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Public summary of opinion on orphan designation

2-((4S)-6-(4-Chlorophenyl)-1-methyl-4H-benzo[C]isoxazolo[4,5-e]azepin-4-yl)acetamide monohydrate for the treatment of myelofibrosis

On 28 February 2020, orphan designation EU/3/20/2247 was granted by the European Commission to IQVIA RDS Ireland Limited, Ireland, for 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[C]isoxazolo[4,5-e]azepin-4-yl)acetamide monohydrate (also known as CPI-0610) for the treatment of myelofibrosis.

What is myelofibrosis?

Myelofibrosis is a disease in which fibrous tissue forms in the bone marrow (the spongy tissue inside the large bones where blood cells are produced), interfering with normal blood cell production. This causes some immature blood cells to move from the bone marrow to other organs, such as the spleen and liver, which become enlarged. Symptoms of the disease include bone pain, tiredness, weakness, weight loss, fever and bleeding.

Myelofibrosis is a debilitating disease that is long-lasting and life-threatening because it can lead to severe anaemia (low red blood cell counts), infections, and can result in leukaemia (cancer of the white blood cells).

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

At the time of designation, myelofibrosis affected less than 1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 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?

At the time of designation, busulfan, hydroxycarbamide and ruxolitinib were authorised in the EU for myelofibrosis. In addition, medicines were authorised to treat the symptoms, including erythropoietin (a hormone that stimulates the production of red blood cells) to treat anaemia, and surgery was used

*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 519,200,000 (Eurostat 2020).

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to remove the enlarged spleen. In some patients, haematopoietic (blood) stem cell transplantation was used to treat the disease. This is a procedure where the patient's bone marrow is cleared of cells and replaced with stem cells from a donor 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 myelofibrosis. This is because early results in patients whose illness did not respond to treatment with ruxolitinib showed improvements when the medicine was added to ruxolitinib treatment or used instead of ruxolitinib. 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 a group of proteins known as BET proteins, which control the production of immature blood cells, inflammation and the development of fibrous tissue in the bone marrow. By blocking the action of these proteins, the medicine is expected to help control the progression of the disease and reduce its symptoms.

What is the stage of development of this medicine?

The effects of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[C]isoxazolo[4,5-e]azepin-4-yl)acetamide monohydrate 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 myelofibrosis were ongoing.

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

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 22 January 2020, 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.

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	2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[C]isoxazolo[4,5-e]azepin-4-yl)acetamide monohydrate	Treatment of myelofibrosis
Bulgarian	2-((4S)-6-(4-хлорфенил)-1-метил-4H-бензо[c]изоксазоло[4,5-e] азепин-4-ил) ацетамид монохидрат	Лечение на миелофиброза
Croatian	2-((4S)-6-(4-chlorfenylklorfenil)-1-metihyl-4H-benzo[cC]isoxazolisoksazol[4,5-e]azepin-4-ylil)acetamid monohydrátmonohidrat	Liječenje mijelofibroze
Czech	Monohydrát 2-((4S)-6-(4-chlorofenyl)-1-methyl-4H-benzo[C]isoxazolo[4,5-e]azepin-4-yl)acetamidu	Léčba myelofibrózy
Danish	2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[C]isoxazolo[4,5-e]azepin-4-yl) acetamidmonohydrat	Behandling af myelofibrose
Dutch	2-((4S)-6-(4-chlorofenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e] azepine-4-yl) acetamide monohydraat	Behandeling van myelofibrose
Estonian	2-((4S)-6-(4-klorofenüül)-1-metüül-4H-benso[c]isoksasolo[4,5-e]asepiin-4-üül)atseetamiid monohüdraat	Müelofibroosi ravi
Finnish	2-((4S)-6-(4-kloorifenyyli)-1-metyyli-4H-bentso[c]isoksatsolo[4,5-e] atsepin-4-yyli) asetamidimonohydraatti	Myelofibroosin hoito
French	2-((4S)-6-(4-chlorophényl)-1-méthyl-4H-benzo[c]isoxazolo[4,5-e] azépin-4-yl) acétamide monohydraté	Traitement de la myélofibrose
German	2-((4S)-6-(4-Chlorophenyl)-1-Methyl-4H-Benzo-[c]-Isoxazolo-[4,5-e]-Azepin-4-yl)-Acetamid-Monohydrat	Behandlung der Myelofibrose
Greek	2-((4S)-6-(4-χλωροφαινυλο)-1-μεθυλο-4H-βενζο[c]ισοξαζολο[4,5-e] αζεπιν-4-υλ) ακεταμίδιο μονοϋδρικό	Θεραπεία της μυελοϊνωσης
Hungarian	2-((4S)-6-(4-klór-fenil)-1-metil-4H-benzo[c]izoxazolo[4,5-e] azepin-4-il)-acetamid-monohidrát	Myelofibrosis kezelése
Italian	2-((4S)-6-(4-clorofenil)-1-metil-4H-benzo[c]isossazolo[4,5-e] azepin-4-il) acetamide monoidrato	Trattamento della mielofibrosi

[1] At the time of designation

Language	Active ingredient	Indication
Latvian	2-((4S)-6-(4-hlorfenil)-1-metil-4H-benzo[c]izoksazolo[4,5-e] azepīn-4-il) acetamīda monohidrāts	Mielofibrozes ārstēšana
Lithuanian	2-((4S)-6-(4-chlorfenil)-1-metil-4H-benzo[c]izoksazolo[4,5-e] azepin-4-il) acetamido monohidratas	Mielofibrozės gydymas
Maltese	2-((4S)-6-(4-klorofenil)-1-metil-4H-benżo[C]isossażol[4,5-e]ażepin-4-il)aċetammid monoidrat	Kura tal-mjelofibrożi
Polish	Monohydrat 2-((4S)-6-(4-chlorofenyl)-1-metylo-4H-benzo[c]izoksazol[4,5-e]azepin-4-ylo)acetamidu	Leczenie mielofibrozy
Portuguese	2-((4S)-6-(4-clorofenil)-1-metil-4H-benzo[c]isoxazolo[4,5-e] azepin-4-il) acetamida mono-hidratada	Tratamento da mielofibrose
Romanian	Moinohidrat de 2-((4S)-6-(4-clorofenil)-1-metil-4H-benzo[c]izoxazolo[4,5-e] azepin-4-il) acetamidă	Tratamentul mielofibrozei
Slovak	2-((4S)-6-(4-chlórfenyl)-1-metyl-4H-benzo[c]izoxazol[4,5-e]azepín-4-yl) acetamid monohydrát	Liečba myelofibrózy
Slovenian	2-((4S)-6-(4-klorofenil)-1-metil-4H-benzo[c]isoksazolo[4,5-e] azepin-4-il) acetamid monohidrat	Zdravljenje mielofibroze
Spanish	2-((4S)-6-(4-clorofenil)-1-metil-4H-benzo[c]isoxazol[4,5-e] azepina-4-il) acetamida monohidrato	Tratamiento de la mielofibrosis
Swedish	2-((4S)-6-(4-klorofenyl)-1-metyl-4H-benso[c]isoxazol[4,5-e]azepin-4-yl)acetamidmonohydrat	Behandling av myelofibros
Norwegian	2-((4S)-6-(4-klorofenyl)-1-metyl-4H-benzo[k]isoksazolo[4,5-e]azepin-4-yl) acetamidmonohydrat	Behandling av myelofibrose
Icelandic	2-((4S)-6-(4-klórfenýl)-1-metýl-4H-bensó[c]ísoxazóló[4,5-e] azepín-4-ýl) asetamíð einhýdrat	Meðferð á mýelófíbrósu