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Questions and answers

Refusal of the marketing authorisation for Qsiva (phentermine / topiramate)

Outcome of re-examination

On 18 October 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 Qsiva, intended for the treatment of obesity. The company that applied for authorisation is Vivus BV.

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 February 2013.

What is Qsiva?

Qsiva is a medicine that contains the active substances phentermine and topiramate. It was to be available as modified release capsules.

What was Qsiva expected to be used for?

Qsiva was expected to be used to treat severely obese patients (BMI $\geq$ 35 kg/m^2), or patients with obesity (BMI $\geq$ 30 kg/m^2) who have weight-related health problems, such as high blood pressure, type 2 diabetes or abnormal levels of fat in the blood.

How is Qsiva expected to work?

The two active substances in Qsiva are appetite suppressants. Phentermine suppresses appetite by releasing a chemical transmitter called norepinephrine (or noradrenaline) in the hypothalamus, the region of the brain that controls hunger.

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Topiramate is thought to act by increasing the body's energy use, reducing energy efficiency and reducing the patients' appetite for food. The exact mechanisms of action of topiramate are not fully understood.

What did the company present to support its application?

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

Four main studies involving a total of approximately 4,000 obese or overweight patients were conducted that compared Qsiva treatment with placebo (a dummy treatment) and with phentermine or topiramate treatments given alone. Two of the studies specifically included patients with weight-related health problems, including diabetes, high blood pressure, and abnormal fat and sugar levels in the blood.

The main measures of effectiveness were the amount of weight loss and the number of patients with at least 5% weight loss after 28 or 56 weeks of treatments. In one of the studies patients were treated for longer and effectiveness measurements were taken after 108 weeks.

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

The CHMP noted that the main studies showed clinically relevant weight loss following treatment with Qsiva but had concerns about the medicine's long-term effects on the heart and blood vessels, particularly due to the effects of phentermine, which is known to increase the heart rate but whose long-term effects are not clear. Secondly, there were concerns about the long-term psychiatric effects (depression and anxiety were reported in the studies) and cognitive effects (such as problems with memory and attention) related to the topiramate component of Qsiva. Topiramate is also known to be potentially harmful to the unborn baby if taken by pregnant women.

The Committee noted that there was a high probability that, if approved, the medicine would not be used strictly for the intended patients. The applicant did propose measures to reduce this risk, but the measures were considered difficult to implement in practice.

Therefore, the CHMP concluded that the benefits of Qsiva did not outweigh its risks and recommended that it be refused marketing authorisation. The CHMP refusal was confirmed after re-examination.

What consequences does this refusal have for patients in clinical trials?

The company informed the CHMP that that there are no consequences for patients involved in clinical trials.