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EMA/COMP/513587/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Methotrexate for the treatment of alkaptonuria

On 29 August 2016, orphan designation (EU/3/16/1723) was granted by the European Commission to aimAKU (Associazione Italiana Malati di Alcaptonuria), Italy, for methotrexate for the treatment of alkaptonuria.

What is alkaptonuria?

Alkaptonuria is an inherited disorder in which patients have a mutation (change) in the gene for producing the enzyme homogentisate 1,2 dioxygenase (HGD). This enzyme is needed for the body to break down a substance called homogentisic acid produced from the amino acids phenylalanine and tyrosine. Patients with the condition cannot produce a properly working enzyme, leading to the build-up of dark coloured deposits in the tissues, including the eyes, skin and connective tissues of the joints and heart valves, and dark coloured pigment in the urine. Patients may also have abnormalities of red blood cells.

Alkaptonuria is a long-term debilitating and life-threatening disease due to symptoms such as joint pain, rupture of ligaments and muscles, kidney stones, heart-valve disease and effects on the blood.

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

At the time of designation, alkaptonuria affected less than 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 5,000 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 application no satisfactory methods of treatment were authorised in the EU for alkaptonuria. Patients received symptomatic treatment such as painkillers and physiotherapy, and surgical joint and heart-valve replacement in later stages of the disease.

*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 513,700,000 (Eurostat 2016).

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How is this medicine expected to work?

In patients with alkaptonuria the build-up of deposits involves a protein called serum amyloid A. Methotrexate reduces the production of this protein. This is expected to reduce the symptoms of the disease.

Methotrexate has been used for many years in the EU in the treatment of cancer and other serious long-term diseases such as rheumatoid arthritis where it blocks the growth of cells and tissues by interfering with the production of new DNA.

What is the stage of development of this medicine?

The effects of methotrexate have been evaluated in experimental models.

At the time of submission of the application for orphan designation, no clinical trials with methotrexate in patients with alkaptonuria had been started.

At the time of submission, methotrexate was not authorised anywhere in the EU for alkaptonuria 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 13 July 2016 recommending the granting of this designation.

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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	Methotrexate	Treatment of alkaptonuria
Bulgarian	Метотрексат	Лечение на алкаптонурия
Croatian	Metotreksat	Liječenje alkaptonurije
Czech	Methotrexate	Léčba alkaptonurie
Danish	Methotrexate	Behandling af alkaptonuri
Dutch	Methotrexate	Behandeling van alkaptonurie
Estonian	Metotreksaat	Alkaptonuuria ravi
Finnish	Metotreksaatti	Alkaptonurian hoito
French	Méthotrexate	Traitement de l'alcaptonurie
German	Methotrexat	Behandlung von Alkaptonurie
Greek	Μεθοτρεξάτη	Θεραπεία της αλκαπτονουρίας
Hungarian	Methotrexate	Alkaptonuria kezelése
Italian	Metotrexato	Trattamento dell'alcaptonuria
Latvian	Metotreksāts	Alkaptonūrijas ārstēšana
Lithuanian	Metotreksatas	Alkaptonurijos gydymas
Maltese	Methotrexate	Kura tal-alkaptonurja
Polish	Metotreksat	Leczenie alkaptonurii
Portuguese	Metotrexato	Tratamento de alcaptonúria
Romanian	Methotrexat	Tratamentul alcaptonuriei
Slovak	Metotrexát	Liečba alkaptonúrie
Slovenian	Methotreksat	Zdravljenje alkaptonurije
Spanish	Metotrexato	Tratamiento de la alcaptonuria
Swedish	Methotrexat	Behandling av alkaptonuri
Norwegian	Methotrexate	Behandling av alkaptonuria
Icelandic	Methotrexat	Meðferð við alkaptónúríu

[1] At the time of designation