European Medicines Agency

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QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF THE MARKETING AUTHORISATION
for
SOVRIMA

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

On 24 July 2008, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Sovrima 150 mg tablets, intended for the treatment of Friedreich's ataxia. The company that applied for authorisation is Santhera Pharmaceuticals (Deutschland) GmbH. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Sovrima?
Sovrima is a medicine that contains the active substance idebenone. It was to be available as tablets (150 mg).

What was Sovrima expected to be used for?
Sovrima was expected to be used to treat Friedreich's ataxia. It was to be used in children and young adults, as well as in adults whose disease had been diagnosed within the past five years and in adults with cardiomyopathy (harm to the heart muscle).
Friedreich's ataxia is an inherited disease. It has a range of symptoms that gradually get worse, including difficulty walking, an inability to co-ordinate movements, muscle weakness, speech problems, damage to the heart muscle, and diabetes. It is usually fatal in adulthood.
Sovrima was designated as an orphan medicinal product on 8 March 2004 for Friedreich's ataxia.
The active substance in Sovrima, idebenone, has been available in some countries in Europe since the 1990s for cognitive disorders (problems with thinking, learning and remembering) and for Alzheimer's disease.

How is Sovrima expected to work?
Patients with Friedreich's ataxia do not have enough of a protein called frataxin. Frataxin plays a role in building the energy-producing parts of cells. When frataxin is missing, the production of energy is severely impaired and highly reactive and toxic forms of oxygen are produced. These highly reactive forms of oxygen damage cells in the brain, the spinal cord and nerves, as well as in the heart and pancreas, causing the symptoms of the disease.
The active substance in Sovrima, idebenone, is an antioxidant agent. It is expected to work by enhancing the production of energy within cells and possibly by neutralising the highly reactive forms of oxygen. This was expected to protect cells from damage and to reduce the symptoms of Friedreich's ataxia.

What documentation did the company present to support its application to the CHMP?
The effects of Sovrima were first tested in experimental models before being studied in humans.
The effectiveness of Sovrima was studied in one main study involving 48 patients. The study compared the effectiveness of three different doses of Sovrima (5, 15 and 40 mg per kg body weight) with that of placebo (a dummy treatment) over six months. The main measure of effectiveness was the change in the level of a substance in the blood called deoxyguanosine, which is a marker of cell damage caused by highly reactive forms of oxygen. The study looked also at the effectiveness of Sovrima in controlling movements, as measured on standard scales for ataxia symptoms, at its impact on daily activities as measured using a questionnaire and its effect on heart function.

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What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?
The CHMP was concerned that the effectiveness of Sovrima had not been demonstrated in the single study performed. Sovrima did not show a significant improvement compared with placebo, with respect to the main measure of effectiveness, as well as to other evaluated parameters. The CHMP had also concerns that there was no clear explanation for the fact that the intermediate dose of Sovrima seemed to be more effective than the higher dose. In addition, the supporting information from the scientific literature was weak and did not demonstrate a consistent clinical benefit of Sovrima for this disease.
At that point in time, the CHMP was of the opinion that the benefits of Sovrima in the treatment of Friedreich's ataxia did not outweigh its risks. Hence, the CHMP recommended that Sovrima be refused marketing authorisation.

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

What is happening with idebenone for cognitive disorders and Alzheimer's disease?
There are no consequences on the use of idebenone in its used indications, for which the balance of benefits and risks remains unchanged.