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## Public summary of opinion on orphan designation

### L-cystine bis(N'-methylpiperazide) for the treatment of cystinuria

On 27 June 2018, orphan designation (EU/3/18/2036) was granted by the European Commission to PharmaKrysto Ltd, United Kingdom, for L-cystine bis(N'-methylpiperazide) (also known as L-CDNMP) for the treatment of cystinuria.

#### What is cystinuria?

Cystinuria is an inherited condition caused by a mutation (change) in the genes that produce the protein rBAT, which transports the amino acid cystine out of the urine and gut. Because the mutation means that rBAT does not work properly, people with the condition develop high concentrations of cystine in their urine. As cystine is poorly soluble, it crystallises in the urine inside the kidney, forming kidney stones that can damage the kidneys and block passage of urine. The condition is long-term debilitating due to the pain, bleeding, obstruction and risk of infection and kidney damage caused by the stones.

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

At the time of designation, cystinuria affected approximately 0.5 in 10,000 people in the European Union (EU). This was equivalent to a total of around 26,000 people<sup>\*</sup>, 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, patients were managed with increased fluid intake, restriction of sodium and protein in the diet, and with substances such as potassium citrate to make the urine more alkaline and so improve the amount of cystine it can dissolve, reducing the risk of stones. In some EU countries the medicines penicillamine and tiopronin were authorised for treatment in patients who could not be managed with other measures.

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<sup>\*</sup>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).

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with cystinuria because it works in a different way to available treatments and laboratory studies suggest that it can reduce formation of cystine kidney stones more effectively. 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?**

Crystals of cystine grow because cystine molecules can lock together in a regular pattern. This medicine is able to attach to the developing crystal and disrupt this pattern, preventing the crystal from forming. When taken by mouth the medicine appears in the urine, and is expected to stop crystal formation and development of stones in the kidney, thus preventing the symptoms and complications 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, no clinical trials with the medicine in patients with cystinuria had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for cystinuria 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 24 May 2018 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<sup>1</sup>, Norwegian and Icelandic

Language	Active ingredient	Indication
English	L-cystine bis(N'-methylpiperazide)	Treatment of cystinuria
Bulgarian	L-цистин бис (N'-метилпиперазид)	Лечение на цистинурия
Croatian	L-cistin bis (N'-metilpiperazid)	Liječenje cistinurije
Czech	L-cystin bis (N'-methylpiperazid)	Léčba cystinurie
Danish	L-cystin-bis (N'-methylpiperazid)	Behandling af cystinuri
Dutch	L-cystine bis (N'-methylpiperazide)	Behandeling van cystinurie
Estonian	L-tsüstiin bis (N'-metüülpiperasiid)	Tsüstiinuria ravi
Finnish	L-kystiini-bis (N'-metyyli-piperatsidi)	Kystinurian hoito
French	L-cystine bis (N'-méthylpipérazide)	Traitement de la cystinurie
German	L-Cystin-bis (N'-methylpiperazid)	Behandlung von Cystinurie
Greek	L-κυστίνη δις (N'-μεθυλοπипеραζίδιο)	Θεραπεία της κυστινουρίας
Hungarian	L-cisztin-bisz (N'-metil-piperazid)	Cystinuria kezelése
Italian	L-cistina bis (N'-metilpiperazide)	Trattamento della cistinuria
Latvian	L-cistīna bis (N'-metilpiperazīds)	Cistinūrijas ārstēšana
Lithuanian	L-cistinas bis (N'-metilpiperazidas)	Cistinurijos gydymas
Maltese	L-ċistin bis (N'-metilpiperazid)	Trattament taċ-ċistinurja
Polish	L-cystyna bis (N'-metylopiperazyd)	Leczenie cystynurii
Portuguese	L-cistina bis (N'-metilpiperazida)	Tratamento da cistinúria
Romanian	L-cistină bis (N'-metilpiperazidă)	Tratamentul cistinuriei
Slovak	L-cystín bis (N'-metyl-piperazid)	Liečba cystinúrie
Slovenian	L-cistin bis (N'-metilpiperazid)	Zdravljenje cistinurije
Spanish	L-cistina bis (N'-metilpiperazida)	Tratamiento de la cistinuria
Swedish	L-cystin-bis (N'-metyl-piperazid)	Behandling av cystinuri
Norwegian	L-cystin-bis (N'-metyl-piperazid)	Behandling av cystinuri
Icelandic	L-cystín bis (N'-metýlpíperasíð)	Meðferð á cystinmigu

<sup>1</sup> At the time of designation