-2-karbonyl]-amino}-3-methoxybenzoová kyselina	Léčba akutní myeloidní leukémie
Danish	4-{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxybenzoesyre	Behandling af akut myeloid leukæmi
Dutch	4-{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-fenyl)-3-(3-chloro-2-fluoro-fenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoëzuur	Behandeling van acute myeloïde leukemie
Estonian	4-{[(2R,3S,4R,5S)-4-(4-kloro-2-fluorofenüül)-3-(3-kloro-2-fluorofenüül)-4-tsüano-5-(2,2-dimetüülpropüül)-pürrolidiin-2-karbonüül]-amino}-3-metoksübentsoehape	Akuutse müeloidse leukeemia ravi
Finnish	4-{[(2R,3S,4R,5S)-4-(4-kloori-2-fluorifenyylä)-3-(3-kloori-2-fluorifenyylä)-4-syaani-5-(2,2-dimetyylipropyli)-pyrrolidiini-2-karbonyyli]-amino}-3-metoksibentsoehappo	Akuutin myelooisen leukemian hoito
French	Acide 4-{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidin-2-carbonyl]-amino}-3-méthoxybenzoïque	Traitement de la leucémie aiguë myéloïde
German	4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino}-3-methoxybenzoesäure	Behandlung der akuten myeloischen Leukämie
Greek	4-{[(2R,3S,4R,5S)-4-(4-χλωρο-2-φθορο-φαινυλο)-3-(3-χλωρο-2-φθορο-φαινυλο)-4-κύανο-5-(2,2-διμεθυλοπροπυλο)-πυρολυδινο-2-καρβονυλο]-αμινο}-3-μεθοξυβενζοϊκό οξύ	Θεραπεία της οξείας μυελοειδούς λευχαιμίας

<sup>1</sup> At the time of designation

Language	Active ingredient	Indication
Hungarian	4-{{[(2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino}}-3-metoxi-benzoésav	Akut myeloid leukaemia kezelése
Italian	4-{{[(2R,3S,4R,5S)-4-(4-cloro-2-fluoro-fenil)-3-(3-cloro-2-fluoro-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidina-2-carbonil]-amino}}-acido-3-metossi-benzoico	Trattamento della leucemia mieloide acuta
Latvian	4-{{[(2R,3S,4R,5S)-4-(4-hloro-2-fluoro-fenil)-3-(3-hloro-2-fluoro-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirolidīn-2-karbonil]-amino}}-3-metoksi-benzoskābe	Akūtas mieloleikozes ārstēšana
Lithuanian	4-{{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-fenil)-3-(3-chloro-2-fluoro-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirolidino-2-karbonil]-amino}}-3-metoksibenzoinė rūgštis	Ūmios mieloleukozės gydymas
Maltese	4-{{[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}}-3-methoxy - benzoic acid	Kura tal-lewkimja mjelojda akuta
Polish	Kwas 4-{{[(2R,3S,4R,5S)-4-(4-chloro-2-fluorofenyl)-3-(3-chloro-2-fluorofenyl)-4-cyano-5-(2,2-dimetylopropyl)-pirolidyno-2-karbonyl]-amino}}-3-metoksybenzoésowy	Leczenie ostrej białaczki szpikowej
Portuguese	Ácido 4-{{[(2R,3S,4R,5S)-4-(4-cloro-2-fluoro-fenil)-3-(3-cloro-2-fluoro-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidina-2-carbonil]-amino}}-3-metoxi-benzóico	Tratamento da leucémia mieloide aguda
Romanian	Acid 4-{{[(2R,3S,4R,5S)-4-(4-Cloro-2-fluoro-fenil)-3-(3-cloro-2-fluoro-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirolidin-2-carbonil]-amino}}-3-metoxi-benzoic	Tratamentul leucemiei mieloide acute
Slovak	Kyselina 4-{{[(2R,3S,4R,5S)-4-(4-chlór-2-fluórfenyl)-3-(3-chlór-2-fluórfenyl)-4-kyano-5-(2,2-dimetylpropyl)-pyrolidín-2-karbonyl]-amino}}-3-metoxybenzoová	Liečba akútnej myeloickej leukémie
Slovenian	4-{{[(2R,3S,4R,5S)-4-(4-kloro-2-fluorofenil)-3-(3-kloro-2-fluorofenil)-4-ciano-5-(2,2-dimetilpropil)-pirolidin-2-karbonil]-amino}}-3-metoksibenzojska kislina	Zdravljenje akutne mieloične levkemije
Spanish	Ácido 4-{{[(2R,3S,4R,5S)-4-(4-cloro-2-fluoro-fenil)-3-(3-cloro-2-fluoro-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidina-2-carbonil]-amino}}-3-metoxi-benzóico	Tratamiento de la leucemia mieloide aguda
Swedish	4-{{[(2R,3S,4R,5S)-4-(4-klor-2-fluorofenyl)-3-3-kloro-2-fluorofenyl)-4-cyano-5-(2,2-dimetylpropyl)-pyrrolidin-2-karbonyl]-amino}}-3-metoxibensoesyra	Behandling av akut myeloisk leukemi
Norwegian	4-{{[(2R,3S,4R,5S)-4-(4-kloro-2-fluoro-fenyl)-3-(3-kloro-2-fluoro-fenyl)-4-cyano-5-(2,2-dimetyl-propyl)-pyrrolidin-2-karbonyl]-amino}}-3-metoksy-benzosyre	Behandling av akutt myelogen leukemi
Icelandic	4-{{[(2R,3S,4R,5S)-4-(4-klóró-2-flúóró-fenýl)-3-(3-klóró-2-flúóró-fenýl)-4-cýaná-5-(2,2-dímetyl-própýl)-pýrrólídín-2-karbónýl]-amínó}}-3-metoxý-benzósýra	Meðferð við bráðu kyrningahvítblæði