11 July 2017
EMA/324973/2017

Public summary of opinion on orphan designation

Decitabine and tetrahydrouridine for the treatment of sickle cell disease

On 20 June 2017, orphan designation (EU/3/17/1881) was granted by the European Commission to Ulrich Muehlner, Germany, for decitabine and tetrahydrouridine 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 other blood cells and to the walls of blood vessels and block them, restricting the flow of oxygen-rich blood to the internal organs such as the heart, lungs and spleen. Because the abnormal red blood cells have a shorter life span, they release haemoglobin into the blood circulation rather than carrying it to the internal organs where it is needed. As a result, patients experience severe pain as well as repeated infections and anaemia (low red-blood-cell counts).

Sickle cell disease is a severe disease that is long-lasting and may be life-threatening because of damage to the heart and the lungs, anaemia and infections.

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

At the time of designation, sickle cell disease affected approximately 1.3 in 10,000 people in the European Union (EU). This was equivalent to a total of around 67,000 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, the only medicine authorised in the EU to treat sickle cell disease was hydroxycarbamide (hydroxyurea). The main treatment for sickle cell disease was blood transfusion. This was usually combined with 'iron chelators' (medicines used to reduce high iron levels in the body

*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 515,700,000 (Eurostat 2017).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

resulting from repeated blood transfusions). In some cases, haematopoietic (blood) stem cell transplantation was used. This is a procedure where the patient's bone marrow is cleared of cells and replaced by stem cells from a donor to form new bone marrow that produces healthy 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 initial studies showed that it could help patients whose condition had not responded to previous treatment with hydroxycarbamide. 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 effects of the abnormal haemoglobin in sickle cell disease (haemoglobin S) can be reduced by fetal haemoglobin, a type of haemoglobin which is normally produced only in the developing baby. The gene that helps make fetal haemoglobin is switched off after birth by an enzyme called DNA methyltransferase-1 (DNMT1). The decitabine in this medicine lowers the amount of DNMT1 in body cells, so effectively switching the gene for fetal haemoglobin back on again. Tetrahydrouridine prevents the breakdown of decitabine in the body. As a result the medicine increases the production of fetal haemoglobin, which reduces the damaging effects of haemoglobin S on red blood cells. This is expected to help control the symptoms of the condition.

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.

Decitabine alone has been authorised in the EU since 20 September 2012 as the medicine Dacogen for the treatment of acute myeloid leukaemia.

At the time of submission, the combination of decitabine and tetrahydrouridine was not authorised anywhere in the EU for sickle cell disease. 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 12 May 2017 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 languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Decitabine and tetrahydrouridine	Treatment of sickle cell disease
Bulgarian	Децитабин и тетрахидроуридин	Лечение на сърповидно-клетъчна анемия
Croatian	Decitabin i tetrahidrouridin	Liječenje bolesti srpastih stanica
Czech	Decitabin a tetrahydrouridine	Léčba srpkovité anémie
Danish	Decitabin og tetrahydrouridin	Behandling af seglcellesygdom
Dutch	Decitabine en tetrahydrouridine	Behandeling van sikkelcelaandoening
Estonian	Detsitabiin ja tetrahüdrouridiin	Sirprakulise aneemia ravi
Finnish	Desitabiini ja tetrahydrouridiini	Sirppisolusyndrooman hoito
French	Décitabine et tétrahydrouridine	Traitement de la drépanocytose
German	Decitabin und Tetrahydrouridin	Behandlung der Sichelzellenanämie
Greek	δεσιταμπίνηκαι τετραϋδρουριδίνη	Θεραπεία της δρεπανοκυτταρικής αναιμίας
Hungarian	Decitabin és tetrahydrouridine	Sarlósejtes anaemia kezelése
Italian	Decitabina e tetraidrouridina	Trattamento dell'anemia falciforme
Latvian	Decitabīns un tetrahidrouridīns	Sirpjveida šūnu anēmijas ārstēšana
Lithuanian	Decitabinas su tetrahidrouridinu	Siklemijos gydymas
Maltese	Decitabine u tetrahydrouridine	Kura tal-marda taċ-ċelluli sura ta' minġel
Polish	Decytabina i tetrahydrourydyna	Leczenie niedokrwistości sierpowatokrwinkowej
Portuguese	Decitabina e tetra-hidrouridina	Tratmento do sindrome das células falciformes
Romanian	Decitabină și tetrahidrouridină	Tratamentul anemiei cu celule falciforme
Slovak	Decitabín a tetrahydrouridín	Liečba kosáčikovej anémie
Slovenian	Decitabin in tetrahidrouridin	Zdravljenje bolezni srpastih celic
Spanish	Decitabina y tetrahidrouridina	Tratamiento de la anemia drepanocítica
Swedish	Decitabin och tetraväteuridin	Behandling av sickle cell syndrom
Norwegian	Decytabin og tetrahydrouridin	Behandling av sigdcellesykdom
Icelandic	Decítabín og tetrahýdróúridín	Meðferð sigðkornablóðleysis

[1] At the time of designation