



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Public summary of opinion on orphan designation

1-(2-hydroxyethyl)-8-{{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl]amino}}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide fumarate salt for the treatment of acute myeloid leukaemia

On 24 August 2018, orphan designation (EU/3/18/2057) was granted by the European Commission to Pharm Research Associates (UK) Limited, United Kingdom, for 1-(2-hydroxyethyl)-8-{{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl]amino}}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide fumarate salt (also known as PCM-075) 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 in 10,000 people in the European Union (EU). This was equivalent to a total of around 52,000 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 laboratory studies showed that combining this medicine with chemotherapy may reduce growth of the leukaemia and improve survival compared with chemotherapy alone. 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 effect of an enzyme called polo-like kinase 1 (PLK1). PLK1 is found in excess amounts in the abnormal bone marrow cells of patients with AML, and plays an important role in allowing the leukaemia cells to grow and divide. By blocking PLK1, the medicine is expected to halt the growth of the leukaemia cells and cause them to die.

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 this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 25 July 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	1-(2-hydroxyethyl)-8-{{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl]amino}}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide fumarate salt	Treatment of acute myeloid leukaemia
Bulgarian	Фумаратна сол на 1-(2-хидроксиетил)-8-{{[5-(4-метилпиперазин-1-ил)-2-(трифлуорометокси)фенил]амино}}-4,5-дихидро-1H-пиразоло[4,3-н]квиназолин-3-карбоксамид	Лечение на остра миелоидна левкемия
Croatian	Fumaratna sol 1-(2-hidroksietil)-8-{{[5-(4-metilpiperazin-1-il)-2-(trifluorometoksi)fenil]amino}}-4,5-dihidro-1H-pirazolo[4,3-h]kinazolin-3-karboksamida	Liječenje akutne mijeloične leukemije
Czech	1-(2-hydroxyethyl)-8-{{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)fenyl]amino}}-4,5-dihydro-1H-pyrazolo[4,3-h]chinazolin-3-karboxamid-fumarát	Léčba akutní myeloidní leukémie
Danish	1-(2-hydroxyethyl)-8-{{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)phenyl]amino}}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazolin-3-carboxamidfumaratsalt	Behandling af akut myeloid leukæmi
Dutch	1-(2-hydroxyethyl)-8-{{[5-(4-methylpiperazine-1-yl)-2-(trifluoromethoxy)fenyl]amino}}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide-fumaraatzout	Behandeling van acute myeloïde leukemie
Estonian	1-(2-hüdroksüetüül)-8-{{[5-(4-metüülpiperasiin-1-üül)-2-(trifluorometoksü)fenüül]amino}}-4,5-dihüdro-1H-pürasolo[4,3-h]kinasoliin-3-karboksamiidi fumaratsioon	Akootse müeloidse leukeemia ravi
Finnish	1-(2-hydroksietyyli)-8-{{[5-(4-metyyilpiperatsiini-1-yyli)-2-(trifluorimetoksi)fenyyli]amino}}-4,5-dihydro-1H-pyratsolo[4,3-h]kinatsoliini-3-karboksamidifumaraattisuola	Akutin myelooisen leukemian hoito
French	Sel de fumarate de 1-(2-hydroxyéthyl)-8-{{[5-(4-méthylpipérazin-1-yl)-2-(trifluorométhoxy)phényl]amino}}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide	Traitement de la leucémie aiguë myéloïde
German	1-(2-Hydroxyethyl)-8-{{[5-(4-methylpiperazin-1-yl)-2-(trifluormethoxy)phenyl]amino}}-4,5-dihydro-1H-pyrazolo[4,3-h]chinazolin-3-carboxamid-fumarat	Behandlung der akuten myeloiden Leukämie
Greek	Φουμαρικό άλας του 1-(2-υδροξυαιθυλο)-8-{{[5-(4-μεθυλοππεραζιν-1-υλο)-2-(τριφθορομεθοξυ)φαινυλ]αμινο}}-4,5-διυδρο-1H-πυραζολο[4,3-η]κιναζολινόνη-3-καρβοξαμιδιου	Θεραπεία της οξείας μυελοειδούς λευχαιμίας
Hungarian	1-(2-hidroxietil)-8-{{[5-(4-metilpiperazin-1-il)-2-(trifluormetoxi)fenil]amino}}-4,5-dihidro-1H-pirazolo[4,3-H]kinazolin-3-karboxamid-fumarát só	Akut myeloid leukaemia kezelése

