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SCIENCE MEDICINES HEALTH

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## Questions and answers on the review of medicines containing trimetazidine (20 mg tablets, 35 mg modified release tablet and 20 mg/ml oral solution)

Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended

On 21 June 2012, the European Medicines Agency completed a review of the safety and effectiveness of trimetazidine following concerns over its effectiveness and reports of movement disorders such as parkinsonian symptoms with these medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits continue to outweigh the risks in patients with angina pectoris but that treatment should be restricted to add-on to existing treatments in patients who are not adequately controlled by or who are intolerant to other medicines for angina pectoris. For the symptomatic treatment of tinnitus, vertigo and visual field disturbances, the CHMP concluded that the benefits no longer outweigh the risks and that these uses should no longer be authorised. In addition, the Committee recommended new contraindications and warnings to reduce and manage the possible risk of movement disorders, associated with the use of this medicine.

### What is trimetazidine?

Trimetazidine is a medicine used to prevent angina attacks, which are sudden pains to the chest, jaw and back brought on by physical effort, due to reduced blood flow to the heart. Angina is commonly associated with a narrowing of the blood vessels that supply the heart, called the coronary arteries.

Trimetazidine is a 'metabolic agent', a medicine which has an effect on metabolism (the process by which substances are broken down in the body). It is believed to protect against myocardial ischaemia (reduced blood supply to the heart muscle) by increasing the rate at which glucose is broken down.

Trimetazidine is also used to treat the symptoms of vertigo (a spinning sensation) and tinnitus (ringing sensation in the ears), and to treat reduced vision and visual field disturbances (unclear or disturbed vision) due to problems affecting the blood vessels.

Medicines containing trimetazidine have been available since the 1970s and are currently marketed in Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia and Spain. They are marketed under the invented name Vastarel and other trade names.



## **Why was trimetazidine reviewed?**

In April 2011, the French medicines regulatory agency concluded that, based on a review of the evidence in France, the risks of medicines containing trimetazidine were greater than the benefits for all the authorised indications. A main concern was that the effectiveness of trimetazidine had not been convincingly demonstrated in any of the authorised indications, since the studies supporting the authorised uses had several methodological weaknesses and only showed a small benefit.

In addition, there were concerns regarding the safety of trimetazidine-containing medicines following reports of Parkinson syndrome (a group of symptoms that include shaking, slow movement and muscle stiffness) and other motor disorders such as tremor (shaking), muscle rigidity and walking disorders, and restless legs syndrome (a disorder where the patient has uncontrollable urges to move the limbs to stop uncomfortable, painful or odd sensations in the body, usually at night). These symptoms were seen in some patients with no previous history of Parkinson syndrome, and in many cases their symptoms resolved when they stopped taking trimetazidine.

Despite strengthening the warnings in the prescribing information of these medicines, the French agency remained concerned that the benefits for trimetazidine did not outweigh its risks. Consequently, on 22 April 2011 it asked the CHMP to issue an opinion on the benefit-risk balance of trimetazidine-containing medicines, and on whether the marketing authorisation for these medicines should be maintained, varied, suspended or withdrawn across the EU.

## **Which data has the CHMP reviewed?**

The CHMP looked at data from clinical studies, the published literature, spontaneous reports of side effects and data submitted by the companies that market medicines containing trimetazidine.

## **What are the conclusions of the CHMP?**

Regarding the use of trimetazidine in angina pectoris, the Committee noted that the studies carried out to show its effects had some limitations and were often of short duration. Although the studies did not show that the benefits outweighed the risks for trimetazidine when used alone as first-line treatment, the studies supported the use of trimetazidine as add-on to existing treatments in patients who are not adequately controlled by or intolerant to other medicines for angina pectoris. To address the lack of long-term data on trimetazidine, a study investigating the long-term effects of trimetazidine will be carried out.

Regarding the use of trimetazidine in tinnitus, vertigo and visual field disturbances, the studies had poor methodology and did not demonstrate a clinical benefit of trimetazidine when compared with placebo (a dummy treatment) or alternative medicines. In addition the CHMP noted that trimetazidine is often used to treat these conditions in older patients for longer and at higher doses than recommended, increasing the risk of side effects such as falls which undermines the use of trimetazidine for these conditions.

An analysis of relevant safety data showed that movement disorders, including Parkinsonism, cannot be excluded with trimetazidine, although these are not common and are reversible after discontinuing trimetazidine. The CHMP therefore recommended that a warning should be included in the product information on trimetazidine-induced parkinsonism, its diagnosis and management. It also recommended contraindicating trimetazidine in patients with Parkinson disease or parkinsonian symptoms and in patients with severely reduced kidney function.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of trimetazidine continue to outweigh its risks when used as add-on treatment in patients with angina pectoris, but that changes should be made to the product information to ensure the safe use of these medicines. For use in tinnitus, vertigo and visual field disturbances, the benefits no longer outweigh the risks and the CHMP recommended that these uses should no longer be authorised. Written communication will be distributed to doctors at national level to inform them of the changes to the approved uses of trimetazidine.

The full changes made to the information to doctors and patients are detailed [here](#).

### **What are the recommendations for patients?**

- There is no need for an urgent change in treatment, but doctors will review their patients' treatment at their next routine appointment.
- Patients currently receiving trimetazidine for tinnitus, vertigo and disturbances in vision should consult their doctor so they can switch to an appropriate alternative treatment.
- Patients currently receiving trimetazidine for angina pectoris should consult their doctor to ensure that it is the most appropriate treatment for their condition or to arrange alternative treatment if necessary.
- Patients who have any questions should speak to their doctor or pharmacist.

### **What are the recommendations for prescribers?**

- There is no need for an urgent change in treatment, but doctors should review their patients' treatment at their next routine appointment.
- Prescribers should no longer prescribe trimetazidine for treating tinnitus, vertigo and disturbances in vision and switch patients to appropriate alternative treatment.
- Trimetazidine should only be used in the symptomatic treatment of angina pectoris, and only as add-on to existing treatments in patients who are not adequately controlled by or who are intolerant to other medicines for angina pectoris.
- Prescribers must not prescribe trimetazidine in patients with Parkinson disease or parkinsonian symptoms and in patients with severely reduced kidney function. For patients with moderately reduced kidney failure and elderly patients, the dose should be reduced.
- Trimetazidine should be discontinued permanently in patients who develop movement disorders such as parkinsonian symptoms. If parkinsonian symptoms persist for more than four months after discontinuation, a neurologist's opinion should be sought.

The European Commission issued a decision on this opinion on 3 September 2012.