



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Public summary of opinion on orphan designation

6-{[(1R,2S)-2-aminocyclohexyl]amino}-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one monocation for the treatment of acute myeloid leukaemia

On 22 February 2018, orphan designation (EU/3/18/1974) was granted by the European Commission to Takeda Pharma A/S, Denmark, for 6-{[(1R,2S)-2-aminocyclohexyl]amino}-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one monocation (also known as TAK-659) 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 infections). In patients with AML, the bone marrow (the spongy tissue inside the large bones, where blood cells are produced) produces 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 blood cells, causing bleeding episodes, blood clots and a reduced ability to fight infections.

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

At the time of designation, AML affected approximately 1.4 in 10,000 people in the European Union (EU). This was equivalent to a total of around 72,000 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).

What treatments are available?

Treatment for AML 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 the time of designation, the main treatments for AML were chemotherapy (medicines to treat cancer) and

^{*}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 517,400,000 (Eurostat 2018).



haematopoietic (blood) stem-cell transplantation (a procedure where the patient's bone marrow is cleared of cells and replaced by stem cells to form new bone marrow that produces healthy blood cells).

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with AML because early studies showed benefits in patients who had previously been treated with several 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?

The medicine blocks the action of two proteins, SYK and FLT3, which are found in cells that develop into blood cells. In patients with AML, these proteins work abnormally and help cancer cells to grow and survive. By blocking SYK and FLT3, this medicine is expected to reduce the number of blood cancer cells and how long they live for, and so improve control of the cancer.

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 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 18 January 2018 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:

Contact details of the current sponsor for this orphan designation can be found on EMA website, on the medicine's [rare disease designations page](#).

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 | 6-[[(1R,2S)-2-aminocyclohexyl]amino]-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one monocation | Treatment of acute myeloid leukaemia |
| Bulgarian | 6-[[(1R,2S)-2-аминоциклохексил]амино}-7-флуоро-4-(1-метил-1H-пиразол-4-ил)-1,2-дихидро-3H-пироло[3,4-с] пиридин-3-он моноцитрат | Лечение на остра миелоидна левкемия |
| Croatian | 6-[[(1R,2S)-2-aminocikloheksil]amino]-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1,2-3H-pirolo[3,4-c]piridin-3-on monocitrat | Liječenje akutne mijeloične leukemije |
| Czech | 6-[[(1R,2S)-2-aminocyklohexyl]amino]-7-fluor-4-(1-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-onu | Léčba akutní myeloidní leukémie |
| Danish | 6-[[(1R,2S)-2-aminocyclohexyl]amino]-7-fluor-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo [3,4-c]pyridin-3-on monocitrat | Behandling af akut myeloid leukæmi |
| Dutch | 6-[[(1R,2S)-2-aminocyclohexyl]amino]-7-fluor-4-(1-methyl-1H-pyrazool-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridine-3-on monocitraat | Behandeling van acute myeloïde leukemie |
| Estonian | 6-[[(1R,2S)-2-aminotsükloheksüül]amino]-7-fluoro-4-(1-metüül-1H-pürasool-4-üül)-1,2-dihüdro-3H-pürrolo[3,4-c]püridiin-3-ooni monotsitraat | Akuutse müeloidse leukeemia ravi |
| Finnish | 6-[[(1R,2S)-2-aminosykloheksyyli]amino]-7-fluori-4-(1-metyyli-1H-pyratsol-4-yyli)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-oni monositraatti | Akuutin myelooisen leukemian hoito |
| French | 6-[[(1R,2S)-2-aminocyclohexyl]amino]-7-fluoro-4-(1-méthyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one monocation | Traitement de la leucémie aiguë myéloïde |
| German | 6-[[(1R,2S)-2-Aminocyclohexyl]amino]-7-fluor-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-on-monocitrat | Behandlung der akuten myeloiden Leukämie |
| Greek | 6-[[(1R,2S)-2-αμινοκυκλοεξυλ]αμινο}-7-φθορο-4-(1H-μεθυλ-4-υλ)-1,2-διυδρο-3H-πυρρολο[3,4-ο]πυριδιν-3-όνη μονοκιτρική | Θεραπεία της οξείας μυελοειδούς λευχαιμίας |
| Hungarian | 6-[[(1R,2S)-2-amino-ciklohexil]-amino]-7-fluor-4-(1-metil-1H-pirazol-4-il)-1,2-dihidro-3H-pirrol[3,4-c]piridin-3-on monocitrát | Akut myeloid leukaemia kezelése |
| Italian | 6-[[(1R,2S)-2-ammino-cicloesil]amino]-7-fluoro-4-(1-metil-1H-pyrazol-4-il)-1,2-diidro-3H-pyrrolo[3,4-c]piridin-3-one monocitrato | Trattamento della leucemia mieloide acuta |
| Latvian | 6-[[(1R,2S)-2-aminocikloheksil]amino]-7-fluor-4-(1-metil-1H-pirazol-4-il)-1,2-dihidro-3H-pirolo[3,4-c]piridīn-3-ona monocitrāts | Akūtas mieloleikozes ārstēšana |

