European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of 2',3',5'-tri-O-acetyluridine for the treatment of 5-fluorouracil overdose

On 15 May 2009, orphan designation (EU/3/09/637) was granted by the European Commission to Wellstat Therapeutics EU Limited, United Kingdom, for 2',3',5'-tri-O-acetyluridine for the treatment of 5-fluorouracil overdose.

What is 5-fluorouracil overdose?
5-Fluorouracil (5-FU) overdose is when a patient receives a dose of 5-FU that is too high. 5-FU is a medicine to treat cancer. An overdose can happen if an error is made when calculating the dose or if there is a problem with the pump that is used to deliver the medicine. A dose can be too high also if the patient's body cannot break down or eliminate 5-FU normally.
The effects of 5-FU overdose are more severe than the normal side effects of the medicine, and include neuropathy (damage to nerve cells), severe damage to organs, sepsis (the presence of a large amount of bacteria in the blood) and septic shock (a steep fall in blood pressure caused by infection). These effects usually begin a few days after overexposure to the medicine. 5-FU overdose can be life threatening.

What is the estimated number of patients affected by the condition?
At the time of designation, 5-FU overdose affected approximately 0.2 people in 10,000 per year in the European Union (EU)*. This is equivalent to a total of around 10,000 people per year, which was considered to be is below the threshold for orphan designation. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?
At the time of designation, no satisfactory methods were authorised in the EU for the treatment of 5-FU overdose. Depending on the severity of the overdose, patients were given 'best supportive care' (any medicines or techniques to help patients), such as fluid replacement to treat dehydration, antibiotics to treat infections, growth factors to increase the production of white blood cells required to fight infection, medicines to keep the blood pressure high and painkillers.

How is this medicine expected to work?
2',3',5'-tri-O-acetyluridine is expected to be used as a rescue medication after an overdose of 5-FU. 5-FU is a cytotoxic medicine (a medicine that kills cells that are dividing rapidly, such as cancer cells). In the body, 5-FU takes the place of uridine, which is part of the fundamental genetic material of cells, and interferes with the enzymes involved in making genetic material. As a result, it slows down the

*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 27), Norway, Iceland and Liechtenstein. This represents a population of 504,800,000 (Eurostat 2009).

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growth of cancer cells, eventually killing them. When 5-FU is given at a dose that is higher than the patient can tolerate, it also damages normal cells.
2',3',5'-tri-O-acetyluridine is a 'prodrug' of uridine, which means that it is converted into uridine in the body. When given to a patient who has received too much 5-FU, the medicine is expected to work by 'competing' with the 5-FU, reducing its incorporation into the genetic material. This is expected to reduce the effects of 5-FU overdose.
2',3',5'-tri-O-acetyluridine is to be used before the appearance of severe symptoms. It is to be given as soon as the doctor recognises that there has been an error in the administration of 5-FU or that the patient cannot break down or eliminate 5-FU normally. It is not supposed to be used when the 5-FU is given at the correct dose or exposure, mainly because it may reduce the effectiveness of 5-FU in treating the cancer.

What is the stage of development of this medicine?
The effects of 2',3',5'-tri-O-acetyluridine have been evaluated in experimental models.
At the time of submission of the application for orphan designation, clinical results with the drug in patients overdosed with 5-FU were known, and no clinical trials for this condition were planned.
At the time of submission, 2',3',5'-tri-O-acetyluridine was not authorised anywhere in the EU for 5-FU overdose or designated as 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 2 April 2009 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 Community) 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.

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Translations of the active ingredient and indication in all official EU languages, Norwegian and Icelandic

Language	Active ingredient	Indication
English	2',3',5'-tri-O-acetyluridine	Treatment of 5-fluorouracil overdose
Bulgarian	2',3',5'-три-О-ацетилуридин	Лечение на свръх-доза от 5-флуороурацил
Czech	2',3',5'-tri-O-acetyluridin	Postup při předávkování 5-fluorouracilem
Danish	2',3',5'-tri-Oxy-acetyluridin	Behandling af 5-fluorouracil overdosis
Dutch	2',3',5'-tri-O-acetyluridine	Behandeling van 5-fluorouracil overdosis
Estonian	2',3',5'-tri-O-atsetüüluridiin	5-fluorouratsiili üleannuse raviks
Finnish	2',3',5'-tri-O-asetyyliuridiini	5-fluorourasiilin yliannoksen hoito
French	2',3',5'-tri-O-acétyluridine	Traitement du surdosage en 5-fluorouracile
German	2',3',5'-Tri-O-Acetyluridin	Behandlung einer 5-Fluorouracil-Überdosierung
Greek	2',3',5'-τρι-Ο-ακετυλο-ουριδίνη	Θεραπεία σε περίπτωση υπερβολικής δόσης της 5-Φθοριοουρακίλης
Hungarian	2',3',5'-tri-O-acetil-uridin	5-fluor-uracil túladadolás kezelése
Italian	2',3',5'-tri-O-acetiluridina	Trattamento del sovradosaggio di 5-fluorouracile
Latvian	2',3',5'-tri-O-acetiluridīns	5-fluorouracila pārdozēšanas ārstēšanai
Lithuanian	2',3',5'-tri-O-acetiluridinas	Gydymas perdozavus 5-fluorouracilą
Maltese	2',3',5'-tri-O-aċitiluridina	Kura ta' doża eċċessiva ta' 5-fluorouracil
Polish	2',3',5'-tri-O-acetylourydyna	Leczenie przedawkowania 5-fluorouracylu
Portuguese	2',3',5'-tri-O-acetiluridina	Tratamento da sobredosagem de 5-fluorouracilo
Romanian	2',3',5'- tri-O acetiluridină	Tratamentul supradozajului cu 5-fluorouracil
Slovak	2',3',5'-tri-O-acetyluridín	Liečba predávkovania 5-fluórouracilom
Slovenian	2',3',5'-tri-O-acetiluridin	Zdravljenje predoziranja 5-fluorouracila
Spanish	2',3',5'-tri-O-acetiluridina	Tratamiento de la sobredosis de 5-fluorouracilo
Swedish	2,3,5-tri-O-acetyluridin	Behandling av överdos av 5-fluorouracil
Norwegian	2',3',5'-tri-O-acetyluridin	Behandling av overdose av 5-fluorouracil
Icelandic	2',3',5'-þrí-O-acetýlúridín	Meðferð á 5-flúoróúrasíl ofskammti