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Questions and answers

Refusal of the marketing authorisation for Glybera (alipogene tiparvovec)

On 23 June 2011, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Glybera, intended for use in patients with lipoprotein lipase deficiency. The negative opinion was confirmed in October 2011, following a re-examination requested by the company, Amsterdam Molecular Therapeutics (AMT) B.V.

Following a request from the European Commission in January 2012, the CHMP re-evaluated Glybera in a restricted group of patients with severe or multiple pancreatitis attacks. The CHMP maintained its previous recommendation that the medicine should not be granted marketing authorisation.

What is Glybera?

Glybera is a medicine that contains the active substance alipogene tiparvovec. It was to be available as a solution for injection.

Glybera was developed as a type of advanced therapy medicine called a 'gene therapy product'. This is a type of medicine that works by delivering a gene into the body to correct a genetic deficiency.

What was Glybera expected to be used for?

Glybera was expected to be used to treat lipoprotein lipase deficiency, a very rare disease where patients lack the gene to produce lipoprotein lipase, an enzyme responsible for breaking down fats in lipoproteins (fat-carrying particles in the blood).

Glybera was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 8 March 2004 for treatment of lipoprotein lipase deficiency.

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How is Glybera expected to work?

The active substance in Glybera, alipogene tiparvovec, is a medicinal product using a virus that has been modified so it can carry a gene for lipoprotein lipase. It was expected to be injected into the patient's muscles, where it would correct the deficiency of lipoprotein lipase by enabling cells of the muscle to produce the enzyme.

The virus used in Glybera is an 'adeno-associated viral vector' that has been modified so that it cannot make copies of itself. The virus does not cause infections in humans.

What did the company present to support its application?

The effects of Glybera were first tested in experimental models before being studied in humans. The company's clinical programme included 27 patients with lipoprotein lipase deficiency on a low-fat diet. The majority of patients who received Glybera also received immunosuppressive treatment to reduce the reactions of the body's immune system against medicine. The main measure of effectiveness was based on a reduction in blood fat levels, with patients being followed up after the study.

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

Because Glybera is an advanced therapy medicine, it was also assessed by the Committee for Advanced Therapies (CAT). Taking into account the initial negative opinion provided by the CAT, the CHMP concluded at its initial assessment that the studies had not shown a consistent long-lasting benefit of Glybera. The applicant had not provided sufficient evidence of a persistence of effect in lowering blood fats in a clinically relevant manner and there were too few patients for whom sufficiently long-term data were available. There was also insufficient evidence of a reduction in the rate of pancreatitis (inflammation of the pancreas), which is a major complication of lipoprotein lipase deficiency. In view of the uncertainty over Glybera's benefits, the CHMP was concerned that there was insufficient evidence that its benefits outweigh its potential risks.

During the re-examination, the CAT concluded that these concerns could be addressed with additional post-marketing studies. Whilst the CHMP considered Glybera to be potentially valuable in the treatment of this very rare disease, it took a different view and concluded that the benefits of the medicine did not outweigh its risks due to questions over the medicine's benefits. The initial recommendation that Glybera should not be granted marketing authorisation was therefore maintained.

When evaluating Glybera in patients with severe or multiple pancreatitis attacks, the CHMP found that the evidence of efficacy from the small number of patients assessed (data from only 12 patients were available) was not sufficiently convincing. In addition, the reduced risk of pancreatitis seen in a few of the patients could have been due to other factors (such as changes in lifestyle and diet, and the natural course of the disease).

In its discussions, the Committee recognized the difficulty of obtaining data in this rare disease and took this into account while assessing the data. However, after careful consideration of all the evidence and circumstances of the disease, the Committee maintained its previous opinion not to recommend marketing authorisation.

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

The company informed the CHMP that there are no consequences for people who have already received the medicine. Their doctor will continue to follow up these patients as previously agreed.

If you are in a clinical trial and need more information about your treatment, contact the doctor who has given it to you.

The summary of the opinion of the Committee for Orphan Medicinal Products for Glybera can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.