¹ At the time of designation

Language	Active ingredient	Indication
Italian	Sal 1-(2-idrossietil)-8-{[5-(4-metilpiperazin-1-il)-2-(trifluorometossi)fenil]amino}-4,5-diidro-1H-pirazolo[4,3-h]chinazolina-3-carbossammide fumarato	Trattamento della leucemia mieloide acuta
Latvian	1-(2-hidroksietil)-8-{[5-(4-metilpiperazīn-1-il)-2-(trifluorometoksi) fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]hinazolīn-3-karboksamīda fumarāta sāls	Akūtas mieloleikozes ārstēšana
Lithuanian	1-(2-hidroksietil)-8-{[5-(4-metilpiperazin-1-il)-2-(trifluorometoksi) fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]kvinazolino-3-karboksamido fumarato druska	Ūmios mieloleukozės gydymas
Maltese	1-(2-hydroxyethyl)-8-{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide fumarate salt	Kura tal-lewkimja mjelojda akuta
Polish	Fumaran 1-(2-hydroksyetylo)-8-{[5-(4-metylopiperazyn-1-ylo)-2-(trifluorometoksy)fenylo]amino}-4,5-dihydro-1H-pirazolo[4,3-h]chinazolino-3-karboksyamidu	Leczenie ostrej białaczki szpikowej
Portuguese	Sal de fumarato de 1-(2-hidroxietil)-8-{[5-(4-metilpiperazina-1-il)-2-(trifluorometoxi)fenil]amino}-4,5-di-hidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida	Tratamento da leucémia mielóide aguda
Romanian	Sare fumarat de 1-(2-hidroxietil)-8-{[5-(4-metilpiperazin-1-il)-2-(trifluorometoxi) fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]chinazolin-3-carboxamidă	Tratamentul leucemiei mieloide acute
Slovak	1-(2-hydroxyetyl)-8-{[5-(4-metyl piperazín-1-yl)-2-(trifluorometoxy)fenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]chinazolín-3-karboxamid fumarátová soľ	Liečba akútnej myeloickej leukémie
Slovenian	1-(2-hidroksietil)-8-{[5-(4-metilpiperazin-1-il)-2-(trifluorometoksi)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]kvinazolin-3-karboksamid fumaratna sol	Zdravljenje akutne mieloične levkemije
Spanish	Sal fumarato de 1-(2-hidroxietil)-8-{[5-(4-metilpiperazin-1-il)-2-(trifluorometoxi)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida	Tratamiento de la leucemia mieloide aguda
Swedish	Fumaratsalt av 1-(2-hydroxyetyl)-8-{[5-(4-metyl piperazin-1-yl)-2-(trifluorometoxy)fenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]kinazolin-3-karboxamid	Behandling av akut myeloisk leukemi
Norwegian	1-(2-hydroksyetyl)-8-{[5-(4-metyl piperazin-1-yl)-2-(trifluorometoksy)fenyl]amino}-4,5-dihydro-1H-pyrazol[4,3-h]kinazolin-3-karboksamid fumarat	Behandling av akutt myelogen leukemi
Icelandic	1-(2-hydroksyetyl)-8-{[5-(4-metyl piperazin-1-yl)-2-(trifluorometoksy)fenyl]amino}-4,5-dihydro-1H-pyrazol[4,3-h]kinazolin-3-karboksamid fumarat salt	Meðferð við bráðu kyrningahvítblæði