

Rio de Janeiro, 14 de janeiro de 2013.

Prezado Médico,

Desejamos informá-lo do resultado da reavaliação risco/benefício de medicamentos que contêm trimetazidina, realizado na União Europeia.

A revisão minuciosa de todos os dados científicos disponíveis, concluída pela Agência Europeia de Medicamentos (EMA) em 21 de junho de 2012, confirmou o balanço positivo de risco/benefício destes medicamentos em cardiologia (veja documentos EMA anexos*).

A Servier compartilha então o parecer da EMA relativo a esse balanço positivo do risco/benefício em cardiologia.

Além disso, a análise de dados relevantes de segurança mostrou que alterações relacionadas ao movimento, incluindo parkinsonismo, permanecem com baixa prevalência e são reversíveis após interrupção do uso do medicamento. A fim de reduzir o risco, as precauções existentes de uso foram reforçadas. O uso de Vastarel é contraindicado em pacientes com doença de Parkinson ou sintomas de parkinsonismo.

Além do mais, em pacientes com insuficiência renal moderada e com aumento da exposição, a dose deve ser reduzida e, em caso de função renal seriamente reduzida, Vastarel é contraindicado.

Além da adoção da referência para produtos médicos que contêm trimetazidina feita pela Comissão Europeia em 3 de setembro de 2012, as Informações do Produto (bula do profissional de saúde e do paciente) foram atualizadas nos países da União Europeia nos quais o produto está registrado.

A fim de permitir que médicos e pacientes possuam as mesmas informações de segurança dos países europeus, nos propomos a atualizar no Brasil a bula do profissional de saúde e do paciente em relação às Informações de Segurança de Referência.

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Informações de Segurança de Referência



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Press Office

Press release

European Medicines Agency recommends restricting use of trimetazidine-containing medicines

Restricted indication for patients with stable angina pectoris and deletion of existing indications for treatment of vertigo, tinnitus and vision disturbance

The European Medicines Agency has recommended restricting the use of trimetazidine-containing medicines in the treatment of patients with angina pectoris to second-line, add-on therapy. For all other indications the Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these medicines were not sufficiently demonstrated and did not outweigh the risks. The CHMP therefore recommended their deletion from the marketing authorisation.

There is no need for an urgent change in treatment, but doctors should review their patients' treatment at their next routine appointment.

Doctors should no longer prescribe trimetazidine for the treatment of patients with tinnitus, vertigo or disturbances in vision. Patients who are taking trimetazidine in these indications should discuss alternatives with their doctor.

Doctors can continue to prescribe trimetazidine for the treatment of angina pectoris, but only as an add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies.

The review was initiated by France, mainly because of concerns that the efficacy of trimetazidine was not sufficiently demonstrated. It also looked at reports regarding the occurrence of movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors and gait instability associated with the medicine. Although patients usually recovered fully within four months after treatment with trimetazidine was discontinued, the Committee recommended new contraindications and warnings to reduce and manage the possible risk of movement disorders associated with the use of this medicine.

Doctors are advised not to prescribe the medicine to patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome or other related movement disorders, nor to patients with severe renal impairment.



Doctors should exercise caution when prescribing trimetazidine to patients with moderate renal impairment and to elderly patients, and consider dose reduction in these patients.

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 CHMP's opinion will be sent to the European Commission for the adoption of a binding decision throughout the European Union.

Notes

1. This press release, together with all related documents, is available on the Agency's website.
2. 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.
3. The review of trimetazidine-containing medicines was conducted in the context of a formal review under Article 31 of Directive 2001/83/EC, initiated at the request of France.
4. More information on the work of the European Medicines Agency can be found on its website: www.ema.europa.eu

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EUROPEAN MEDICINES AGENCY
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.

A European Commission decision on this opinion will be issued in due course.

Reference Safety Information

4.3 Contra-indications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders,
- Severe renal impairment (creatinine clearance < 30ml/min).

4.4 Special warnings and precautions for use

This medicine is not a curative treatment for angina attacks, nor is it indicated as an initial treatment for unstable angina or myocardial infarction, nor in the pre-hospital phase or during the first days of hospitalisation.

In the event of an angina attack, the coronaropathy should be reevaluated and an adaptation of the treatment considered (medicinal treatment and possibly revascularisation).

Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations.

The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.

These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.

Falls, may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment (see section 4.8).

Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:

- moderate renal impairment (see sections 4.2 and 5.2),
- elderly patients older than 75 years old (see section 4.2).

Excipients

20 mg tablet : Trimetazidine 20 mg tablet contains sunset yellow FCF S (E 110) and cochineal red A (E 124), it may cause allergic reactions.

20 mg/ml solution: Trimetazidine 20 mg/ml solution contains parahydroxymethylbenzoate and parahydroxypropylbenzoate, it may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interactions

No drug interactions have been identified.

4.6 Fertility, Pregnancy and lactation

Pregnancy:

There are no data from the use of trimetazidine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3.) As a precautionary measure, it is preferable to avoid the use of Vastarel during pregnancy.

Breastfeeding:

It is unknown whether trimetazidine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Vastarel should not be used during breast-feeding.

Fertility

Reproductive toxicity studies have shown no effect on fertility in female and male rats (see section 5.3)

4.7 Effects on ability to drive and use machines

Trimetazidine does not have haemodynamic effects in clinical studies, however cases of dizziness and drowsiness have been observed in post-marketing experience (see section 4.8), which may affect ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions, defined as adverse events considered at least possibly attributable to trimetazidine treatment are listed below using the following convention frequency:

Very common ($\geq 1/10$); common ($\geq 1/100, <1/10$); uncommon ($\geq 1/1000, <1/100$); rare ($\geq 1/10000, <1/1000$); very rare ($<1/10000$); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Preferred Term
Nervous system disorders	Common	Dizziness, headache
	Not known	Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation
	Not known	Sleep disorders (insomnia, drowsiness)
Cardiac disorders	Rare	Palpitations, extrasystoles, tachycardia
Vascular disorders	Rare	Arterial hypotension, Orthostatic hypotension that may be associated with malaise, dizziness or fall, in particular in patients taking antihypertensive treatment, flushing

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Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, dyspepsia, nausea and vomiting
	Not known	Constipation
Skin and subcutaneous tissue disorders	Common	Rash, pruritus, urticaria.
	Not known	Acute generalized exanthematus pustulosis (AGEP), angioedema
General disorders and administration conditions	Common	Asthenia
Blood and lymphatic system disorders	Not known	Agranulocytosis Thrombocytopenia Thrombocytopenic purpura
Hepatobiliary disorders	Not known	Hepatitis

4.9 Overdose

Limited information is available on Trimetazidine overdose. Treatment should be symptomatic.