13 November 2020
EMADOC-628903358-2749

Public summary of opinion on orphan designation

6-((3S,4S)-4-Methyl-1-(pyrimidin-2-yl-methyl)pyrrolidin-3-yl)-3-tetrahydropyran-4-yl-7H-imidazo(1,5-a)pyrazin-8-one for the treatment of sickle cell disease

On 21 August 2020, orphan designation EU/3/20/2322 was granted by the European Commission to TMC Pharma (EU) Limited, Ireland, for 6-((3S,4S)-4-methyl-1-(pyrimidin-2-yl-methyl)pyrrolidin-3-yl)-3-tetrahydropyran-4-yl-7H-imidazo(1,5-a)pyrazin-8-one (also known IMR-687) for the treatment of sickle cell disease.

What is sickle cell disease?

Sickle cell disease is a genetic disease in which the red blood cells become rigid and sticky and change from being disc-shaped to being crescent-shaped (like a sickle). The change in shape is caused by the presence of an abnormal form of haemoglobin, the protein in red blood cells that carries oxygen around the body. In patients with sickle cell disease, the abnormal red blood cells attach to walls of blood vessels and block them, restricting the flow of nutrients and oxygen to the internal organs, such as the heart, the lungs, and the spleen. Episodes of such blockages (called vaso-occlusive crises) cause severe pain and damage to these organs. Since the abnormal red blood cells have a shorter life span, the disease also causes anaemia (low red blood cell counts).

Sickle cell disease is a severe disease that is long lasting and may be life threatening because of its effects on the heart and the lungs.

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

At the time of designation, sickle cell disease affected approximately 2 in 10,000 people in the European Union (EU). This was equivalent to a total of around 104,000 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).

*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, Iceland, Liechtenstein, Norway and the United Kingdom. This represents a population of 519,200,000 (Eurostat 2020).

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What treatments are available?

At the time of designation, the medicine hydroxycarbamide was authorised in the EU for sickle cell disease. Symptoms of the condition were treated with painkillers and by increasing fluid intake. Blood transfusions were used to treat anaemia and increase the blood's capacity to carry oxygen. Medicines called iron chelators were also used to reduce the high iron levels in the body caused by repeated blood transfusions. In some cases, patients also had haematopoietic stem cell transplantation (a procedure where the patient receives stem cells from a matched donor to help restore the bone marrow) to allow them to produce red blood cells containing normal haemoglobin.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with sickle cell disease because data from early studies showed that taking the medicine in combination with hydoxycarbamide reduced vaso-occlusive crises. 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 is thought to work by encouraging the red cells forming in the bone marrow to produce a form of haemoglobin called fetal haemoglobin. Red cells that contain this type of haemoglobin become resistant to sickling and sticking together. The medicine may also stop white blood cells from sticking to the blood vessel walls. The actions of this medicine are expected to reduce blockages in blood vessels and so reduce symptoms of sickle cell disease.

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 sickle cell disease were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of sickle cell disease. Orphan designation of the medicine had been granted in the United States for the treatment of sickle cell disease.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 16 July 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

