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Questions and answers

Refusal of the marketing authorisation for Kynamro (mipomersen)

Outcome of re-examination

On 13 December 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Kynamro, intended for the treatment of patients with certain forms of familial hypercholesterolaemia. The company that applied for authorisation is Genzyme Europe B.V.

The applicant requested a re-examination of the opinion. After considering the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 21 March 2013.

What is Kynamro?

Kynamro is a medicine that contains the active substance mipomersen. It was to be available as a solution for injection under the skin.

What was Kynamro expected to be used for?

Kynamro was expected to be used to treat patients with an inherited disease causing high blood cholesterol levels, called familial hypercholesterolaemia. It was initially expected to be used to treat two closely related forms of the disease called 'severe heterozygous' and 'homozygous' familial hypercholesterolaemia. During the assessment of Kynamro, the indication was restricted to the most severely affected patients with homozygous and compound heterozygous familial hypercholesterolaemia only.

It was expected to be used together with other cholesterol-lowering medicines and a low-fat diet.

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How is Kynamro expected to work?

The active substance in Kynamro, mipomersen, is an 'antisense oligonucleotide', a very short fragment of DNA designed to block the production of a protein called apolipoprotein B, by attaching to the genetic material of cells responsible for producing it. Apolipoprotein B is the main component of 'low density lipoprotein' (LDL) cholesterol, commonly known as 'bad cholesterol', and of two closely related types of cholesterol called 'intermediate density lipoprotein' (IDL) and 'very low density lipoprotein' (VLDL) cholesterol. Patients with homozygous familial hypercholesterolaemia have high blood levels of these types of cholesterol, which increases the risk of coronary heart disease (heart disease caused by the obstruction of the blood vessels that supply the heart muscle). By blocking the production of apolipoprotein B, Kynamro was expected to reduce the levels of these types of lipoproteins in the blood of patients.

What did the company present to support its application?

The effects of Kynamro were first tested in experimental models before being studied in humans.

The company submitted the results of two main studies. One involved 51 patients with homozygous familial hypercholesterolaemia and the other involved 58 patients with severe heterozygous familial hypercholesterolaemia. The studies compared the effects of Kynamro with placebo when added onto treatment with other cholesterol-lowering medicines and a low-fat diet, for a treatment period of 26 weeks. The main measure of effectiveness was the reduction in the patients' LDL cholesterol levels.

What were the CHMP's main concerns that led to the refusal?

In December 2012, the CHMP was concerned that a high proportion of patients stopped taking the medicine within two years, even in the restricted group of patients with homozygous familial hypercholesterolaemia, mainly due to side effects. This was considered an important limitation because Kynamro is intended for long-term treatment. The CHMP was also concerned by the potential long-term consequences of liver test results showing a build-up of fat in the liver and increased enzyme levels, and was not convinced that the company had proposed sufficient measures to prevent the risk of irreversible liver damage. Moreover, the Committee was concerned that more cardiovascular events (problems with the heart and blood vessels) were reported in patients taking Kynamro than in patients taking placebo. This prevented the CHMP from concluding that Kynamro's intended cardiovascular benefit, in terms of reducing cholesterol levels, outweighed its potential cardiovascular risk. Therefore, at that point in time, the CHMP was of the opinion that the benefits of Kynamro did not outweigh its risks and recommended that it be refused marketing authorisation.

During the re-examination in March 2013, the CHMP's concerns remained unresolved and were not fully addressed by measures proposed by the company. Therefore, the CHMP refusal was confirmed after re-examination.

What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

The company informed the CHMP that patients receiving the medicine in clinical trials will continue to do so as planned. Patients applying for compassionate use programmes will continue to be evaluated and will receive the medicine if eligible.

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.