European Medicines Agency

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Questions and answers on the referral for Tritace tablet and hard capsules containing ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg

The European Medicines Agency (EMEA) has completed a review of Tritace. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that there is a need to harmonise the prescribing information for Tritace in the European Union (EU) and the European Economic Area (EEA).
The review was carried out under an 'Article 30' referral[1].

What is Tritace?

Tritace is used to treat hypertension and symptomatic heart failure. Tritace is also used to prevent cardiovascular disease in patients who are at cardiovascular risk (such as patients who already have coronary artery disease), and to prevent any further heart attack (acute myocardial infarction [MI]) in patients who have already had one. The active substance in Tritace, ramipril, is an angiotensin-converting enzyme (ACE) inhibitor. ACE inhibitors lower the production of angiotensin II, a powerful vasoconstrictor (a substance that narrows blood vessels). When the production of angiotensin II is lowered, the blood vessels relax and widen. This allows the heart to pump blood more easily, and the blood flow increases due to more blood being pumped into and through larger passageways.

Tritace has been authorised in the EU since 1989, first in France and then in the following countries: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

Tritace can also be available in the EU and the EEA under other trade names: Triatec, Triatec Hope, Cardace, Delix, Delix Protect, Delix Protect Startset, Delix P, Ramipril Winthrop, Ramipril Prevent, Loavel, Ramiwin, Ramipril Medgenerics, Ramilich, Tritace Titration, Acovil, Tritace Mite, Triateckit, Ramikit, Hypren, Ramace, Vesdil, Vesdil Protect, Ramipril-Zentiva, Unipril, Quark, Zenra, Pramace. The company that markets it is Sanofi-aventis

Why was Tritace reviewed?
Tritace is authorised in the European Union (EU) via national procedures. This has led to divergences across member states on the way the medicine can be used, as seen in the differences observed in the Summaries of Product Characteristics (SPCs), labelling and package leaflets in the countries where the product is marketed. Tritace has been identified as needing harmonisation by the Co-ordination Group on the Mutual and Decentralised Procedures – Human (CMD(h)).
On 3 January 2008 the European Commission referred the matter to the Committee for Medicinal Products for Human Use (CHMP) in order to harmonise the marketing authorisations for Tritace in the EU and the EEA.

[1] Article 30 of Directive 2001/83/EC as amended, referral on the grounds of divergent decisions adopted by member States

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What are the conclusions of the CHMP?
The CHMP, in the light of the data submitted and the scientific discussion within the Committee, was of the opinion that the SPCs, labelling and package leaflets should be harmonised across the EU.

The areas harmonised include:

4.1 Therapeutic Indications

- The CHMP agreed on the indication: *Treatment of hypertension.*
- When considering the indication in heart failure, the CHMP took into consideration previous harmonisations referrals for other ACE-inhibitors (enalapril, perindopril and lisinopril), and agreed on the indication*: Treatment of symptomatic heart failure.*
- The CHMP also discussed the indications in the treatment of cardiovascular secondary prevention, and primary prevention in high-risk patients, and endorsed the harmonised indication: *Cardiovascular prevention: reduction cardiovascular morbidity and mortality in patients with: i) manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or ii) diabetes with at least one cardiovascular risk factor.*
- For the secondary prevention after MI in patients with heart failure, the CHMP endorsed the harmonised indication: *Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started >48 hours following acute myocardial infarction.*

The CHMP also noted that Tritace had an indication for nephroprotection in some countries. After discussion the CHMP agreed on including the harmonised indication: *Treatment of renal disease*
- *Incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria*
- *Manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor*
- *Manifest glomerular non-diabetic nephropathy as defined by macroproteinuria ≥ 3g/day*

4.2 Posology and method of administration

The CHMP discussed the areas where there was a divergence identified in the dose recommendations per indication: For each indication, the posology is presented as starting dose, titration schedule, maintenance dose and maximum dose.

4.3 Contraindications

The CHMP endorsed six contraindications:
- *Hypersensitivity to the active substance, to any of the excipients or any other ACE (Angiotensin Converting Enzyme) inhibitors (see section 6.1)*
- *History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs (Angiotensin II Receptor Antagonists))*
- *Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)*
- *Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney*
- *2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)*
- *Ramipril must not be used in patients with hypotensive or haemodynamically unstable states.*

The CHMP noted that there were contraindications present in one or several local SPCs. The CHMP agreed adding a seventh contraindication: *Ramipril must not be used in patients in patients with hypotensive or haemodynamically unstable states*

4.4 Special warnings and special precautions for use

The CHMP decided to include under this section the harmonised wording:

- *Pregnancy: ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).*
- *Hypotension and renal dysfunction after acute myocardial infarction occurred more frequently with ramipril than placebo in the target population in the AIRE study. Therefore the CHMP agreed on including the wording: Transient or persistent heart failure post MI*
- *Surgery: It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.*
- *Hyperkalaemia*
- *Neutropenia/agranulocytosis*
- *Cough*

4.6 Pregnancy and lactation

The CHMP recommended a contra indication only for the second and third trimester of pregnancy. This is in line with the recommendation of the CHMP's Pharmacovigilance Working Party on the use of ACE inhibitors in pregnancy.

The European Commission issued a decision on 6 March 2009.

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