



13 December 2012
EMA/792736/2012
EMA/H/C/002429

Questions and answers

Refusal of the marketing authorisation for Kynamro (mipomersen)

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. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

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 patients with homozygous familial hypercholesterolaemia only.

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

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?

The CHMP noted that Kynamro was effective at reducing LDL cholesterol levels in patients with homozygous and severe heterozygous familial hypercholesterolaemia. After 26 weeks, the approximate average reduction seen in patients taking Kynamro was between 25% and 36%, while it was between 3% and 13% in patients taking placebo.

However, the CHMP was concerned about the medicine's safety. The Committee noted 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 such as flu-like symptoms, injections site reactions and liver toxicity. This was considered important because Kynamro is intended for long-term treatment in order to maintain the cholesterol-lowering effect. The CHMP was also concerned by liver test results in patients taking Kynamro 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 a greater proportion of patients taking Kynamro experienced serious cardiovascular events (problems with the heart and blood vessels) than patients taking placebo. This prevented the CHMP from concluding that Kynamro's intended cardiovascular benefit, in terms of reducing cholesterol levels, outweighed its 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.

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.