¹ At the time of designation

| Language | Active ingredient | Indication |
|------------|--|---|
| Lithuanian | 6-[[[(1R,2S)-2-aminocikloheksil]amino]-7-fluor-4-(1-metil-1H-pirazol-4-il)-1,2-dihidro-3H-pirol[3,4-c]piridin-3-ono monocitratas | Ūmios mieloleukozės gydymas |
| Maltese | 6-[[[(1R,2S)-2-amminoċikloeżil]ammino]-7-fluwor-4-(1-metil-1H-pirażol-4-il)-1,2-diidro-3H-pirrolo[3,4-c]piridina-3-wieħed monoċitrat | Kura tal-lewkimja mjelojda akuta |
| Polish | 6-[[[(1R,2S)-2-aminocykloheksylo]amino]-7-fluoro-4-(1-metylo-1H-pirazol-4-ylo)-1,2-dihydro-3H-pirol[3,4-c]pirydino-3-onu | Leczenie ostrej białaczki szpikowej |
| Portuguese | Monocitrato de 6-[[[(1R,2S)-2-aminociclo-hexil]amino]-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1,2-dihidro-3H-pirrol[3,4-c]piridin-3-ona | Tratamento da leucémia mielóide aguda |
| Romanian | Monocitrat de 6-[[[(1R,2S)-2-aminociclohexil]amino]-7-fluor-4-(1-metil-1H-pirazol-4-il)-1,2-dihidro-3H-pirol[3,4-c]piridin-3-onă | Tratamentul leucemiei mieloidice acute |
| Slovak | 6-[[[(1R,2S)-2-aminocyklohexyl]amino]-7-fluór-4-(1-metyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-[3,4-c]pyridín-3-ón | Liečba akútnej myeloidkej leukémie |
| Slovenian | 6-[[[(1R,2S)-2-aminocikloheksil]amino]-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1,2-dihidro-3H-pirol[3,4-c]piridin-3-on monocitrat | Zdravljenje akutne mieloične levkemije |
| Spanish | 6-[[[(1R,2S)-2-aminociclohexil]amino]-7-fluoro-4-(1-metil-1H-pirazol-4-il)-1,2-dihidro-3H-pirrol[3,4-c]piridin-3-ona | Tratamiento de la leucemia mieloidice aguda |
| Swedish | 6-[[[(1R,2S)-2-aminocyklohexyl]amino]-7-fluor-4-(1-metyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-onmonokitrat | Behandling av akut myeloidisk leukemi |
| Norwegian | 6-[[[(1R,2S)-2-aminosykloheksyl]amino]-7-fluor-4-(1-metyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo-[3,4-c]pyridin-3-on monositrat | Behandling av akutt myelogen leukemi |
| Icelandic | 6-[[[(1R,2S)-2-aminósýklóhexýl]amínó]-7-flúor-4-(1-metýl-1H-pýrasól-4-ýl)-1,2-díhýdró-3H-pýrról[3,4-c]pýridín-3-ón mónósítrat | Meðferð við bráðu kynningahvítblæði |