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Questions and answers on the suspension of medicines containing sibutramine

Outcome of a procedure under Article 107 of Directive 2001/83/EC

The European Medicines Agency has completed a review of the safety and effectiveness of sibutramine. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of sibutramine do not outweigh its risks, and that all marketing authorisations for medicines containing sibutramine should be suspended throughout Europe.

What is sibutramine?

Sibutramine is a 'serotonin-noradrenaline re-uptake inhibitor' (SNRI). It works by preventing the neurotransmitters 5-hydroxytryptamine (also called serotonin) and noradrenaline from being taken back up into nerve cells in the brain. Neurotransmitters are chemicals that allow nerve cells to communicate with one another. By blocking their re-uptake, sibutramine increases the amount of these neurotransmitters in the brain.

Sibutramine-containing medicines are used in the management of obesity. The increased levels of neurotransmitters in the brain help patients to feel full after a meal, and this helps to reduce their food intake. They are used, alongside diet and exercise, in patients who are obese (very overweight) with a body mass index (BMI) greater than or equal to 30 kg/m², and in patients who are overweight (with a BMI greater than or equal to 27 kg/m²) and also have other obesity-related risk factors, such as type 2 diabetes or dyslipidaemia (abnormal levels of fat in the blood).

Sibutramine-containing medicines have been authorised in the European Union (EU) since 1999. They are available as capsules containing 10 mg or 15 mg sibutramine, under the trade names Reductil and other names¹, and as generic medicines.

Why was sibutramine reviewed?

Sibutramine was originally reviewed by the Agency in 1999 and 2002, following concerns over its safety, especially cardiovascular side effects (increased blood pressure and heart rate). At that time, the CHMP concluded that the benefits of sibutramine for the management of obese and

¹ Afibon, Ectiva, Lindaxa, Meissa, Meridia, Minimacin, Minimectil, Obesan, Sibutral, Sibutril, Siluton, Sitrane, Redoxade, Zelixa and Zelium.



overweight patient outweighed its risks. However, the Committee also asked the company that makes Reductil, Abbott Laboratories, to start a study of sibutramine in patients with cardiovascular risk factors, looking particularly at the medicine's safety. The Committee also asked the company to provide six-monthly updates on the progress of the study.

As a result, in 2002, the company started the SCOUT study (Sibutramine Cardiovascular Outcome Trial) to determine the impact of weight loss with sibutramine on cardiovascular problems in a large group of overweight and obese patients at high risk for cardiovascular disease. The study compared sibutramine with placebo (a dummy treatment), and looked not only at how much weight the patients were losing, but also at the occurrence of cardiovascular events, such as heart attack, stroke and cardiac arrest. In total, about 9,800 patients have been followed up for six years.

Although the full data from the SCOUT study have not yet been analysed, the study's Data Safety Monitoring Board (a body of independent experts appointed to review regularly the outcome of the clinical trial) informed the Agency in October 2009 of preliminary data indicating that sibutramine is associated with more cardiovascular problems than placebo.

On the basis of these data, the German medicines regulatory agency (BfArM) triggered in November 2009 a review under Article 107 of Directive 2001/83/EC. They requested that the CHMP assess the impact of the new data on the benefit-risk balance of sibutramine to prepare an opinion on whether the marketing authorisations for products containing sibutramine should be maintained, changed, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP reviewed the responses from the company to a list of questions on the SCOUT study. The Committee also looked at other studies on the effectiveness of sibutramine for weight loss.

The Committee also consulted a group of experts specialising in the treatment of metabolic diseases.

What are the conclusions of the CHMP?

The CHMP noted that the SCOUT study showed an increased risk of serious cardiovascular events (such as heart attack or stroke) in patients with known cardiovascular disease taking sibutramine.

Most of the patients in the SCOUT study would not normally be given sibutramine, as the medicine is contra-indicated in patients with cardiovascular disease. Nevertheless the Committee considered that an increased risk can also apply to patients for whom sibutramine can be prescribed because obese and overweight patients are likely to be at risk of cardiovascular disease.

Finally, looking at all of the studies of sibutramine in the management of obesity, the CHMP noted that the weight loss achieved with sibutramine treatment is modest in comparison with that obtained with placebo, with patients losing on average two to four kilograms more than with placebo. The Committee also noted that it is not clear if this effect on weight loss can be maintained when sibutramine treatment is stopped.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of sibutramine-containing medicines do not outweigh their risks, and therefore recommended that the marketing authorisations for sibutramine-containing medicines be suspended across the EU. The suspension will remain in place until the company can provide data that are sufficient to allow the identification of a group of patients for whom sibutramine's benefits clearly outweigh its risks.

What are the recommendations for prescribers and patients?

- Doctors should stop prescribing sibutramine-containing medicines to obese or overweight patients. They should also review the treatment of patients currently treated with the medicine.
- Pharmacist should no longer dispense sibutramine-containing medicines.
- Patients who are taking a medicine containing sibutramine to help them to lose weight should make an appointment with their doctor at the next convenient time to discuss alternative measures to lose weight. Patients who wish to stop treatment before seeing their doctor can do so at any time.
- Patients who have any questions should speak to their doctor or pharmacist.

The European Commission issued a decision on 6 August 2010.