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EMA/COMP/384853/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Citric acid monohydrate for the treatment of acute liver failure

On 27 June 2016, orphan designation (EU/3/16/1675) was granted by the European Commission to CATS Consultants GmbH, Germany, for citric acid monohydrate for the treatment of acute liver failure.

What is acute liver failure?

Acute liver failure is the sudden loss of normal liver function in a patient with a previously normal liver and without evidence of chronic (long-term) liver disease.

The most common first sign of liver failure is jaundice (yellowing of the skin). Acute liver failure brings serious complications such as excessive bleeding due to impaired blood clotting, swelling around the brain, convulsions (fits) and coma.

The most common causes of acute liver failure are viral hepatitis (an infectious disease that affects the liver), overdose of medicines such as paracetamol or consumption of toxic substances such as poisonous mushrooms.

Acute liver failure is a life-threatening disease because of its damaging effects on the liver, brain and other organs.

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

At the time of designation, acute liver failure affected approximately 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 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 designation, the main treatment option for acute liver failure was liver transplantation. Patients with acute liver failure caused by paracetamol overdose were treated with N-acetylcysteine.

^{*}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).

The sponsor has provided sufficient information to show that citric acid monohydrate might be of significant benefit for patients with acute liver failure because early laboratory studies indicate that it may prolong survival of patients until a liver transplant is possible. 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?

One function of the liver is to transform ammonia into urea which is then harmlessly eliminated in the urine. When the liver fails, it cannot transform ammonia into urea. The ammonia then builds up in the blood and the brain causing many of the symptoms of acute liver failure.

This medicine is a fluid made of microscopic fat particles, called liposomes, containing a solution of citric acid. The fluid is to be injected into the space inside the abdomen (belly). Ammonia is then expected to pass from the blood vessels lining the abdomen into the liposomes, where it is trapped and removed from the body when the fluid is drained out of the abdomen. Citric acid may also help to eliminate other toxic substances.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, the evaluation of the effects of this medicine in experimental models was ongoing.

At the time of submission, no clinical trials with the medicine in patients with acute liver failure had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for acute liver failure 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 19 May 2016 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 languages¹, Norwegian and Icelandic

Language	Active ingredient	Indication
English	Citric acid monohydrate	Treatment of acute liver failure
Bulgarian	Монохидрат на лимонената киселина	Лечение на остра чернодробна недостатъчност
Croatian	Monohidrat limunske kiseline	Liječenje akutnog zatajenja jetre
Czech	Monohydrát kyseliny citronové	Léčba akutní jaterní insuficience
Danish	Citronsyremonohydrat	Behandling af akut leversvigt
Dutch	Citroenzuurmonohydraat	Behandeling van acuut leverfalen
Estonian	Tsitraathappemonohüdraat	Akuutse maksapuudulikkuse ravi
Finnish	Sitruunahappo monohydraatti	Akuutin maksan vajaatoiminnan hoito
French	Acide citrique monohydraté	Traitement de l'insuffisance hépatique aiguë
German	Zitronensäuremonohydrat	Behandlung des akuten Leberversagens
Greek	Μονοϋδρικό κιτρικό οξύ	Θεραπεία της οξείας ηπατικής ανεπάρκειας
Hungarian	Citromsav monohidrát	Akut májelégtelenség kezelése
Italian	Acido citrico monoidrato	Trattamento della insufficienza epatica acuta
Latvian	Citronskābes monohidrāts	Akūtas aknu mazspējas ārstēšana
Lithuanian	Citrinų rūgšties monohidratas	Ūminio kepenų nepakankamumo gydymas
Maltese	Citric acid monohydrate	Kura ta' insuffiċjenza akuta tal-fwied
Polish	Monohydrat kwasu cytrynowego	Leczenie ostrej niewydolności wątroby
Portuguese	Ácido cítrico monohidratado	Tratamento da insuficiência hepática aguda
Romanian	Acid citric monohidrat	Tratamentul insuficienței hepatice acute
Slovak	Monohydrát kyseliny citrónovej	Liečba akútneho zlyhania pečene
Slovenian	Monohidrat limonske kisline	Zdravljenje akutne jetrne odpovedi
Spanish	Ácido cítrico monohidrato	Tratamiento de la insuficiencia hepática aguda
Swedish	Citronsyra monohydrat	Behandling av akut leversvikt
Norwegian	Sitronsyre monohydrat	Behandling av akutt leversvikt
Icelandic	Sítrónsýru einhýdrat	Meðferð bráðrar lifrabilunar

¹ At the time of designation