European Medicines Agency

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Questions and answers on recommendation for the refusal of the marketing authorisation for Vedrop

International non-proprietary name (INN): ***tocofersolan***

On 22 January 2009, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Vedrop 50 mg/ml oral solution, intended for the treatment of children with vitamin E deficiency due to cystic fibrosis, or to congenital or hereditary chronic cholestasis. The company that applied for authorisation is Orphan Europe S.A.R.L. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Vedrop?
Vedrop is an oral solution (a solution that is taken by mouth) that contains the active substance tocofersolan.

What was Vedrop expected to be used for?
Vedrop was expected to be used to treat or prevent vitamin E deficiency in children with cystic fibrosis or with congenital or hereditary chronic cholestasis who cannot absorb the vitamin from the gut. Cystic fibrosis is an inherited disease that affects the glands in the lungs, gut and pancreas that secrete fluids such as mucus and digestive juices. Congenital or hereditary chronic cholestasis is an inherited disease in which the body cannot secrete bile into the gut. Bile is a fluid produced in the liver that helps to break down fats.

How is Vedrop expected to work?
Vitamin E is a natural substance that cannot be made by the body and is therefore needed in the diet. It has a number of actions in the body, including protecting the nervous system (brain and nerves) from damage due to oxidation. Because vitamin E is soluble in fats and not water, it can only be absorbed from the gut into the body alongside fat particles. Low vitamin E levels occur in patients with cystic fibrosis and cholestasis because they have problems absorbing fats from the gut. In cystic fibrosis, the pancreas does not secrete enough digestive juices to break fats down so that they can be absorbed. In cholestasis, the body cannot secrete enough bile, which is also needed to help break down fats.
The active substance in Vedrop, tocofersolan, is vitamin E that has been made water-soluble by attaching it to a chemical called polyethylene glycol. It was expected that tocofersolan would be absorbed from the gut in patients who have difficulty absorbing fats and vitamin E from the diet due to cystic fibrosis or cholestasis. The use of vitamin E preparations in this population is expected to prevent neurological deterioration (problems in the nervous system) due to vitamin E deficiency.

What documentation did the company present to support its application to the CHMP?
The effects of Vedrop were first tested in experimental models before being studied in humans.
The company presented data on human studies from the scientific literature. In the largest of the three main studies, 60 children with chronic cholestasis were given Vedrop for about two years. The children all had vitamin E deficiency that was not responding to other vitamin E treatments given by mouth. The main measure of effectiveness was the number of children whose symptoms affecting the brain and nerves improved or stayed the same.
The company presented very little information on patients with cystic fibrosis.

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What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?
The CHMP noted that further information would be needed to show that potential impurities in the medicine were safe and to justify why ingredients called propylparabens were included. The Committee also noted that information was lacking on the processes and tests used when making the medicine.
The CHMP was concerned that there was insufficient evidence from children with cystic fibrosis to show how the body would respond to Vedrop and whether it would be beneficial for patients with this disease. There was also not enough evidence to prove that the medicine used in the studies was the same as Vedrop that was intended for marketing, particularly as the studies were performed 15 to 20 years ago.

What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using Vedrop?
The company informed the CHMP that there are no consequences for patients currently included in clinical trials, compassionate use programmes or named patient programme with Vedrop. If you are in a clinical trial, compassionate use programme or named patient programme and need more information about your treatment, contact the doctor who is giving it to you.