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	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one	Treatment of sickle cell disease
Bulgarian	6-[(3S,4S)-4-метил-1-(пиримидин-2-илметил)пиролидин-3-ил]-3-тетрахидропиран-4-ил-7H-имидазо[1,5-a]пиразин-8-он	Лечение на сърповидно-клетъчна анемия
Croatian	6-[(3S,4S)-4-metilhyl-1-(piyrimidin-2-ylmethylilmetil)pyrrolidinpirolidin-3-ylil]-3-tetrahiydropyiran-4-ylil-7H-imidazo[1,5-a]pyrazinpirazin-8-one	Liječenje bolesti srpastih stanica
Czech	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-on	Léčba srpkovité anémie
Danish	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-on	Behandling af seglcellesygdom
Dutch	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one	Behandeling van sikkelcelaandoening
Estonian	6-[(3S,4S)-4-metüül-1-(pürimidiin-2-üülmetüül)pürrolidiin-3-üül]-3-tetrahüdropüraan-4-üül-7H-imidaso[1,5-a]pürasiin-8-oon	Sirprakulise aneemia ravi
Finnish	6-[(3S,4S)-4-metyyli-1-(pyrimidiini-2-yylimetyyli)pyrrolidiini-3-yyli]-3-tetrahydropyraani-4-yyli-7H-imidatso[1,5-a]pyraz=tsiini-8-oni	Sirppisolusyndrooman hoito
French	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one	Traitement de la drépanocytose
German	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-on	Behandlung der Sichelzellenanämie
Greek	6-[(3S,4S)-4-μεθυλ-1-(πυριμιδιν-2-υλμεθυλ)πυρολιδιν-3-υλ]-3-τετραϋδροπυραν-4-υλ-7H-ιμιδαζο[1,5-a]πυραζιν-8-όνη	Θεραπεία της δρεπανοκυτταρικής αναιμίας
Hungarian	6-[(3S,4S)-4-metil-1-(pirimidin-2-ilmetil)pirrolidin-3-il]-3-tetrahidropiran-4-il-7H-imidazo[1,5-a]pirazin-8-one	Sarlósejtes anaemia kezelése
Italian	6-[(3S,4S)-4-metil-1-(pirimidin-2-ilmetil)pirrolidin-3-yl]-3-tetraidropiran-4-il-7H-imidazo[1,5-a]pirazin-8-one	Trattamento dell'anemia falciforme
Latvian	6-[(3S,4S)-4-metil-1-(pirimidīn-2-ilmetil)pirrolidīn-3-il]-3-tetrahidropirān-4-il-7H-imidazo[1,5-a]pirazīn-8-ons	Sirpjveida šūnu anēmijas ārstēšana
Lithuanian	6-[(3S,4S)-4-metil-1-(pirimidin-2-ilmetil)pirolidin-3-il]-3-tetrahidropiran-4-il-7H-imidazo[1,5-a]pirazin-8-onas	Siklemijos gydymas
Maltese	6-[(3S,4S)-4-metil-1-(pirimidina-2-ilmetil)pirrolidina-3-il]-3-tetraidropiran-4-il-7H-imidażo[1,5-a]pirażina-8-on	Kura tal-marda taċ-ċelluli sura ta' minġel

[1] At the time of designation

Language	Active ingredient	Indication
Polish	6-[(3S,4S)-4-metylo-1-(pirymidyno-2-ylmetyl)pirolidino-3-yl]-3-tetrahydropiran-4-yl-7H-imidazo[1,5-a]pirazyn-8-on	Leczenie niedokrwistości sierpowatokrwinkowej
Portuguese	6-[(3S,4S)-4-Metil-1-(pirimidin-2-ilmetill)pirrolidin-3-il]-3-tetra-hidropiran-4-il-7H-imidazo[1,5-a]pirazin-8-ona	Tratmento do sindrome das células falciformes
Romanian	6-[(3S,4S)-4-methil-1-(pirimidin-2-ilmetil)pirrolidin-3-il]-3-tetrahidropiran-4-il-7H-imidazo[1,5-a]pirazin-8-one	Tratamentul anemiei cu celule falciforme
Slovak	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one	Liečba kosáčikovej anémie
Slovenian	6-[(3S,4S)-4-metil-1-(pirimidin-2-ilmetil)pirolidin-3-il]-3-tetrahidropiran-4-il-7H-imidazo[1,5-a]pirazin-8-one	Zdravljenje bolezni srpastih celic
Spanish	6-[(3S,4S)-4-methyl-1-(pirimidin-2-ilmetil)pirrolidin-3-il]-3-tetrahidropiran-4-il-7H-imidazo[1,5-a]pirazin-8-one	Tratamiento de la anemia drepanocítica
Swedish	6-[(3S,4S)-4-metyl-1-(pyrimidin-2-ylmetyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one	Behandling av sickle cell syndrom
Norwegian	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-3-tetrahydropyran-4-yl-7H-imidazo[1,5-a]pyrazin-8-one	Behandling av sigdcellesykdom
Icelandic	6-[(3S,4S)-4-metýl-1-(pýrimídín-2-ýlmetýl)pýrrolídín-3-ýl]-3-tetrahýdropýran-4-ýl-7H-ímídazó[1,5-a]pýrazín-8-on	Meðferð sigðkornablóðleysis