European Medicines Agency

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Questions and answers on the referral for Tritazide tablets containing ramipril and hydrochlorothiazide 2.5/12.5 mg, 5/12.5 mg, 5/25 mg

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

What is Tritazide?

Tritazide contains two active substances, ramipril and hydrochlorothiazide. 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. Hydrochlorothiazide (HCTZ) is a diuretic. It works by increasing urine output, reducing the amount of fluid in the blood and lowering the blood pressure. Tritazide is used in the treatment of hypertension and it is indicated in patients whose blood pressure is not adequately controlled with ramipril alone or hydrochlorothiazide alone.

Tritazide has been authorised in the EU since 1993, first in Germany and then in the following countries: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia and Sweden.

Tritazide can also be available in the EU and the EEA under other trade names: Tritace Plus, Triatec Plus, Triatec Comp, Tritace Comp, Tritace Comb, Triatec Composto, Triatec Composto Forte, Cardace Comp, Cardace Plus, Cotriatec, Delix Plus, Ramilich Comp, Tritace HCT, Triatec HCT, Ramipril e Idrocloritiazide, Ramicor D, and Triatec Comp Mite,Hypren Plus, Hypren Plus Forte, Vesdil Plus, Ramipril HCT Zentiva, Unipril Diur, Idroquark.. The company that markets Tritazide is Sanofi-aventis.

Why was Tritazide reviewed?

Tritazide 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. Tritazide has been identified as needing harmonisation by the Co-ordination Group on the Mutual and Decentralised Procedures – Human (CMD(h)).

[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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On 18 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 Tritazide in the EU and the EEA.

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 noted inconsistencies in the wording of the indication across countries, with terms including 'essential hypertension', 'arterial hypertension' and 'arterial essential hypertension' being used. The CHMP highlighted that fact that the indication should be hypertension, and as add-on therapy when each monotherapy has failed.
The combination ramipril 2.5 mg/ HCTZ 12.5 mg led to greater reduction in blood pressure than the treatment with individual components and the combination of 5 mg/25 mg produced a better therapeutic effect than doubling the ramipril dose to 10 mg.
Considering that no major concern can be established concerning the safety, efficacy and clinical adverse event of the ramipril/HCTZ combination in non responders to HCTZ and ramipril alone, the CHMP adopted the following two harmonised wordings for indications:

- *Treatment of hypertension*
- *This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled with ramipril alone or hydrochlorothiazide alone.*

4.2 Posology and method of administration

The CHMP discussed the areas where there was a divergence identified in the dose recommendations. In most cases the initial recommended dose was the same, but there were differences with respect to subsequent titration (both in terms of frequency of increase and maximum daily dose). The CHMP also noted that there were limited trial data regarding titration steps with the combination. The CHMP adopted the harmonised wording:
The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control. The administration of the fixed combination of ramipril and hydrochlorothiazide is usually recommended after dosage titration with one of the individual components.
Tritazide and associated names should be started at the lowest available dosage. If necessary, the dose can be progressively increased to achieve target blood pressure; the maximum permitted doses are 10 mg of ramipril and 25 mg of hydrochlorothiazide daily.

4.3 Contra-indications

The majority of the contraindications are related to use of ramipril as a component of Tritazide. They are extended with the contraindications of HCTZ. The CHMP noted that some of the contraindications in local SPCs (such as acute hypertension or primary aldosteronism) were in fact non-indications.

The CHMP adopted the following harmonised wording:

- *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 wit 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)*
- *Lactation (see section 4.6)*

- *Severe impairment of renal function with a creatinine clearance below 30 ml/min in undialysed patients*
- *Clinically relevant electrolyte disturbances which may worsen following treatment with TRITAZIDE (see section 4.4)*
- *Severe impairment of liver function, hepatic encephalopathy*

4.4 Special warnings and special precautions for use

The CHMP included under this session the warning about primary hyperaldosteronism, therefore adopted the following harmonised wording: *The combination ramipril + hydrochlorothiazide does not represent a treatment of choice for primary hyperaldosteronism. If ramipril + hydrochlorothiazide is used in a patient with primary hyperaldosteronism, then careful monitoring of plasma potassium level is required.*
The CHMP included also new warnings for: pregnancy, surgery, electrolyte disturbances, and cough.

4.5 Interactions

The CHMP endorsed the current list of products which interact or may interact with Tritazide, including additional text reinforcing lithium toxicity.

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 use of ACE inhibitors in pregnancy.

The European Commission issued a decision on 6 March 2009.

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